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Adjunctive Role of Some Blood Based Parameters to Serum Prostate Specific Antigen and Its Derivations on Prostate Cancer in Men with "Gray-Zone" Prostate Specific Antigen Levels: Prospective Clinical Study

Gri Zondaki Prostat Spesifik Antijen Düzeyleri Olan Erkeklerde Prostat Kanseri Tahmininde Bazı Kan Bazlı Parametrelerin Serum Prostat Spesifik Antijen ve Türevlerine Yardımcı Rolü: Prospektif Klinik Çalışma

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ABSTRACT Objective: To investigate the adjunctive role of some peripheral blood parameters to serum prostate specific antigen (PSA) in predicting the patients with prostate cancer (PCa) prior to prostate biopsy, and clinically significant PCa among those. **Material and Methods:** This prospective study included men aged ≥45 years, who were scheduled to undergo a prostate biopsy due to gray-zone PSA levels. The levels of free and total PSA (fPSA and tPSA), total testosterone (TT), PSA density (PSAD), C-reactive protein (CRP), De Ritis ratio (aspartate aminotransferase/alanine transaminase) and hemograms were recorded. Patients were divided into 2 groups as benign prostatic hyperplasia (Group 1) and PCa (Group 2) groups. The PCa group was further divided into 2 subgroups as clinically significant and clinically insignificant PCa. The pre-biopsy values of the variables were compared between the groups. **Results:** A total of 210 patients were included in the study (Group 1, n=105; Group 2, n=105). The mean age was 65.1±7.4 years, the mean tPSA level was 6.14±2.05 ng/mL, and the mean TT level was 15.46±5.47 nmol/L. Age, prostate volume, the values of fPSA, PSAD, CRP, and the ratios of fPSA/tPSA, CRP/albumin and De Ritis were statistically different between the groups. In the PCa group, only the tPSA level was significantly different between the subgroups (p=0.005). The area under curve and the cut-off value for tPSA to predict clinically significant PCa were 0.669 and 5.8 ng/mL, respectively. **Conclusion:** CRP, the CRP/albumin ratio and De Ritis ratio may further help predict a diagnosis of PCa.

Keywords: Alanine transaminase; aspartate aminotransferases; C-reactive protein; prostate cancer; testosterone

ÖZET Amaç: Biyopsi öncesi biyokimyasal ve hematolojik parametrelerin, prostat kanseri [prostate cancer (PCa)] hastalarını ve bunlardan da klinik anlamlı PCa hastalarını öngörmede prostat spesifik antijene (PSA) yardımcı etkisinin olup olmadığını araştırmaktır. **Gereç ve Yöntemler:** Çalışmamıza, gri zondaki prostat spesifik antijen (PSA) düzeyleri nedeniyle prostat biyopsisi yapılması planlanan 45 yaş ve üzeri erkekler dâhil edildi. Serbest ve total PSA (sPSA ve tPSA), total testosteron (TT), PSA dansitesi (PSAD), C-reaktif protein (CRP), De Ritis oranı (aspartat aminotransferaz/alanin transaminaz) ve hemogramları kaydedildi. Hastalar benign prostat hiperplazisi (Grup 1) ve PCa (Grup 2) grupları olarak 2'ye ayrıldı. PCa grubu ayrıca klinik anlamlı ve klinik anlamsız PCa olarak 2 alt gruba ayrıldı. Biyopsi öncesi değişkenler gruplar arasında karşılaştırıldı. **Bulgular:** Çalışmaya toplam 210 hasta dâhil edildi (Grup 1, n=105; Grup 2, n=105). Ortalama yaş 65,1±7,4 yıl, ortalama tPSA seviyesi 6,14±2,05 ng/mL ve ortalama TT seviyesi 15,46±5,47 nmol/L idi. Gruplar arasında yaş, prostat hacmi, sPSA, PSAD, CRP değerleri ve sPSA/tPSA, CRP/albumin ve De Ritis oranları istatistiksel olarak farklı bulundu. PCa grubunda alt gruplar arasında sadece tPSA düzeyi anlamlı olarak farklı bulundu (p=0,005). Klinik olarak anlamlı Pca'yı öngörmek için tPSA'nın eğri altında kalan alan ve cut-off değeri sırasıyla 0,669 ve 5,8 ng/mL idi. **Sonuç:** CRP, CRP/albumin oranı ve De Ritis oranı, PCa tanısını öngörmede daha fazla yardımcı olabilir.

Anahtar Kelimeler: Alanin transaminaz; aspartat aminotransferazlar; C reaktif protein; prostat kanseri; testosteron

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Prostate cancer (PCa) is the 2nd most common cancer in men, with approximately 1.4 million diagnoses worldwide in 2020.[1] The incidence of PCa increases with age. Prostate specific antigen (PSA) is a serum biomarker frequently used for PCa screening and early diagnosis.[2] Although PSA is organ-specific, it is not cancer-specific and may be elevated in non-malignant conditions such as benign prostatic hyperplasia (BPH) and prostatitis. The low specificity of PSA testing can lead to unnecessary biopsies, overdiagnosis, and overtreatment, especially at PSA values of 2.5-10 ng/mL, referred to as the gray zone levels.[3] Therefore, several studies have examined the diagnostic value of PSA-based parameters, including the ratio of free PSA to total PSA levels (fPSA/tPSA), PSA density (PSAD), PSA velocity and doubling time for the purpose of improving cancer detection rates and reducing the rates of unnecessary biopsies. However, the roles of systemic inflammatory response markers such as neutrophil, lymphocytes, monocyte, platelet counts and their ratios, and C-reactive protein (CRP) levels, and the ratio of serum aspartate aminotransferase (AST) level to alanine transaminase (ALT) level, called as De Ritis ratio, have been studied only in a few studies for predicting the diagnosis of PCa.[4-6] Furthermore, a significant portion of PCa patients with gray-zone PSA levels are found in the low-risk and clinically insignificant PCa group. Curative treatment may not be started in this group immediately and such patients can be monitored through watchful waiting or active surveillance options as appropriate.

The synthesis and secretion of PSA are under androgenic control. Androgens and androgen receptors play critical roles in both development and hyperplasia of the prostate gland, and both genesis and treatment of PCa.[7,8] Hypogonadism is defined as testosterone deficiency and its incidence increases with age in a manner similar to PCa. It is considered that, even if a hypogonadal patient has prostatic adenocarcinoma, low serum testosterone levels may lead to low synthesis of serum PSA. Therefore, several studies with different outcomes investigated the predictive role of serum testosterone levels and the serum total testosterone (TT)/total PSA (tPSA) ratio on PCa through different methodologies in this population.[9-16]

In this study, we have aimed to investigate the adjunctive role of some hematological and biochemical parameters in patients with gray-zone serum PSA levels (2.5-10 ng/mL) for making the differential diagnosis between benign and malignant diseases of the prostate gland prior to prostate biopsy. Furthermore, we have aimed to examine the role of such parameters in predicting the clinically significant PCa grouped according to Epstein criteria.[17]

MATERIAL AND METHODS

All the study process was carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki; and it was approved by the Ethics Committee of the University of Health Sciences, Bursa Yüksek İhtisas Training and Research Hospital, Bursa (date: October 6, 2021, no: 2011-KAEK-252021/10-15). We included the patients aged ≥45 years, who presented to the urology outpatient clinic of our hospital with the complaints of lower urinary system symptoms in the period between October 2021-September 2022. Patients who had PSA levels in the range of 2.5-10 ng/mL and normal findings in the digital rectal examination, and who underwent a 12-core prostate biopsy under transrectal ultrasonography, were included in this prospective study.

Patients' age, comorbidities, smoking status, body mass index values, pre-biopsy serum tPSA and free PSA (fPSA) levels, prostate volumes as measured in the ultrasonographic examination, serum levels of hormones including the levels of TT and luteinizing hormone, peripheral blood levels of hematological and biochemical parameters including the counts of neutrophil, lymphocytes, and platelet, and the levels of CRP, albumin, AST, and ALT, De Ritis ratio, and findings from the histopathological examination of biopsy specimens were recorded. Serum hormone levels were measured in blood samples, which were collected from the patients in the morning (in the period between 09:00-11:00 a.m.) after a period of fasting. Control blood samples from patients with TT levels of <12 nmol/L were collected on a different day for verification.

Patients with conditions that could affect serum TT levels such as patients using anticonvulsants, thyroid hormones, glucocorticoids, etc., and patients with hypo/hyperthyroidism or metabolic syndrome, etc. were excluded. Patients with inflammatory pathologies (autoimmune diseases, hepatitis, acute or chronic infections, etc.), which could lead to elevated levels of serum inflammation markers, patients using 5-alpha reductase inhibitors, patients with indwelling urethral catheters, and patients with malignant diseases of the prostate gland other than adenocarcinoma were not included in the study. In addition, patients diagnosed with primary or secondary hypogonadism of a known cause were excluded. Patients with serum TT levels of <12 nmol/L were classified as patients with hypogonadism, and patients with serum TT levels of <8 nmol/L were classified as patients with severe hypogonadism.[18] Based on the histopathological examination findings of biopsy specimens, patients diagnosed with BPH were classified as Group 1 and patients diagnosed with PCa were classified as Group 2. In the PCa group, patients, who met Epstein criteria.[17] (a Gleason score of <7 on biopsy, <3 cancer-positive biopsy cores, <50% of tumor involvement in positive cores, clinical T1c stage, PSAD of <0.15 ng/mL), were classified as the clinically insignificant tumor group. Patients, who were diagnosed with PCa but did not meet those criteria, were classified as the clinically significant tumor group. The values of fPSA/tPSA, PSAD, TT/tPSA, CRP, CRP/albumin, De Ritis ratio, the neutrophil/lymphocyte ratio (NLR), and the platelet/lymphocyte ratio (PLR) were compared between the groups.

All participants provided oral consent for participation.

STATISTICAL ANALYSIS

Statistical analysis was performed using IBM SPSS version 21 (IBM Corp., Armonk, NY, USA). The Kolmogorov-Smirnov test was used to examine the normality of the distribution. Continuous variables were reported as means±standard deviations (SD), median (interquartile ranges) and compared with Student's t-test and Mann-Whitney U test. Categorical variables were reported as number (percentage) and compared with Pearson's chi-square test. Spearman's rho correlation analysis was used to examine the relationship of the parameters with PCa. The receiver operating characteristic (ROC) curve was used to examine the role of the parameters in predicting PCa and clinically significant PCa. The sample size of the study was calculated using the G-Power 3.1.9.4 (Kiel University, Kiel, Germany) statistical power analysis program. Differences were considered significant where 2-tailed p-values were <0.05.

RESULTS

Based on the results of the power analysis [2-way correlation, Type-1 error rate (α)=0.05, power of the study (1-β)=0.90, and effect size=0.45], it was found enough to include 105 patients in each group. Therefore, when an adequate number of patients was included, new patient recruitment was stopped. A total of 210 patients were included in the study. The mean age was 65.1±7.4 years (minimum-maximum: 46-87), mean tPSA was 6.14±2.05 ng/mL (minimum-maximum: 2.5-10), mean fPSA was 1.41±0.85 ng/mL (minimum-maximum: 0.22-5.26), and mean TT was 15.46±5.47 nmol/L (minimum-maximum: 4.84-34.89). The patients were divided into 2 groups as the BPH (Group 1, n=105) and PCa (Group 2, n=105). Age, prostate volume, fPSA, fPSA/tPSA, PSAD, CRP, the CRP/albumin ratio, and De Ritis ratio were found statistically different between the 2 groups (Table 1).

As per the results of Spearman's correlation analysis; age, PSAD, CRP, the CRP/albumin ratio, De Ritis ratio were weakly, positively, and significantly correlated (correlation coefficient and p-values=+0.198, 0.004; +0.275, 0.002; +0.248, 0.004; +0.182, 0.038; +0.219, and 0.029, respectively), and fPSA, the fPSA/tPSA ratio were weakly, negatively, and significantly correlated (correlation coefficient and p-values=-0.248, 0.003; -0.310, 0.001, respectively) with PCa (Table 2).

Based on Epstein criteria, the patients with PCa were divided into clinically insignificant (n=43) and clinically significant (n=62) PCa groups. Only tPSA values were statistically significantly different between the 2 groups (p=0.005) (Table 3).

TABLE 1: Comparison of data between BPH and PCa groups (n=210).

Data	Group 1-BPH (n=105)	Group 2-PCa (n=105)	p value
Age (year), (mean±SD)	63.7±6.4	66.5±8.1	**0.006**
BMI (kg/m^2), median (IQR)	29 (27-32)	30 (27-32)	0.459
Cigarette consuption, n (%)			
Yes	54 (51.4%)	61 (58.1%)	0.167
No	51 (48.6%)	44 (41.9%)	
Prostate volume (cc), median (IQR)	68 (53-93)	62 (36-77)	**0.028**
Total PSA (ng/mL), (mean±SD)	6.2±1.8	6.1±2.2	0.387
Free PSA (ng/mL), median (IQR)	1.2 (0.9-1.8)	0.9 (0.6-1.3)	**0.004**
f/t PSA ratio, median (IQR)	0.22 (0.17-0.28)	0.16 (0.09-0.23)	**<0.001**
PSA density, median (IQR)	0.08 (0.06-0.11)	0.11 (0.08-0.18)	**0.002**
TT (nmol/L), (mean±SD)	15.6±5.8	15.3±5.1	0.682
TT/tPSA ratio, (mean±SD)	2.8±1.5	2.9±1.6	0.435
LH (mIU/mL), median (IQR)	3.7 (2.6-5.1)	3.6 (2.8-5.2)	0.947
CRP (mg/L), median (IQR)	3.3 (3.3-3.3)	3.3 (3.3-8.3)	**0.005**
Albumin (g/L), (mean±SD)	46.9±2.7	46.7±2.3	0.680
CRP/albumin ratio, median (IQR)	0.07 (0.06-0.08)	0.07 (0.06-0.16)	**0.038**
Neutrophil (10^3/mL), median (IQR)	4.4 (3.5-5.6)	5.1 (3.4-5.6)	0.320
Lymphocyte (10^3/mL), median (IQR)	2.1 (1.7-2.6)	2 (1.7-2.6)	0.809
Thrombocyte (10^3/mL) median (IQR)	234 (201-270)	229 (205-278)	0.953
NLR, median (IQR)	2.1 (1.5-2.7)	2.2 (1.6-2.8)	0.584
PLR, median (IQR)	111 (86-143)	117 (91-156)	0.380
AST (U/L), median (IQR)	21 (17-25)	17 (14-23)	0.070
ALT (U/L), (mean±SD)	23.1±11.1	17.8±12.9	0.066
De Ritis ratio, median (IQR)	1 (0.7-1.2)	1.2 (0.9-1.9)	**0.030**

BPH: Benign prostate hyperplasia; PCa: Prostate cancer; Mean±SD: Mean±standart deviation; BMI: Body mass index; IQR: Interquartile range; TT: Total testosterone; tPSA: Total prostate specific antigen; LH: Luteinizing hormone; CRP: C-reactive protein; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

Of biochemical variables, only tPSA was weakly, positively, and significantly correlated with clinically significant PCa (the correlation coefficient and the p-value were +0.288 and 0.003, respectively) (Table 4).

All patients were divided into hypogonadism (<12 nmol/L) or normal (≥12 nmol/L) according to TT levels. TT levels were not different between the BPH and PCa groups or the clinically insignificant PCa and clinically significant PCa groups (p-values=0.763 and 0.903, respectively). Furthermore, all patients were divided into severe hypogonadism (<8 nmol/L), mild hypogonadism (8-12 nmol/L), and normal (≥12 nmol/L) according to TT levels. The comparison of these 3 groups did not reveal any differences between the BPH and PCa groups or the clinically insignificant PCa and clinically significant PCa groups (p-values=0.471 and 0.760, respectively) (Table 5).

In the ROC analysis, the area under the curve (AUC) values for age, prostate volume, fPSA, fPSA/tPSA, PSAD, CRP, the CRP/albumin ratio, and De Ritis ratio in predicting PCa were 0.614, 0.632, 0.666, 0.707, 0.684, 0.650, 0.626, and 0.642, respectively (Table 6). The cut-off value for tPSA as a predictor of clinically significant PCa risk was 5.8 ng/mL, with sensitivity and specificity values of 68% and 65%, respectively, and with an AUC value of 0.669 (95% confidence interval=0.564-0.773, p= 0.003) (Table 6).

DISCUSSION

The rate of clinically significant PCa in patients with gray-zone PSA values is substantially low. In order to avoid unnecessary biopsies, combinations of several biochemical parameters are studied to improve the odds of predicting PCa before a biopsy. Because PCa

TABLE 2: Correlation analysis of the parameters in terms of predicting prostate cancer in our entire cohort.

Parameters	Spearman's rho correlation coefficient	p value
Age	+0.198	**0.004**
BMI	+0.051	0.460
Cigarette consuption	+0.095	0.168
Prostate volume	-0.197	0.027
Total PSA	0.058	0.401
Free PSA	-0.248	**0.003**
f/t PSA ratio	-0.310	**0.001**
PSA density	+0.275	**0.002**
TT	-0.004	0.955
TT/tPSA ratio	+0.040	0.566
LH	+0.006	0.947
CRP	+0.248	**0.004**
Albumin	-0.025	0.777
CRP/albumin ratio	+0.182	**0.038**
Neutrophil	+0.085	0.322
Lymphocyte	-0.021	0.810
Thrombocyte	+0.005	0.953
NLR	+0.047	0.586
PLR	+0.075	0.382
AST	-0.182	0.070
ALT	-0.100	0.320
De Ritis ratio	+0.219	**0.029**

BMI: Body mass index; PSA: Prostate specific antigen; f/t PSA: Free and total Prostate specific antigen; TT: Total testosterone; LH: Luteinizing hormone; CRP: C-reactive protein; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

is known to be associated with systemic inflammation markers, the relationship of PCa with several inflammation markers such as CRP, the counts of neutrophil, lymphocytes, monocyte, platelet, NLR, and PLR, and several biochemical markers including De Ritis ratio have been investigated in some studies.[19-26] However, data are currently inadequate to include the tests of such parameters in routine screening programs. Therefore, we investigated whether some biochemical parameters could help to serum PSA in predicting PCa and clinically significant PCa before biopsy in our study. Our results have shown that the only variable correlated to predict clinically significant PCa was tPSA. However, fPSA, fPSA/tPSA, PSAD, CRP, the CRP/albumin ratio, and De Ritis ratio were found to be correlated in predicting PCa.

Several studies have investigated the relationship of PCa with inflammation markers such as CRP. In a meta-analysis of data from 9 studies investigating the relationship between CRP levels and survival, CRP was reported to be a prognostic marker for overall survival, cancer-specific survival, and progression-free survival in PCa.[20] In another study, which included 140 patients with BPH and 63 patients with PCa based on biopsy results, Kim et al. reported a statistically significant difference in CRP levels between the 2 groups.[21] Toriola et al. followed up on 2,571 patients over a mean period of 24 months and investigated the association of PCa with CRP, fibrinogen, and leukocyte counts. They reported an association only between elevated prediagnostic leukocyte counts and cancer but they did not find any associations of PCa with CRP or fibrinogen.[22] Uchimoto et al. investigated the effect of the CRP/albumin ratio on mortality and survival in 221 patients with castration-resistant metastatic PCa. They reported that patients with a CRP/albumin ratio of higher than 0.5 had shorter overall survival and cancer-specific survival times compared to patients with a CRP/albumin ratio of lower than 0.5.[23] Similarly, in our study, CRP and the CRP/albumin ratio were significantly higher in the PCa group compared to the BPH group. We found a cut-off value of 0.7 for the CRP/albumin ratio in our study.

We have not found a relationship between the TT/tPSA ratio and PCa in our study. Different from our results, Xu et al. compared 92 patients with BPH and 164 patients with PCa from the Chinese population in their study and reported lower TT/tPSA ratios in the PCa group compared to the BPH group.[13] However, they reported that serum TT levels were similar in those 2 groups. Rhoden et al. reported a 3-fold increased risk of PCa in patients with a TT/tPSA ratio of less than 1.8.[12] Gurbuz et al. reported a higher likelihood of detecting PCa in patients with low serum testosterone levels (<3 ng/mL) compared to patients with normal levels.[9]

Another result of our study is the relationship between De Ritis ratio and PCa. The value of De Ritis ratio has been investigated for predicting risk stratification in localized PCa. The mentioned study reported the association of an increased De Ritis ratio with advanced clinical and pathological stages, increased Gleason scores, increased seminal vesicle invasion, positive surgical margins, and the likelihood

TABLE 3: Comparison of data between groups in patients with prostate cancer (n=105).

Data	Insignificant PCa (n=43)	Significant PCa (n=62)	p value
Age (year), (mean±SD)	65.8±7.1	67.1±8.7	0.452
BMI (kg/m^2), (mean±SD)	29.5±3.3	29.9±3,1	0.531
Cigarette consuption, n (%)			
Yes	20 (46.5%)	24 (38.7%)	0.547
No	23 (53.5%)	38 (61.3%)	
Prostate volume (cc), (mean±SD)	68.2±39.4	57.8±23.1	0.358
Total PSA (ng/mL), (mean±SD)	5.3±2.1	6.5±2.2	**0.005**
Free PSA (ng/mL), median (IQR)	1.1 (0.8-1.4)	0.8 (0.6-1.2)	0.257
f/t PSA ratio, (mean±SD)	0.2±0.07	0.15±0.009	0.195
PSA density, (mean±SD)	0.11±0.06	0.14±0.06	0.270
TT (nmol/L), (mean±SD)	14.9±4.8	15.5±5.2	0.579
TT/tPSA ratio, median (IQR)	3.1 (1.9-4.3)	2.4 (1.7-3.4)	0.055
LH (mIU/mL), median (IQR)	3.7 (2.9-5.6)	3.3 (2.7-5.1)	0.347
CRP (mg/L), median (IQR)	3.3 (3.3-8.7)	4.9 (3.3-8.9)	0.771
Albumin (g/L), (mean±SD)	46.9±2.5	46.5±2.1	0.669
CRP/albumin ratio, median (IQR)	0.07 (0.06-0.15)	0.11 (0.06-0.19)	0.425
Neutrophil (10^3/mL), (mean±SD)	5.4±1.4	4.6±1.3	0.141
Lymphocyte (10^3/mL), median (IQR)	2.1 (1.6-2.7)	2.1 (1.7-2.5)	0.920
Thrombocyte (10^3/mL), (mean±SD)	250.4±76.1	242.5±47.7	0.709
NLR, (mean±SD)	2.6±1.2	2.2±1.8	0.243
PLR, (mean±SD)	143.7±68.1	118.4±38.6	0.171
AST (U/L), median (IQR)	16 (12.5-21.5)	18 (14-30)	0.520
ALT (U/L), median (IQR)	16 (9-18.5)	14 (11-20)	0.737
De Ritis ratio, (mean±SD)	1.3±0.4	1.3±0.5	0.912

PCa: Prostate cancer; BMI: Body mass index; Mean±SD: Mean±standart deviation; PSA: Prostate specific antigen; IQR: Interquartile range; f/t PSA: Free and total prostate specific antigen; TT: Total testosterone; LH: Luteinizing hormone; CRP: C-reactive protein; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

of lymph node involvement.[24] Also, it reported a cut-off value of 1.325 for De Ritis ratio in predicting the occurrence of biochemical recurrence based on the ROC analysis. In our study, we found a cut-off value of 1.12 for De Ritis ratio in predicting PCa. A systematic review and meta-analysis investigating the relationship between survival and De Ritis ratio in urological cancers reported that De Ritis ratio was not associated with overall survival but was associated with biochemical recurrence-free survival in PCa.[25] Karamık et al. investigated the relationship between preoperative De Ritis ratios and biochemical recurrence in 302 radical prostatectomy patients and concluded that De Ritis ratio was an independent predictive factor for biochemical recurrence.[26] In that study, Karamık et al. found a cut-off value of 1.1 for De Ritis in predicting biochemical recurrence. This result is similar to the value in our present study.

The relationship between testosterone levels and PCa is unclear. However, some studies report that low testosterone levels are associated with more aggressive cancers than others. It is considered that this results from the inhibition of testosterone secretion by hormones such as inhibin in patients with PCa.[27] In their study, which included 568 patients, Shin et al. found that low serum testosterone levels were statistically significant predictors of the risk of developing PCa. They found that only tPSA was significantly associated with a high-grade Gleason score.[28] Similarly, tPSA was the only variable associated with clinically significant PCa in our study. Kwon et al. reported that a low serum testosterone level was highly associated with a Gleason score of >8 in patients, who underwent radical prostatectomy.[29] Conversely, a meta-analysis reported a 23% lower risk of PCa in patients with low serum free

TABLE 4: Correlation analysis of the parameters in terms of predicting clinically significant prostate cancer.

Parameters	Spearman's rho correlation coefficient	p value
Age	+0.067	0.496
BMI	+0.088	0.370
Cigarette consuption	+0.078	0.430
Prostate volume	-0.079	0.672
Total PSA	+0.288	**0.003**
Free PSA	-0.198	0.263
f/t PSA ratio	-0.299	0.086
PSA density	+0.226	0.221
TT	+0.067	0.496
TT/tPSA ratio	-0.188	0.055
LH	-0.181	0.356
CRP	+0.054	0.777
Albumin	-0.159	0.410
CRP/albumin ratio	+0.151	0.435
Neutrophil	-0.208	0.231
Lymphocyte	-0.017	0.921
Thrombocyte	+0.009	0.961
NLR	-0.139	0.427
PLR	-0.150	0.389
AST	+0.132	0.513
ALT	+0.066	0.744
De Ritis ratio	-0.071	0.726

BMI: Body mass index; PSA: Prostate specific antigen; TT: Total testosterone; f/t PSA: Free and total prostate specific antigen; LH: Luteinizing hormone; CRP: C-reactive protein; NLR: Neutrophil/lymphocyte ratio; PLR: Platelet/lymphocyte ratio; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

testosterone levels than in patients with high concentrations.[19] Other authors suggest that the development of PCa is independent of endogenous sex hormone levels. In their study comparing pre-biopsy testosterone levels in 85 patients, who underwent a prostate biopsy, Temel et al. concluded that neither TT nor free testosterone was an effective predictor of the Gleason score.[14] In our study, the TT level was not associated with PCa or clinically significant PCa.

There is no consensus about the cut-off values of suggested parameters such as the fPSA/tPSA ratio and PSAD to improve the specificity of PSA in predicting PCa. In our study, the cut-off value for the fPSA/tPSA ratio was found to be 20%. Erol et al. analyzed the fPSA/tPSA ratio by age groups in their cohort study of 4,955 patients. The fPSA/tPSA cut-off values were reported as 10%, 15%, and 15% for the 50-59, 60-69, and >70 year-old age groups, respectively. That study reported an overall fPSA/tPSA cut-off value of 10% for all age groups.[30] Another parameter is PSAD, for which cut-off values were studied. Heidenreich, A. et al. reported a cut-off value of 0.1-0.15 ng/mL/cc for that parameter in their study.[19] In our study, the PSAD cut-off value for the PCa risk has been found to be 0.1 ng/mL/cc, which is in line with the literature.

Our study shows the relationship of some biochemical parameters (De Ritis ratio, CRP, the CRP/albumin ratio) with PCa in patients with gray-zone PSA levels; however, it is not free of limitations. Firstly, our study appears to have included a small number of patients. Secondly, we could not examine any radiological findings because most patients did not undergo multi-parametric magnetic resonance imaging. Finally, the outcomes of our study were in-

TABLE 5: Relationship between hypogonadism and PCa.

Serum testosterone level	BPH (n=105)	PCa (n=105)	p value	
<12 nmol/L	30 (28.5%)	33 (31.4%)	0.763	
≥12 nmol/L	75 (71.5%)	72 (68.6%)		
<8 nmol/L	7 (6.6%)	4 (3.8%)	0.471	
8-12 nmol/L	23 (21.9%)	29 (27.6%)		
≥12 nmol/L	75 (71.5%)	72 (68.6%)		
Serum testosterone level	**BPH (n=105)**	**Insignificant PCa (n=43)**	**Significant PCa (n=62)**	**p value**
<12 nmol/L	30 (28.5%)	14 (32.5%)	19 (30.6%)	0.903
≥12 nmol/L	75 (71.5%)	29 (67.5%)	43 (69.4%)	
<8 nmol/L	7 (6.6%)	1 (2.3%)	3 (4.8%)	0.760
8-12 nmol/L	23 (21.9%)	13 (30.2%)	16 (25.8%)	
≥12 nmol/L	75 (71.5%)	29 (67.5%)	43 (69.4%)	

PCa: Prostate cancer; BPH: Benign prostate hyperplasia.

TABLE 6: Data of the ROC curves in terms of differentiating PCa patients from BPH patients and clinically significant prostate cancer from clinically insignificant prostate cancer.

Variables	AUC	%95 CI	Cut-off value	Sensitivity (%)	Specificity (%)	p value
Age*	0.614	0.537-0.691	65.5	60	58	0.004
PV*	0.632	0.517-0.747	65.5	59	61	0.028
fPSA*	0.666	0.560-0.771	1.07	67	59	0.004
f/t PSA*	0.707	0.605-0.810	0.20	62	68	<0.001
PSAD*	0.684	0.573-0.795	0.1	61	69	0.002
CRP*	0.650	0.536-0.764	4.9	46	84	0.013
CRP/albumin ratio*	0.626	0.512-0.740	0.7	66	54	0.038
De ritis ratio*	0.642	0.517-0.767	1.12	60	65	0.030
tPSA**	0.669	0.564-0.773	5.8	68	65	0.003

*Predictors of PCa; **Predictor of clinically significant; ROC: Receiver operating characteristic; PCa: Prostate cancer; BPH: Benign prostatic hyperplasia; AUC: Area under curve; CI: Confidence interval; PV: Prostate volume; f/t PSA: Free and total prostate specific antigen; PSA: Prostate specific antigen; PSAD: PSA density; CRP: C-reactive protein.

terpreted according to the results of univariate analysis.

CONCLUSION

In order to avoid unnecessary biopsies, some biochemical parameters such as CRP, the CRP/albumin ratio, and De Ritis ratio may provide benefits in addition to known indicators such as PSA, PSAD, and the fPSA/tPSA ratio in men with gray-zone PSA levels. Our results have not revealed a marker other than tPSA to predict clinically significant PCa. Future studies, which will provide supporting results and overcome our study's limitations may help develop combined prediction models using the abovementioned markers to be used before a prostate biopsy.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Abdullah Gül;* ***Design:*** *Abdullah Gül, Salim Zengin;* ***Control/Supervision:*** *Abdullah Gül, Özgür Ekici;* ***Data Collection and/or Processing:*** *Salim Zengin, Çağlar Boyacı;* ***Analysis and/or Interpretation:*** *Abdullah Gül, Özgür Ekici;* ***Literature Review:*** *Çağlar Boyacı;* ***Writing the Article:*** *Abdullah Gül, Özgür Ekici;* ***Critical Review:*** *Salim Zengin, Çağlar Boyacı;* ***References and Fundings:*** *Salim Zengin, Çağlar Boyacı;* ***Materials:*** *Abdullah Gül, Özgür Ekici.*

REFERENCES

1. Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent global patterns in prostate cancer incidence and mortality rates. Eur Urol. 2020;77(1):38-52. [Crossref] [PubMed]
2. Stamey TA, Yang N, Hay AR, McNeal JE, Freiha FS, Redwine E. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med. 1987;317(15):909-16. [Crossref] [PubMed]
3. Salman JW, Schoots IG, Carlsson SV, Jenster G, Roobol MJ. Prostate specific antigen as a tumor marker in prostate cancer: biochemical and clinical aspects. Adv Exp Med Biol. 2015;867:93-114. [Crossref] [PubMed]
4. Murray NP, Fuentealba C, Reyes E, Lopez MA, Salazar A, Minzer S, et al. Predictive value of neutrophil to lymphocyte ratio in the diagnosis of significant prostate cancer at initial biopsy: a comparison with free percent prostate specific antigen, prostate specific antigen density and primary circulating prostate cells. Asian Pac J Cancer Prev. 2019;20(11):3385-9. [Crossref] [PubMed] [PMC]
5. Santotoribio JD, Jimenez-Romero ME. Serum biomarkers of inflammation for diagnosis of prostate cancer in patients with nonspecific elevations of serum prostate specific antigen levels. Transl Cancer Res. 2019;8(1):273-8. [Crossref] [PubMed] [PMC]
6. Ha H, Chung JW, Ha YS, Choi SH, Lee JN, Kim BS, et al. Clinical significance of the De Ritis ratio for detecting prostate cancer in a repeat prostate biopsy. Investig Clin Urol. 2019;60(6):447-53. [Crossref] [PubMed] [PMC]
7. Lonergan PE, Tindall DJ. Androgen receptor signaling in prostate cancer development and progression. J Carcinog. 2011;10:20. [Crossref] [PubMed] [PMC]
8. Schulman CC, Irani J, Morote J, Schalken JA, Montorsi F, Chlosta PL, et al. Testosterone measurement in patients with prostate cancer. Eur Urol. 2010;58(1):65-74. [Crossref] [PubMed]
9. Gurbuz C, Canat L, Atis G, Guner B, Caskurlu T. The role of serum testosterone to prostate-specific antigen ratio as a predictor of prostate cancer risk. Kaohsiung J Med Sci. 2012;28(12):649-53. [Crossref] [PubMed]
10. Karamanolakis D, Lambou T, Bogdanos J, Milathianakis C, Sourla A, Lembessis P, et al. Serum testosterone: A potentially adjunct screening test for the assessment of the risk of prostate cancer among men with modestly elevated PSA values (> or =3.0 and <10.0 ng/ml). Anticancer Res. 2006;26(4B):3159-66. [PubMed]
11. Morote J, Planas J, Ramirez C, Gómez E, Raventós CX, Placer J, et al. Evaluation of the serum testosterone to prostate-specific antigen ratio as a predictor of prostate cancer risk. BJU Int. 2010;105(4):481-4. [Crossref] [PubMed]
12. Rhoden EL, Riedner CE, Morgentaler A. The ratio of serum testosterone-to-prostate specific antigen predicts prostate cancer in hypogonadal men. J Urol. 2008;179(5):1741-4. [Crossref] [PubMed]
13. Xu L, Hu X, Zhu Y, Lu J, Xu Y, Wang G, et al. Additional value of the ratio of serum total testosterone to total prostate-specific antigen in the diagnosis of prostate cancer in a Chinese population. Andrologia. 2018;50(2). [Crossref] [PubMed]
14. Temel MC, Ediz C, Akan S, Ozer E, Yilmaz O. Association of Gleason score with PSA values and serum testosterone levels measured prior to prostate biopsy. J Coll Physicians Surg Pak. 2020;30(4):399-402. [Crossref] [PubMed]
15. Haider A, Zitzmann M, Doros G, Isbarn H, Hammerer P, Yassin A. Incidence of prostate cancer in hypogonadal men receiving testosterone therapy: observations from 5-year median followup of 3 registries. J Urol. 2015;193(1):80-6. [Crossref] [PubMed]
16. Watts EL, Appleby PN, Perez-Cornago A, Bueno-de-Mesquita HB, Chan JM, Chen C, et al. Low free testosterone and prostate cancer risk: a collaborative analysis of 20 prospective studies. Eur Urol. 2018;74(5):585-94. [Crossref] [PubMed] [PMC]
17. Epstein JI, Walsh PC, Carmichael M, Brendler CB. Pathologic and clinical findings to predict tumor extent of nonpalpable (stage T1c) prostate cancer. JAMA. 1994;271(5):368-74. [Crossref] [PubMed]
18. Corona G, Rastrelli G, Morgentaler A, Sforza A, Mannucci E, Maggi M. Meta-analysis of results of testosterone therapy on sexual function based on international index of erectile function scores. Eur Urol. 2017;72(6):1000-11. [Crossref] [PubMed]
19. Heidenreich A, Aus G, Bolla M, Joniau S, Matveev VB, Schmid HP, et al; European Association of Urology. [EAU guidelines on prostate cancer]. Actas Urol Esp. 2009;33(2):113-26. [Crossref] [PubMed]
20. Liu ZQ, Chu L, Fang JM, Zhang X, Zhao HX, Chen YJ, et al. Prognostic role of C-reactive protein in prostate cancer: a systematic review and meta-analysis. Asian J Androl. 2014;16(3):467-71. [Crossref] [PubMed] [PMC]
21. Kim Y, Jeon Y, Lee H, Lee D, Shim B. The prostate cancer patient had higher C-reactive protein than BPH patient. Korean J Urol. 2013;54(2):85-8. [Crossref] [PubMed] [PMC]
22. Toriola AT, Laukkanen JA, Kurl S, Nyyssönen K, Ronkainen K, Kauhanen J. Prediagnostic circulating markers of inflammation and risk of prostate cancer. Int J Cancer. 2013;133(12):2961-7. [Crossref] [PubMed]
23. Uchimoto T, Komura K, Fujiwara Y, Saito K, Tanda N, Matsunaga T, et al. Prognostic impact of C-reactive protein-albumin ratio for the lethality in castration-resistant prostate cancer. Med Oncol. 2019;37(1):9. [Crossref] [PubMed]
24. Wang H, Fang K, Zhang J, Jiang Y, Wang G, Zhang H, et al. The significance of De Ritis (aspartate transaminase/alanine transaminase) ratio in predicting pathological outcomes and prognosis in localized prostate cancer patients. Int Urol Nephrol. 2017;49(8):1391-8. [Crossref] [PubMed]
25. Su S, Liu L, Li C, Zhang J, Li S. Prognostic role of pretreatment de ritis ratio (aspartate transaminase/alanine transaminase ratio) in urological cancers: a systematic review and meta-analysis. Front Oncol. 2020;10:1650. [Crossref] [PubMed] [PMC]
26. Karamık K, Aktaş Y, Yıldız A, Erol İ, İslamoğlu E, Ateş M, et al. Predictive role of de ritis ratio in biochemical recurrence after radical prostatectomy. Med Bull Haseki. 2020;58(1):84-93. [Crossref]
27. Miller LR, Partin AW, Chan DW, Bruzek DJ, Dobs AS, Epstein JI, et al. Influence of radical prostatectomy on serum hormone levels. J Urol. 1998;160(2):449-53. [Crossref] [PubMed]
28. Shin BS, Hwang EC, Im CM, Kim SO, Jung SI, Kang TW, et al. Is a decreased serum testosterone level a risk factor for prostate cancer? A cohort study of korean men. Korean J Urol. 2010;51(12):819-23. [Crossref] [PubMed] [PMC]
29. Kwon T, Jeong IG, You D, Park MC, Hong JH, Ahn H, et al. Effect of prostate size on pathological outcome and biochemical recurrence after radical prostatectomy for prostate cancer: is it correlated with serum testosterone level? BJU Int. 2010;106(5):633-8. [Crossref] [PubMed]
30. Erol B, Gulpinar MT, Bozdogan G, Ozkanli S, Onem K, Mungan G, et al. The cutoff level of free/total prostate specific antigen (f/t PSA) ratios in the diagnosis of prostate cancer: a validation study on a Turkish patient population in different age categories. Kaohsiung J Med Sci. 2014;30(11):545-50. [Crossref] [PubMed]