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Evaluation of free-to-total prostate specific antigen(F/T PSA) ,prostate specific antigen density(PSAD) and (F/T)PSAD sensitivity on reduction of unnecessary prostate biopsies for patients with PSA in gray zone

AIM: *We evaluated the influence of ratio between free-to-total prostate specific antigen (F/T PSA) and prostate specific antigen density (PSAD)-(F/T)/PSAD on reduction of unnecessary prostate biopsies in grey zone (prostate specific antigen (psa) value 4.0-10.0 ng/ml).*
METHODS: The *study included 108 patients. For all patients serum total PSA (T PSA), free PSA (F PSA), F/T PSA and PSAD were analyzed. The group was divided due to the prostate volume into: entire group (regardless the prostate VOL-Group 1) and group with prostate VOL<40 (Group 2*).
RESULTS: *Seventy five patients were diagnosed with benign prostatic hyperplasia (BPH) and 33 with prostate cancer (CaP). F/T PSA and (F/T)/PSAD showed significantly lower values in patients with CaP versus those with BPH, while PSAD had significantly higher values. For the cutoff values of 1.12 for (F/T)/PSAD, we found sensitivity to be 67% and specificity 60%, and the (AUC) 0.701. For patients with VOL<40, statistical significance remained with AUC of 0.732 (p=0.003), cutoff was 0.82, and with sensitivity 77% and* specificity 68%.
CONCLUSIONS: *Most significant prostate carcinoma predictors were PSAD and (F/T)/PSAD, where we proposed that patients with (F/T)/PSAD values below 1.49 ± 0.94 and PSAD values above 0.17±0.06 should be included for biopsy.*

KEY WORDS: Biopsy, Benign prostatic hyperplasia, Prostate cancer, Prostate specific antigen (PSA), Prostate specific antigen density (PSAD)

Introduction

Prostate specific antigen (PSA) is considered to be the most significant tumor marker in prostate cancer diagnostics [1]. It is used for the determination of disease stadium and disease follow-up as well [1]. Since 1980s the application of such marker brought the revolution in prostate cancer diagnostics [1,2]. However, it is important to underline that PSA is not the ideal tumor marker due to its low specificity, which leads to the possible biopsy for the patients without prostate cancer. Therefore, increased value of PSA is not always a confirmation of prostate cancer existence. Other conditions like benign prostatic hyperplasia (BPH) and chronic inflammation can lead to the increased level of PSA in circulation as well. Jemal et al, stated that beside other

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urological examinations, the introduction of the PSA managed to disclose about every fourth patient with prostate cancer in its first stadium (stadium A) [3].
In the gray zone, which refers to the PSA interval between 4.0-10.0 ng/ml, there is still a problem how to separate the patients who have prostate cancer from those who don't have it, since roughly every fourth patient (about 25%) in the gray zone has been diagnosed with prostate cancer [4]. Therefore, for the evaluation of new diagnostic strategies new parameters have to be included, namely prostate specific antigen density (PSAD), the ratio between index of free prostate specific antigen (F PSA) and total prostate specific antigen (T PSA) – (F/T PSA), etc. Considering that, it is justified to examine as well the ratio between F/T PSA and PSAD - (F/T)/PSAD.
We hypothesized that the (F/T)/PSAD marker could be effective in predicting necessity of biopsies in patients with PSA within gray zone interval. Therefore, the aim of our study was to evaluate the influence of F/T PSA, PSAD and (F/T)/PSAD on reduction of unnecessary prostate biopsies in grey zone (PSA value 4.0-10.0 ng/ml).

Material and Methods

STUDY GROUP

The study included 108 patients that were treated at Clinic of Urology at Clinical Center of Serbia between 2007-2012 years. The criteria for inclusion of eligible participants were the PSA values between 4.0-10.0 ng/ml. For all patients, serum T PSA, F PSA, F/T PSA and PSAD by means of Abbott test, were analyzed. The prostate volume was measured with trans rectal ultrasound (TRUS), and TRUS biopsies were performed in entire group. The group was divided due to the prostate volume (VOL) into: entire group (regardless the prostate VOL- Group 1) and group with prostate VOL <40 (Group 2). From evaluated population 75 were initially diagnosed with benign prostatic hyperplasia (BPH), which was histopathologically verified – BPH group, while 33 patients from entire study group referred to the Clinic due to the increase in PSA values and were histopathologically confirmed to have prostate cancer (CaP) - CaP group. The clinical evaluation and diagnostics were done by Board Certified Urologists while histopathological confirmation was done by Board Certified Pathologists. Prior inclusion in the study eligible participants were informed about the treatment protocol and informed consent was obtained. The study was approved by the Institutional Review Board of Faculty of Medicine and followed the principles of good clinical practice.
The parameters that were analyzed included: T PSA, F PSA, F/T PSA, PSAD, (F/T)/PSAD and VOL. (F/T)/PSAD was generated via division of F/T PSA by PSA/VOL [5].

STATISTICAL ANALYSIS

Mean values with standard deviation (SD) were used to present the values for observed parameters. For evaluation of statistical significance of these values between BPH and CaP groups students T test was used. In order to examine diagnostical significance of the test for determination of PSAD, F/T PSA and (F/T)/PSAD, sensitivity and specificity was determined by means of receiver operating characteristics curve (ROC). The cutoff with the best sensitivity and specificity was evaluated. The area under the ROC curve (AUC) was meant to compare all those parameters. Pearson correlation was done to evaluate presence of statistical correlation between F/T PSA, PSAD and (F/T)/PSAD. For the evaluation of tumor predictor parameters we used linear regression. Statistical significance was set at $p<0.05$.

Results

From 108 evaluated patients 75 had a pathohistologically verified benign prostatic hyperplasia (BPH), age between 51-82 years old, while 33 had a pathohistologically verified prostate cancer (CaP), from 52 to 76 years old. We found no significant difference in mean values of T PSA and VOL parameters, while for: F PSA, PSAD, F/T PSA and (F/T)/PSAD there was significant difference of mean values (Table I).
ROC curve for PSAD shows the value under the ROC curve. Even though ROC curve for PSAD was not significant (p=0.133) (Fig. 1A), for patients with VOL up to 40 we found statistical significance because AUC is 0.667 (p=0.023), were cutoff for PSAD is 0.22, with sensitivity 62% and specificity 71% (Fig. 1B).

TABLE I - *Mean values of evaluated parameters in BPH and CaP groups of patients*

Parameters	Group	Mean±SD	p values
(F/T)/PSAD	BPH	1.49 ± 0.94	0.003
	CaP	0.94 ± 0.61	
T PSA	BPH	6.68 ± 1.73	0.622
	CaP	6.86 ± 1.82	
F PSA	BPH	1.50 ± 0.86	0.003
	CaP	1.01 ± 0.54	
F/T PSA	BPH	0.21 ± 0.09	0.000
	CaP	0.15 ± 0.06	
VOL	BPH	42.15 ± 13.52	0.531
	CaP	40.15 ± 18.50	
PSAD	BPH	0.17 ± 0.06	0.030
	CaP	0.20 ± 0.08	

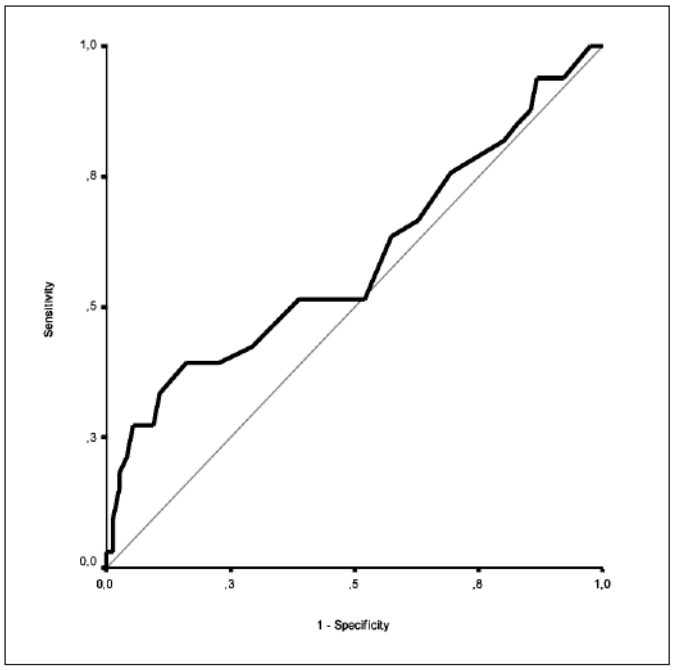

Fig. 1A: ROC for PSAD

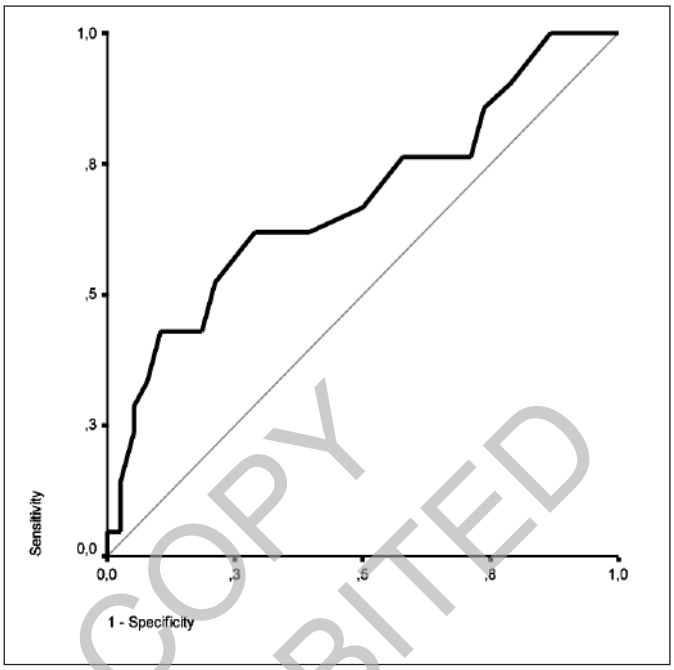

Fig. 1B: ROC for PSAD for VOL up to 40

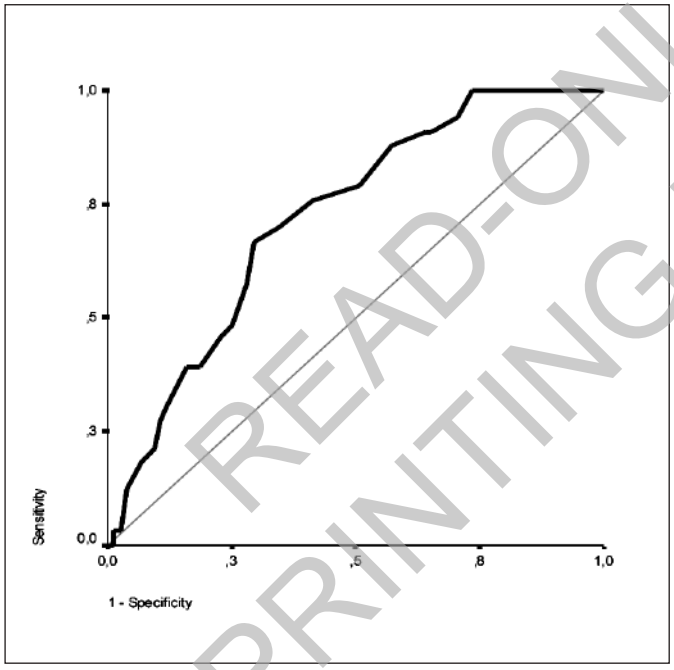

Fig. 2A: ROC for F/T PSA

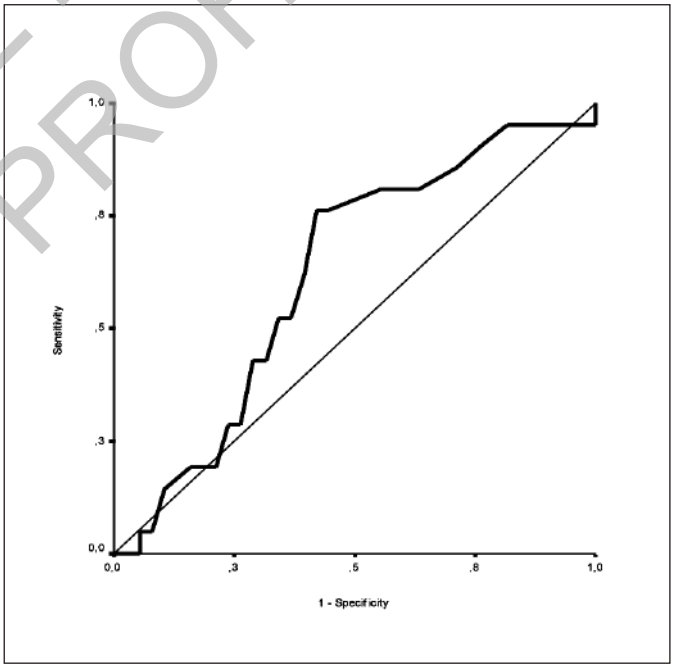

Fig. 2B: ROC for F/T PSA for VOL up to 40

ROC curve for F/T PSA shows the value under the ROC curve. We found statistical significance for ROC curve for F/T PSA, since AUC is 0.720 (p=0.001) were cutoff is 0.20, with sensitivity 76% and specificity 60% (Fig. 2A).

For patients with VOL up to 40 we found non statistical significance therefore cutoff values were not analyzed further (Fig. 2B).

ROC curve for (F/T)/PSAD shows the value under the ROC curve. We found statistical significance for ROC curve for (F/T)/PSAD, since AUC is 0.701 (p=0.001) were cutoff is 1.12, with sensitivity 67% and specificity 60% (Fig. 3A). For patients with VOL up to 40 statistical significance remained with AUC of 0.732 (p=0.003), were cutoff for (F/T)/PSAD is 0.82, with sensitivity 77% and specificity 68% (Fig. 3B).

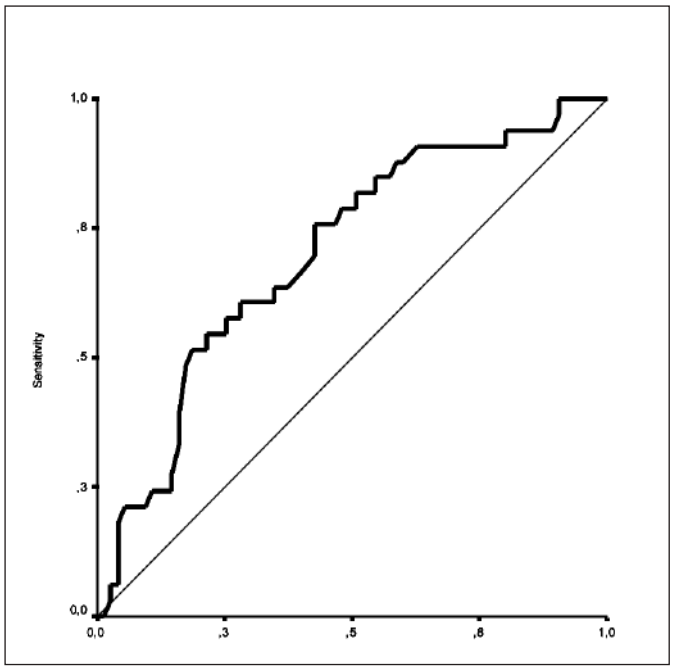

Fig. 3A: ROC for (F/T)/PSAD

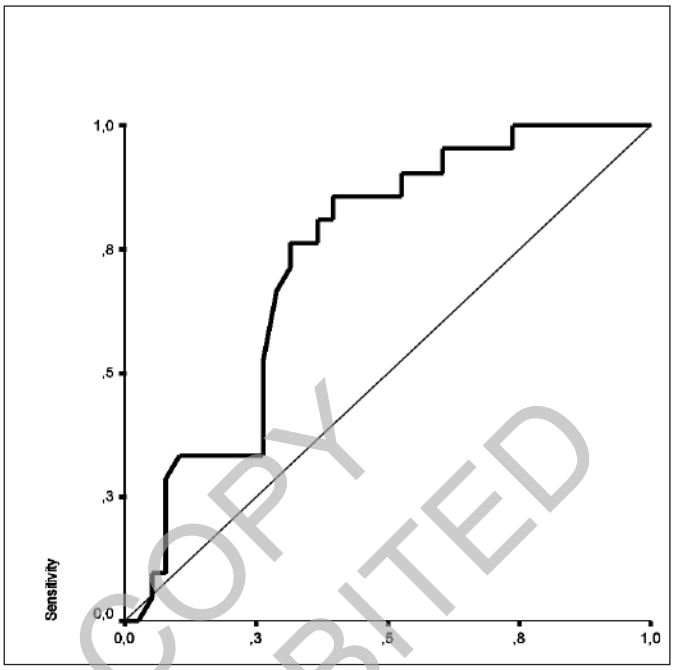

Fig. 3B: ROC for (F/T)/PSAD for VOL up to 40

TABLE II - *Correlation between PSAD, F/T PSAD and (F/T)/PSAD* Pearson

Correlation		r value	p value
F/T PSA	PSAD	-0.321	0.001
	(F/T)/PSAD	0.788	0.000
PSAD	(F/T)/PSAD	-0.670	0.000

TABLE III - *Predictor parameters in evaluated patients*

Parameters	B	SE	Wald's coefficient	df	p value
F/T/PSAD	0.276	0.221	6.559	1	0.007
T	0.021	0.119	0.032	1	0.857
F	-0.602	0.326	3.407	1	0.065
F/T	-0.397	1.268	0.098	1	0.754
VOL	0.015	0.020	0.568	1	0.451
PSAD	13.529	4.913	7.583	1	0.006
Constant	-1.531	2.528	0.367	1	0.545

B – registration coefficient, SE – standard error, df - degree of freedom.

We have shown that there is statistically significant correlation between F/T PSA and PSAD as well as between F/T PSA and (F/T)/PSAD and between PSAD and (F/T)/PSAD (Table II). However, there is only positive significant correlation between F/T PSA and (F/T)/PSAD pointing out that increase in F/T PSA leads to the increase in (F/T)/PSAD.

Our results pointed out that the most significant tumor predictors are F/T/PSAD and PSAD, so it is clear that on a person with F/T/PSAD lower than 1.0, or PSAD higher than 0.160 a biopsy must be performed (Table III).

Discussion

Evaluation of the connection between F/T PSA and PSAD should bring to the distinction of patients with prostate carcinoma versus those without one in gray zone and therefore to the reduction in necessity of unnecessary biopsies. The usefulness of F/T PSA ratio is more reliable in the diagnosis of prostate cancers since it improves PSA specificity, with higher ratio observed in patients with benign pathology that was also shown in the results of our study with a statistical significance [6]. We have demonstrated as well that patients with BPH have significantly increased (F/T)/PSAD values versus those with prostate carcinoma and suggesting that the patients with (F/T)/PSAD values up to 1.50 should be screened for the presence of prostatic cancer. The justification for PSAD evaluation was elaborated in numerous studies previously, where it was stated that such marker is better predictor for prostate carcinoma then PSA particularly in interval between 4.0-10.0 ng/mL (referring to the area of grey zone) [7,8].

Previous studies have pointed out that PSAD depends on prostate volume indicating that the most significant specificity is for the volumes below 40 (<40 VOL) [9-11]. In our study we have shown that for the entire group of patients regardless the prostate volume PSAD does

not tend to present with statistical significance (p=0.133), but for patients with <40 VOL of prostate, PSAD presents with statistical significance (p=0.023), and with sensitivity of 62% and specificity of 71%. Such findings point out to the possible assumption that smaller prostate volumes (particularly in our study for patients with <40 VOL) that were analyzed for PSAD are more sensitive markers in cancer diagnosis together (prostate volume and PSAD) than evaluation of PSAD alone. These observations correlate to the certain degree with previous reports [9,11].

Previously it was shown that lower ratio of F/T PSA tends to be good indicator for prostate carcinoma, but the selection of cutoff values particularly in clinical practice is complicated due to the partial dependence of F/T PSA on patients age, prostate size and T PSA [4,10,11]. Further, such marker is shown to be valid parameter for estimation of necessity of prostate biopsy in high risk groups [12].

In our study we have demonstrated that for those patients that were diagnosed with prostate carcinoma, the cutoff value for F/T PSA is 0.20 with sensitivity of 76% and specificity of 60%, presenting with high statistical significance. Contrary to these findings when we excluded patients with prostate volumes above 40 we gained non statistical significance due to the fact that the prostate size cannot separate patients with carcinoma from those who don't have one. The justification for such findings could be found in the observation of Carvalhal et al, who stated that PSA correlates better with tumor volume then with prostate size [9]. In the study of Kuriyama et al F/T PSA cutoff values of 0.155 will bring sensitivity of 85% and specificity of 56.5% [13]. Different values for sensitivity and specificity of F/T PSA could be in the fact that different PSA intervals and different tests that were used lead to the different F/T PSA values [14].

Previous reports for the PSA range between 4-10 ng/ml correlate with our findings of 1.12 for cutoff values and AUC 0.701 for (F/T)/PSAD [15]. Differences in sensitivity and specificity between different studies could be explained to the certain degree by the different ranges of PSA values, pointing out to the possible assumption that such values could have certain influence on the sensitivity and specificity for the prostate carcinoma [15]. When we excluded the patients with prostate volume above 40 VOL we found that both sensitivity and specificity increased, stressing out that beside (F/T)/PSAD prostate volume plays significant role in prostate carcinoma evaluation.

Our results showed as well that there is inversion in PSAD versus F/T PSAD and (F/T)/PSAD, where increase in PSAD values lead to the significant reduction in other two parameters values.

Conclusion

Given the facts above, we have shown that the most significant prostate carcinoma predictors are PSAD and (F/T)/PSAD, where we proposed that those patients with (F/T)/PSAD values below 1.49±0.94 and PSAD values above 0.17±0.06 should be included for biopsy.

Riassunto

Scopo: Abbiamo valutato il significato del rapporto tra PSA libero e totale (F/T PSA) e la densità (PSAD)-(F/F)/PSAD quale dato per ridurre le biopsie prostatiche non necessarie nell'ambito della "zona grigia", e cioè con valori di PSA compresi tra 4.0 e 10.0 ng/ml.

Metodo: Lo studio ha riguardato 108 pazienti. Per tutti è stato analizzato il PSA totale, il PSA libero, il rapporto F/T PSA e la densità (PSAD). Il gruppo è stato suddiviso in rapporto al volume prostatico: da una parte l'intero gruppo (Gruppo 1) e dall'altra i pazienti con volume prostatico <40 (Gruppo 2).

Risultati: In 75 pazienti era stata diagnosticata una iperplasia prostatica benigna (BPH) e in 33 un cancro della prostata (CaP). F/T PSA e (F/T)/PSAD hanno mostrato valori significativamente inferiori nei pazienti con CaP ripsetto a quelli BPH, mentre la PSAD presentava valori significativamente superiori. Per il valore limite 1,2 per (F/T)/PSAD abbiamo constato una sensibilità del 67%, una specificità del 60% ed una AUC (Area under ROC [ROC= Receiver Operating Curve]) pari a 0.701. Nei pazienti con volume <40 il significato statitico rimaneva con AUC di 0.732 (P=0.003), ed il limite era 0.82, con una sensibilità del 77% e una specificità del 68%.

Conclusioni: I valori maggiormente produttivi del carcinoma prostatico sono risultati essere la PSAD e il rapporto (F/T)/PSAD, per cui noi proponiamo che dovrebbero essere destinati alla biopsia prostatica i pazienti con valori di (F/T)/PSAD al di sotto 1.49 ± 0.94 e di valori di PSAD al di sopra di 0.17 ± 0.06.

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