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Diagnostic value of free-to-total PSA proportion and PSA density in prostate cancer detection for prostate volumes ≥ 100 cc

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ABSTRACT

Introduction: Free to total PSA proportion (f/t FPSA) and PSA density (PSAD) are mostly used PSA derivatives for better cancer detection. In this study, we aimed to evaluate whether or not f/t PSA and PSAD had any diagnostic contribution to prostate cancer (pCa) detection in patients that had prostate volumes ≥ 100 cc.

Material and Methods: The medical records of transrectal ultrasound guided prostate biopsy performed patients were retrospectively evaluated and divided into two categories according to their prostate volumes (<100 cc and ≥100 cc). The diagnostic value of total PSA, PSAD and f/t PSA in prostate cancer detection for prostate volumes ≥ 100 cc were statistically evaluated.

Results: Among 311 patients 51 and 260 had prostate volumes ≥100 cc and <100 cc, respectively. pCa detected patients with greater prostate volumes had slightly increased serum PSA levels, but the difference was not statistically significant. f/t PSA was higher, and PSAD was lower in greater prostate volumes when compared prostate volumes <100 cc and the differences was significant. Moreover, the AUC for PSAD and f/t PSA for prostate volumes ≥100 cc were 0.51 and 0.58, respectively. All was suggestive for the insufficient diagnostic contribution of both PSA derivatives in greater prostate volumes ≥100 cc.

Conclusions: The most significant value of our study was demonstrating the inability of pCa detection of PSAD and f/t PSA in prostate volumes ≥100 cc. Although larger and prospective studies are warranted to make better inferences, up to that time our results may guide clinicians in their daily practice.

Key words: *Free-to-total PSA proportion, PSA density, large prostate, prostate cancer, screening*

Introduction

Prostate carcinoma (pCa) is one of the most common malignancies among men. Increasing mortality rates raise the importance of the screening tests and programs [1]. After the advent of prostate-specific antigen (PSA) testing in prostate cancer detection over 20 years ago, it became the best available screening tool in daily clinical practice and recognized as the best molecular marker for early cancer diagnosis [2]. However, the non-cancer specific nature of the marker [3] obliged all clinicians to find and adopt new PSA derivatives in clinical use to diagnose prostate cancer more accurately [4-6]. PSA density (PSAD) and free-to-total PSA proportion (f/t PSA) are the widely used and investigated ones in the clinical practice [4,7,8]. Despite several studies indicating the effectiveness of both f/t PSA and PSAD in several conditions such as different total PSA levels and prostate volumes; there are no studies evaluating their diagnostic efficiency in prostate volumes ≥100 cc.

This study aimed to investigate whether or not f/t PSA and PSAD had any diagnostic contribution to pCa

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detection in patients that had prostate volumes ≥100 cc.

Material and Methods

The study was conducted after the approval of the Local Ethical Committee. The medical records of a total 360 Patients who underwent transrectal ultrasound (TRUS) guided prostate biopsy due to PSA elevation between 2013 and 2017 were retrospectively evaluated. Patient age, prostate volume, free and total PSA, f/t PSA, PSAD and TRUS prostate biopsy results were recorded. The indications of TRUS prostate biopsy were elevated serum PSA levels (≥2.5 ng/ml) or abnormal digital rectal examination. In patients with more than 10-years life expectancy, 12 core TRUS prostate biopsy was performed to all patients. The patients with incomplete medical records were excluded from the study. The patients who had serum PSA levels <4 ng/ml and ≥20 ng/ml were also excluded.

First, the patients were divided into two categories according to their prostate volumes (<100 cc and ≥100 cc). The capability of total PSA, PSAD and f/t PSA in prostate cancer diagnosis for prostate volumes ≥100 cc were statistically evaluated and compared with prostate volumes <100cc.

Statistical analysis: All statistical calculations were performed with Statistical Package for Social Sciences software program (SPSS 22.0 for Windows). The Mann-Whitney U test was used for comparisons between groups. The diagnostic value of f/t PSA and PSAD was evaluated by receiver operation characteristics (ROC) curve analysis. The significance was defined as $p<0.05$.

Results

From the 360 patients recruited in the study, 49 were excluded because of the absence of data. Among 311 remaining patients, 51 (17%) and 260 (83%) had prostate volumes ≥100 cc and <100 cc, respectively. Of the entire group, 94 (30%) had prostate cancer. Mean patient age, prostate volume, total PSA, f/t PSA, PSAD were 64.5±8.3, 66.36±39.2 cc, 8.1±3.6 ng/ml, 0.21±0.09ng/ml, 0.16±0.13 ng/ml/cc, respectively. Mean age, PSA kinetics, and prostate volumes according to groups (prostate ≥100 cc and <100 cc) were summarized in Table 1. Statistical analysis revealed significance only for f/t PSA, PSAD, and prostate volume. Consequently, the PSA kinetics and patient characteristics were compared for prostate cancer (pCa) patients according to prostate volumes. The results are summarized in Table 2. Interestingly there was a slight increase in serum PSA levels in patients with greater prostate volumes, but the difference was not statistical-

Table 1. Patient characteristics and PSA kinetics for the entire group according to prostate size.

	Prostate ≥100 cc (n:51)	Prostate <100 cc (n:260)	P value
Age (years) (Mean±SD)	66.29±6.4	64.15±8.6	p≥0.05
PSA (ng/ml) (Mean±SD)	8.9±4.1	7.9±3.9	p≥0.05
Free PSA (ng/ml) (Mean±SD)	2.0±1.0	1.5±1.0	p<0.05
f/t PSA (ng/ml) (Mean±SD)	%25±8	%20±9	p<0.05
PSAD (ng/ml/cc) (Mean±SD)	0.06±0.03	0.17±0.14	p<0.05
Prostate volume (cc) (Mean±SD)	138.7±37	52.15±18.3	p<0.05

PSA: Prostate Specific Antigen, f/t PSA: free-to-total PSA proportion, PSAD: PSA density, pCa: prostate cancer.

Table 2. Patient characteristics and PSA kinetics for prostate cancer patients according to prostate size.

	pCa + prostate ≥100 cc (n:9)	pCa+prostate <100 cc (85)	P value
Age (years) (Mean±SD)	69.4±8.0	66.71±9.6	p≥0.05
PSA (ng/ml) (Mean±SD)	10.0±4.1	9.5±4.3	p≥0.05
Free PSA (ng/ml) (Mean±SD)	2.2±1.0	1.6±1.4	p<0.05
f/t PSA (ng/ml) (Mean±SD)	%25±11	%17±8	p<0.05
PSAD (ng/ml/cc) (Mean±SD)	0.07±0.04	0.24±0.19	p<0.05
Prostate volume (cc) (Mean±SD)	154.5±54.9	45.1±17.9	p<0.05

PSA: Prostate Specific Antigen, f/t PSA: free-to-total PSA proportion, PSAD: PSA density, pCa: prostate cancer.

Table 3. Patient characteristics, PSA kinetics, and comparisons between pCa + and pCa – patients who have prostates ≥100 cc.

	pCa + (n:9)	pCa - (42)	P value
Age (years) (Mean±SD)	69.4±8.0	65.6±5.9	p≥0.05
PSA (ng/ml) (Mean±SD)	10.0±4.1	8.7±4.1	p≥0.05
Free PSA (ng/ml) (Mean±SD)	2.2±1.0	2.0±1.0	p≥0.05
f/t PSA (ng/ml) (Mean±SD)	0.25±0.11	0.26±0.08	p≥0.05
PSAD (ng/ml/cc) (Mean±SD)	0.07±0.04	0.06±0.03	p≥0.05
Prostate volume (cc) (Mean±SD)	154.5±54.9	135.3±32.7	p≥0.05

PSA: Prostate Specific Antigen, f/t PSA: free-to-total PSA proportion, PSAD: PSA density, pCa: prostate cancer.

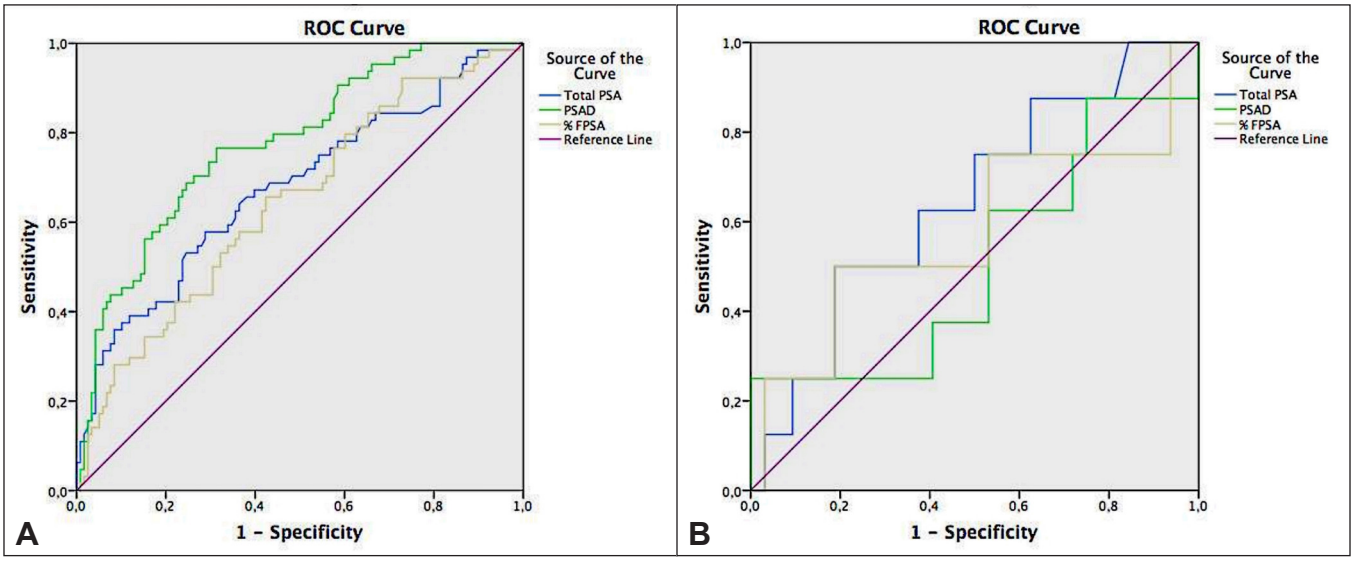

Figure 1. Receiver operating characteristics curve analysis of total prostate-specific antigen (PSA), free-to-total PSA proportion (%FPSA), and PSA density (PSAD). **(A)** Data are shown for 260 patients with prostate volumes <100 cc and total PSA in the range of 4-20 ng/ml; **(B)** 51 patients with prostate volumes ≥100 cc and total PSA in the range of 4-20 ng/ml.

ly significant. On the other hand, f/t PSA was higher, and PSAD was lower in greater prostate volumes when compared prostate volumes <100 cc and the differences was significant. Table 3 summarizes the patient characteristics, PSA kinetics and comparisons between pCa (+) and pCa (–) patients who have prostate volumes ≥100 cc. Conspicuously there were no statistically significant differences between all parameters including total PSA, PSAD and f/t PSA, indicating the insufficiency of current pCa detection tools in larger prostate volumes. Moreover, we performed ROC analysis to evaluate the cancer detection rates of f/t PSA, PSAD and serum total PSA for prostate volumes <100 cc and ≥100 cc. Not surprisingly the AUC for PSAD and f/t PSA for prostate volumes <100 cc were 0.75 and 0.65, respectively. But strikingly these values were 0.51 and 0.58 for prostate volumes ≥100 cc. For total serum PSA, the AUC was 0.66 for prostate volumes <100 cc and 0.61 for prostate volumes ≥100 cc. All ROC analysis was demonstrated in Figure 1 a and b. The results demonstrated the diagnostic insufficiency of serum f/t PSA and PSAD and diagnostic inferiority of total PSA in prostate volumes ≥100 cc.

Of 51 patients with prostate volumes ≥100cc, all had PSAD <0.15 ng/ml/cc and all but two had f/t PSA >0.15ng/ml. There were 9 pCa detected patients whit in this group, and similar results were demonstrated. Strikingly, all pCa detected patients had PSAD <0.15 ng/ml/cc and all but one had f/t PSA >0.15ng/ml. There were no pCa detected patients with high PSAD and low f/t PSA according to previously reported cut-off levels. Moreover, four patients had f/t PSA >0.25ng/ml. These results may indicate the usefulness of current cut-off levels of PSAD and f/t PSA for prostate volumes ≥100 cc and need for new cut-off levels.

Discussion

There is a widespread consensus that the total PSA measurements are the best methods that we currently

have except digital rectal examination (DRE). It increases the cancer detection rates up to 81% when compared DRE [9]. But the primary drawback is that the increased PSA level is not specific to cancer and may elevate in several benign conditions [3]. To optimize the PSA testing and avoid unnecessary prostate biopsies; several PSA derivatives are introduced in the time chart of modern PSA era [4-6]. F/t PSA and PSAD are the most clinically used derivatives of these measurements.

Initial data demonstrated that f/t PSA resulted with an increase in specificity from 55% to 73% without compromising the sensitivity of the PSA test.4 Several investigators made an effort to establish appropriate reference ranges for concentration and proportion, and also confirmed the ability to improve specificity for several PSA levels [10,11]. But none investigated the diagnostic importance of f/t PSA in larger prostates. The clinical advantage had been demonstrated in the PSA levels between 4 and 10 ng/ml [3-5,11-14]. In many studies 0.15 ng/ml is used as a cut-off level [15,16]. In a study conducted by Catalona et al. [9], pCa was detected by biopsy in 56% of men with f/t PSA <0.10, but in only 8% with f/t PSA >0.25 ng/ml. Erol et al. [11] demonstrated that f/t PSA ratio has different AUC values for different age categories. In their study, Stephen et al. [4] demonstrated that the data on men with total PSA in the 4-10 ng/ml range showed 0.731 AUC for f/t PSA. Our results demonstrated 0.65 AUC for f/t PSA for prostate volumes <100 cc. But the AUC decreased significantly to 0.58 in the prostate volumes ≥100 cc, demonstrating the insufficient diagnostic ability in larger prostates. Moreover, our results demonstrated that 8 of 9 pCa patients who had prostate volumes ≥100 cc had f/t PSA levels >0.15 mg/ml. This PSA value may be a new cut-off value for biopsy indication for larger prostate volumes (≥100 cc).

After the introduction by Benson et al., [17] several studies demonstrated the advantage of PSAD over total PSA [8,18,19]. Several studies also conducted to evaluate which total PSA range most benefit from PSAD testing [4,20]. But again, none investigated the diagnostic value for larger prostate volumes (≥100 cc). In their study, Stephan and colleagues reached 0.74 AUC for total PSA range 4-10 ng/ml and 0.739 AUC for 2-4 ng/ml [4]. In another study, Castro et al. reported 0.72 AUC for total PSA range 2.6-10 ng/ml [20]. Consistently with these studies, our results demonstrated 0.75 AUC for prostate volumes <100 cc and total PSA range 4-20 ng/ml. But only 0.51 AUC was showed when the prostate volumes were ≥100cc, demonstrating the insufficient diagnostic ability in larger prostates alike with f/t PSA. Our study also demonstrated that all 9 pCa patients who had prostate volumes ≥100 cc had PSAD <0.15 ng/ml/cc. These results may suggest that PASD is not a good predictive test for prostate cancer diagnosis in patients with prostates ≥100 cc and total PSA 4-20 ng/ml.

The major limitation of the study except its retrospective nature is the relatively small sample size for larger prostates (prostate volumes ≥100cc), and the number of pCa patients within this group. Secondly, prostate volumes of all study population were measured by different operators. Despite these limitations, the results of our study give an invaluable contribution to the English literature, yet there is no data regarding PSA derivatives for prostate volumes ≥100 cc.

Conclusions

The most significant value of our study is demonstrating the inability of pCa detection of PSAD and f/t PSA in prostate volumes ≥100 cc. Although there is a great effort to reduce unnecessary biopsies and better predict prostate cancer with several PSA derivatives like PSAD and f/t PSA, larger prostates need different derivatives or at least different cut-off levels. Larger and prospective studies are warranted to make better inferences, but up to that time, our results may guide clinicians in their daily practice.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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