

Voiding Dysfunction/Female Urology

Prostate-Specific Antigen Mass and Free Prostate-Specific Antigen Mass for Predicting the Prostate Volume of Korean Men With Biopsy-Proven Benign Prostatic Hyperplasia

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Purpose: It has been reported that prostate-specific antigen (PSA) correlates with prostate volume. Recently, some studies have reported that PSA mass (PSA adjusted for plasma volume) is more accurate than PSA at predicting prostate volume. In this study, we analyzed the accuracy of PSA and the related parameters of PSA mass, free PSA (fPSA), and fPSA mass in predicting prostate volume.

Materials and Methods: We retrospectively investigated 658 patients who underwent prostate biopsy from 2006 to 2012 and had a confirmed negative biopsy result. International Prostate Symptom Score (IPSS) questionnaire, PSA, fPSA, and prostate volume were investigated. PSA mass and fPSA mass were calculated by use of established formulas. The association between PSA-related parameters and IPSS and prostate volume was assessed by using Pearson correlation coefficient and receiver operating characteristic curves.

Results: There was no significant difference between PSA and PSA mass, fPSA, or fPSA mass in predicting prostate volume except in obese patients (p-value of PSA-PSA mass for 40 cm³, 0.54; p-value of fPSA-fPSA mass for 40 cm³, 0.34). fPSA performed significantly better than PSA at predicting prostate volume (p-value for 40 cm³, < 0.001). IPSS and the aforementioned PSA-related parameters were not significantly correlated.

Conclusions: PSA mass was not a better predictive value than PSA for estimating the prostate volume in Korean men except in obese men. This finding was also applicable to the relationship of fPSA and fPSA mass, which appeared to be more accurate predictors of prostate volume than either PSA or PSA mass.

Keywords: Benign prostatic hyperplasia; Prostate-specific antigen; ROC curve

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INTRODUCTION

Prostate volume is the primary factor in estimating the severity of lower urinary tract symptoms (LUTS) and the risk of acute urinary retention [1]. Furthermore, prostate volume is essential in dictating the treatment course in the management of patients with LUTS. Ultrasonography, especially transrectal ultrasonography (TRUS), is considered to be the gold standard for measurement of prostate

volume. Despite its accuracy, however, routine measurement of prostate volume by TRUS is clinically not feasible owing to its cost and invasiveness.

Therefore, several studies have investigated alternative methods for predicting the prostate volume, and prostate-specific antigen (PSA) was propounded as a feasible proxy for predicting prostate volume [2,3]. Several authors have estimated an equation for predicting prostate volume by use of serum in Caucasian men [4]. The Korean pop-

ulation has also been subjected to investigation of the relationship between PSA and prostate volume, predictably showing a general concordant association as well [5,6].

It has been reported that serum PSA is inversely correlated with body mass index (BMI) [7,8], and it has been suggested that obesity can decrease the ability of PSA to predict prostate volume, because dilution of PSA can lead to underestimation of prostate volume in obese men. Recently, serum PSA mass, the concept of the total circulating amount of PSA in the body, was introduced to compensate for variability in body habitus in modifying PSA in the estimation of prostate volume [9,10]. The new parameter, PSA mass, represents the total circulating amount of PSA produced in the body. PSA mass, which is serum PSA multiplied by plasma volume, is expected to be a better metric tool of prostate volume than serum PSA because it is independent of body habitus variables such as plasma volume or body size.

PSA mass has been reported to be more accurate for predicting prostate volume than PSA itself [9], but few studies have analyzed the utility of PSA mass as a predictor of prostate volume in Korean men. Furthermore, there have been no studies of the correlation between free PSA-related factors (free PSA [fPSA], fPSA mass) and prostate volume in a Korean male population. The purpose of this study was therefore to determine the predictive power of plasma volume-adjusted PSA (PSA mass, fPSA mass) for prostate volume in Korean men.

MATERIALS AND METHODS

1. Study population

After the study protocol was approved by the Institutional Review Board of Korea University Guro Hospital, we retrospectively investigated the medical data of 1,009 patients who underwent TRUS-guided prostate biopsy at Korea University Guro Hospital from 2006 until 2012. Prostate volume was measured before the prostate biopsy by TRUS (HDXE11, Philips, Beckley, WV, USA) and was calculated according to the following formula: $\pi/6 \times \text{width} \times \text{height} \times \text{length}$ [11].

All patients underwent TRUS-guided prostate biopsy with protocols requiring 10 to 12 cores. The following parameters were obtained in each patient: age, body weight (BW), height, PSA, and fPSA. The degree of LUTS of each patient was assessed by using the International Prostate Symptom Score (IPSS) Questionnaire.

Exclusion criteria were patients with a history of receiving 5-alpha reductase inhibitor therapy and those with a history of invasive surgical treatment of benign prostatic hyperplasia (BPH), such as transurethral resection or laser prostatectomy. Patients with a history of acute prostatitis, with a history of urinary retention within the past month, or lacking data on any of the aforementioned parameters were excluded. Prostate cancer patients with results confirmed by subsequent TRUS-guided prostate biopsy were excluded. Only patients proven to have benign

results by the prostate biopsy were included in this study. Patients with PSA above 20 ng/mL were also omitted to decrease the possibility of occult prostate cancer. After all exclusions, 658 men were enrolled in this study.

2. PSA mass and fPSA mass formulas

The following formulas were used to determine BMI, body surface area (BSA), plasma volume, PSA mass, and fPSA mass as described previously [12]:

$$\text{BMI (kg/m}^2\text{)} = \text{BW (kg)} / \text{height (m}^2\text{)},$$

$$\text{BSA (m}^2\text{)} = \text{BW (kg)}^{0.425} \times \text{height (m)}^{0.72} \times 0.007184,$$

$$\text{Plasma volume (L)} = \text{BSA (m}^2\text{)} \times 1.670,$$

$$\text{PSA mass} = \text{serum PSA (ng/mL)} \times \text{plasma volume [BSA (m}^2\text{)} \times 1.670], \text{ and}$$

$$\text{fPSA mass} = \text{serum fPSA (ng/mL)} \times \text{plasma volume [BSA (m}^2\text{)} \times 1.670]$$

3. Statistical analysis

Prostate volume, PSA, PSA mass, fPSA, and fPSA mass were analyzed after logarithmic transformation because of their skewed distributions. Patients were classified by BMI on the basis of Asian criteria as follows: < 23.0, 23.0–27.5, and > 27.5 [13]. Pearson correlation analysis was performed to evaluate the relationship of prostate volume and IPSS with PSA and its related parameters: PSA mass, fPSA, and fPSA mass. Receiver operating characteristic (ROC) curves were analyzed to assess the predictive ability of the PSA-related parameters (PSA, PSA mass, fPSA, and fPSA mass) in predicting a prostate volume of 20 cm³, 30 cm³, 40 cm³, and 50 cm³. Accuracy was quantified by the area under the curve (AUC) values of the ROC analysis.

All analyses were performed by using SPSS ver. 14 (SPSS Inc., Chicago, IL, USA). Comparison of AUC was carried out by using MedCalc ver. 12.5.0 (MedCalc software, Ostend, Belgium). Statistical significance was defined as a two-tailed $p < 0.05$.

RESULTS

The patient characteristics of our study population are presented in Table 1. The patients' mean age was 64.8 years (range, 28 to 91 years). The number of patients in each BMI group was as follows: 225 men in group 1 (BMI, < 23.0 kg/m²), 367 men in group 2 (BMI, 23.0–27.5 kg/m²), and 66 patients with BMI above 27.5 kg/m². About 10% (n=66) of our cohort was obese (BMI, > 27.5 kg/m²). The mean volume of the prostate was 45.13 cm³, which ranged from 12.3 to 152 cm³. The mean BMI and plasma volume of our cohort were 23.98 kg/m² and 2.90 L, respectively. Mean PSA and fPSA were 5.68 ng/mL and 1.08 ng/mL, respectively.

The correlation coefficients between prostate volume and PSA, fPSA, and their mass-estimated values are shown in Table 2. Prostate volume was significantly correlated with PSA and their related parameters ($p=0.004$ for PSA, PSA mass; $p=0.000$ for fPSA, fPSA mass). The correlation between fPSA, fPSA mass and PV ($r=0.330$) was apparently stronger than that between PSA, PSA mass and PV

($r=0.111$). On the contrary, the correlation between PSA, fPSA and PV was not significantly different from that between PSA mass, fPSA mass and PV (0.111 vs. 0.111; 0.330 vs. 0.330).

The ROC curve and estimated AUCs for predicting various volumes of the prostate (20 cm³, 30 cm³, 40 cm³, and 50 cm³) are shown in Fig. 1 and Table 3. Among the total patients, PSA mass and fPSA mass did not have stronger predictive power than PSA and fPSA for predicting any prostate volume in our study. In the BMI-classified analysis, PSA mass did not have stronger predictive ability than PSA did except for predicting relatively large prostates of 40 cm³ and 50 cm³ in obese patients (BMI, > 27.5 kg/m²; $p < 0.05$). This was also applicable to fPSA and fPSA mass.

In our study, fPSA almost always performed sig-

nificantly better than PSA at predicting prostate volume in the analysis of the total patients and the BMI-stratified patients. The AUC of fPSA was always significantly higher than that of PSA (0.716 vs. 0.566 for 20 cm³, 0.677 vs. 0.543 for 30 cm³, 0.654 vs. 0.534 for 40 cm³, and 0.656 vs. 0.560 for 50 cm³).

In the correlation analysis, IPSS, which was used to represent LUTS, was not correlated with any of the PSA-related parameters or prostate volume ($p > 0.05$).

DISCUSSION

Excessive prostate enlargement is the one of the most common causes of LUTS in men and is closely associated with comorbidity, such as acute urinary retention, which has a negative impact on quality of life and on the performance of activities of daily living. Thus, assessment of prostate volume provides important information in determining the appropriate treatment of patients with LUTS, especially that associated with prostate enlargement. The European Association of Urology guidelines recommend 5-alpha reductase inhibitors for patients whose prostate volume is > 40 cm³ and open surgery and holmium laser enucleation for those with prostate volumes > 80 cm³ [14].

Although TRUS has been considered the standard method for measuring prostate volume, as described, some limitations exist in performing TRUS routinely in the clinical field. It is labor-intensive as a screening test for physicians and is uncomfortable for patients, especially those who have hemorrhoids or anal fissures. Furthermore, TRUS is an expensive test to perform in the primary clinic setting compared with other examinations. Therefore, development of other modalities that can be used for the prediction

TABLE 1. Characteristic mean

Characteristic	Mean (range)
Age (y)	64.8 (28.0-91.0)
Body weight (kg)	66.45 (40.30-102.30)
Height (cm)	166.32 (148.00-186.70)
Body mass index (kg/m ²)	23.99 (15.50-35.40)
Body surface area (m ²)	1.74 (1.34-2.19)
Plasma volume (L)	2.90 (2.24-3.67)
PSA (ng/mL)	5.680 (0.193-19.412)
fPSA (ng/mL)	1.080 (0.046-8.464)
PSA mass (µg)	16.50 (0.59-55.12)
fPSA mass (µg)	3.14 (0.14-22.21)
Prostate volume (total) (mL)	45.13 (12.30-152.00)
Prostate volume (transition zone) (mL)	23.47 (0.85-92.90)

PSA, prostate-specific antigen; fPSA, free prostate-specific antigen.

TABLE 2. Correlation analysis between PV, IPSS, and PSA derivatives by Pearson correlation coefficient (R)

	PV	IPSS	PSA	PSA mass	fPSA	fPSA mass
PV						
Correlation coefficient	-	0.005	0.111	0.111	0.330	0.330
p-value	-	0.919	0.004	0.004	0.000	0.000
IPSS						
Correlation coefficient	0.005	1.000	-0.075	-0.072	-0.152	-0.150
p-value	0.919	-	0.135	0.151	0.068	0.070
PSA						
Correlation coefficient	0.111	-0.075	1.000	0.993	0.717	0.718
p-value	0.004	0.135	-	0.000	0.000	0.000
PSA mass						
Correlation coefficient	0.111	-0.075	1.000	0.993	0.717	0.718
p-value	0.004	0.135	-	0.000	0.000	0.000
fPSA						
Correlation coefficient	0.330	-0.152	0.717	0.704	1.000	0.994
p-value	0.000	0.068	0.000	0.000	-	0.000
fPSA mass						
Correlation coefficient	0.330	-0.150	0.718	0.718	0.994	1.000
p-value	0.000	0.070	0.000	0.000	0.000	-

IPSS, International Prostate Symptom Score; PV, prostate volume; PSA, prostate-specific antigen; fPSA, free prostate-specific antigen.

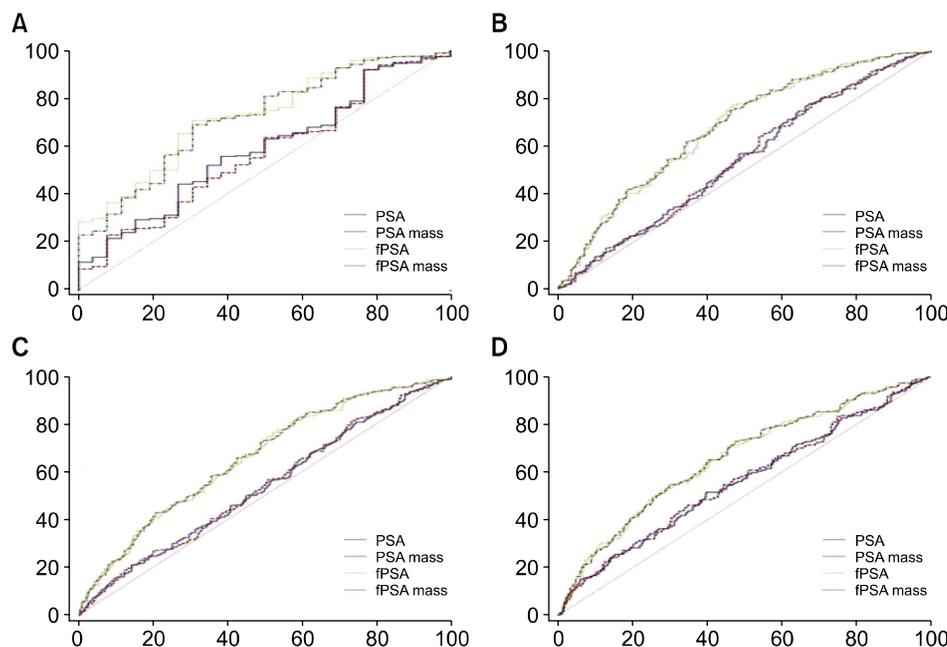


FIG. 1. Receiver operating characteristic curves for prostate-specific antigen (PSA), PSA mass, free PSA (fPSA), and fPSA mass to predict a prostate volume of 20 cm³ (A), 30 cm³ (B), 40 cm³ (C), and 50 cm³ (D).

of prostate volume may be useful in the clinical field and in the field of large cohort medical study.

Many studies have reported that a reliable relationship between serum PSA, serum fPSA, and prostate volume exists, although the relationship appears to vary by ethnicity [3,15-17]. This relationship has also been studied in Korean men [6]. Serum PSA may be useful as a convenient proxy parameter of prostate volume.

It has been reported that an inverse association exists between BMI and PSA [7-8]. Men with higher BMI are prone to have larger plasma volumes, which is considered to decrease serum tumor markers like PSA, possibly through hemodilution. Theoretically, hemodilution may hamper the detection of prostate cancer or may have a negative impact on predicting prostate volume by serum PSA. On the basis of these notions, several studies have investigated the clinical importance of PSA mass for the detection of prostate cancer or for estimating the prostate volume. For instance, Bryniarski et al. [18] reported that PSA mass may be a better predictor of biochemical recurrence after prostatectomy than PSA. However, a study from Japan showed that PSA mass did not have stronger predictive accuracy for prostate cancer risk at biopsy than did PSA [9]. A study in Korean men also showed that the PSA mass ratio, PSA mass per prostate volume, was not more accurate than PSA for prediction of prostate cancer in Korean men [10], which suggests that PSA mass contributes little to prostate cancer detection in Asian men.

In contrast with the small effect of PSA mass on prostate cancer detection, Masuda et al. [9] reported that PSA mass had stronger predictive power than did PSA for predicting prostate volume in Japanese men with biopsy-proven BPH.

Considering the racial similarity between the Korean and the Japanese, we expected that PSA mass would be bet-

ter at predicting prostate volume in Korean men. However, in general, PSA mass was not better than PSA at predicting prostate volume in our study. It had limited better predictive ability in the obese patients only. This may support the aforementioned theory of hemodilution as a cause of the inverse relationship between serum PSA and BMI.

Our results showed that fPSA had better predictive ability than serum PSA at predicting prostate volume, and other studies have reported that fPSA is a good predictor of prostate volume. In Europe, Morote et al. [19] reported that fPSA was an effective predictor, as was PSA. In a study of 656 Turkish men, it was shown that fPSA performed better than total PSA. Those authors reported that the AUC of PSA for predicting prostate volume of > 40 cm³ was 0.668, whereas that of fPSA was 0.721. They suggested that a cutoff of fPSA might provide clinically important information because the European Association of Urology guideline recommends not prescribing 5-alpha reductase inhibitors to patients with a prostate volume less than 40 cm³. They proposed a cutoff of free PSA of 0.495 for predicting a prostate volume of 40 cm³ [4].

Another study in a Chinese population also showed that fPSA was more strongly associated with prostate volume than was PSA. Chinese men reported correlation coefficients of 0.278 for PSA and 0.456 for fPSA. In that study, the AUC of PSA for predicting a prostate volume of 30 cm³ was 0.61, whereas that of fPSA was 0.72 [20].

The current results also showed data compatible with previous studies, although our results showed slightly lesser values for the AUC of fPSA (0.654 for 40 cm³) compared with other studies, which ranged from 0.71 to ~0.72. In our study, the cutoffs of PSA and fPSA were 2.61 and 0.38, respectively. At these cutoffs, PSA and fPSA could predict a prostate volume of 40 cm³ with sensitivity and specificity of 85%. These findings suggest the clinical potential of fPSA

TABLE 3. Area under the curve (AUC) estimates for ROC curves predicting a prostate volume of 20 cm³, 30 cm³, 40 cm³ and 50 cm³

AUC	PV, 20 cm ³			PV, 30 cm ³			PV, 40 cm ³			PV, 50 cm ³		
	Total	BMI, <23.0	BMI, ≥27.5									
	PSA	0.566	0.660	0.516	0.615	0.527	0.556	0.421	0.511	0.552	0.428	0.567
PSA mass	0.568	0.660	0.517	0.617	0.529	0.557	0.454	0.517	0.563	0.449	0.562	0.566
fPSA	0.716	0.808	0.654	0.781	0.647	0.685	0.720	0.591	0.684	0.664	0.656	0.690
fPSA mass	0.720	0.806	0.653	0.782	0.651	0.687	0.734	0.598	0.696	0.681	0.658	0.680
p-value												
PSA-PSA mass	0.155	1.000	0.457	0.384	0.736	0.324	0.102	0.329	0.352	0.042	0.548	0.421
fPSA-fPSA mass	0.103	0.765	0.175	0.479	0.495	0.247	0.322	0.239	0.475	0.037	0.472	0.654
PSA-fPSA	0.031	0.099	0.019	0.018	0.001	0.001	0.021	0.014	<0.001	0.012	<0.001	<0.001

ROC, receiver operating characteristic; PV, prostate volume; BMI, body mass index; PSA, prostate-specific antigen; fPSA, free prostate-specific antigen.

and fPSA mass as predictors of prostate volume in the Korean population.

In the correlation analysis of our study, IPSS had no statistically significant relationship with PSA or PSA mass. Another study that investigated the correlation between the IPSS and PSA also found no correlation except for IPSS quality of life and IPSS question 7 (nocturia) [15]. This may be because LUTS has many causes other than bladder outlet obstruction, such as BPH.

The present study is not without flaws. First, the number of participants in our study was relatively small, especially the number of participants (n=66) in the group of obese patients with BMI above 27.5 kg/m². Furthermore, our study retrospectively included and reviewed patients who underwent TRUS-guided prostate biopsy owing to suspicion of prostate cancer for reasons such as abnormal digital rectal exam result, high PSA, or hypochoic lesion on ultrasonography. Thus, the existence of occult prostate cancer is possible, although we only included patients with negative prostate biopsy results and with PSA less than 20 ng/mL. For the aforementioned reason, the serum PSA of our study population may be higher than in an aged-matched population. To our knowledge, our study is one of the first to show the relationship between fPSA and prostate volume in Korean men. Acknowledging the limitations of our study, it is not easy to generalize our results to the general Korean population; however, we suspect that, at the very least, our study will stimulate interest in this field. Additional investigation with larger cohorts should be performed.

CONCLUSIONS

PSA mass and fPSA mass are not better predictors of prostate volume than are PSA and fPSA, although they apparently showed better predictive ability in obese patients with large prostates. The present study showed that fPSA and fPSA mass have better predictive power for prostate volume than do PSA or PSA mass in Korean men. These findings suggest the possible clinical use of fPSA and fPSA mass as surrogate markers of prostate volume in Korean men. Further investigation with larger cohorts is needed for verification of the results.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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