



Open Access

ORIGINAL ARTICLE

Prostate Disease

Does prostate-specific antigen (PSA) mass or free PSA mass improve the accuracy of predicting total prostate volume in relation to obesity in men with biopsy-proven benign prostatic hyperplasia?

Jin-Woo Jung¹, Young Dong Yu², Young Ju Lee², Jung Jun Kim², Hak Min Lee², Jong Jin Oh², Sangchul Lee², Sang Wook Lee³, Sang Eun Lee², Seong Jin Jeong²

We evaluated whether the prostate-specific antigen (PSA) mass or free PSA (fPSA) mass (*i.e.*, absolute amount of total circulating PSA or fPSA protein, respectively), versus serum PSA or fPSA concentration, improves the accuracy of predicting the total prostate volume (TPV) in relation to obesity. Among men whose multicore (≥ 12) transrectal prostate biopsy was negative, 586 who had a PSA of ≤ 10 ng ml⁻¹ and underwent the fPSA test prior to biopsy were enrolled. The PSA mass or fPSA mass (μg) was calculated by multiplying the serum level by plasma volume. At each TPV cut-off point (30 ml, 40 ml, and 50 ml), the areas under the receiver operating characteristics curve (AUCs) of each variable were compared in obesity-based subgroups. AUCs of fPSA and fPSA mass for predicting TPV were significantly larger than those for PSA and PSA mass by 8.7%–12.1% at all cut-off points. Subgroup analyses based on obesity showed that, although PSA mass and fPSA mass enhanced accuracy by 4% ($P = 0.031$) and 1.8% ($P = 0.003$), respectively, for determining TPVs of ≥ 30 ml and ≥ 50 ml in obese and overweight men, they did not improve the accuracy in most other combinations of the degrees of obesity with TPV cut-off points. Thus, compared with serum PSA or fPSA, the absolute amount of PSA or fPSA protein mass improved the accuracy of predicting TPV in obese men very minimally and only for certain TPV cut-off points. Hence, these indicators may not provide clinically meaningful improvement in predicting TPV in obese men.

Asian Journal of Andrology (2019) 21, 86–91; doi: 10.4103/aja.aja_66_18; published online: 4 September 2018

Keywords: benign prostatic hyperplasia; obesity; prostate volume; prostate-specific antigen mass

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a common disease that occurs in almost 50% of men >50 years of age.¹ Given that total prostate volume (TPV) predicts the morbidities arising from BPH, practical use of individual patient's TPV has a significant role in the management of patients with BPH. In several multinational trials, men with a large TPV are at increased risk of acute urinary retention or surgery for BPH.² In addition, in the placebo group of the Medical Therapy of Prostatic Symptoms (MTOPS) trial, TPV was identified to be a significant factor for the progression of the disease and symptoms.³ TPV is also a predictive factor for the efficacy of medical treatment in men with BPH who are taking 5 α -reductase inhibitors.⁴ The current European Association of Urology guidelines recommend the use of 5 α -reductase inhibitors for men with an TPV ≥ 40 ml.⁵ Therefore, estimating TPV is necessary to predict the clinical course of the patient's BPH and select the appropriate treatment for that individual.

The planimetric measurement of TPV through transrectal ultrasonography (TRUS) is considered as the gold standard

among the various methods utilized.⁶ However, TRUS is not economically viable in many areas and is not routinely recommended for the initial evaluation of men with lower urinary tract symptoms (LUTS) suggestive of BPH.⁷ Moreover, patients may experience pain during the TRUS examination. Thus, the assessment of TPV using a simpler method would be more useful in the clinical setting.

It has been suggested that the serum prostate-specific antigen (PSA) concentration may be useful for detecting an enlarged prostate in men for whom a diagnosis of prostate cancer has been excluded.⁸ Approximately 10%–30% of circulating PSAs are not bound to proteins and are referred to as free PSAs (fPSAs).⁹ A few studies have suggested that TPV can be estimated using serum fPSA levels.^{10,11} Several studies, however, have reported that obesity is negatively associated with serum PSA concentration, a phenomenon attributed to hemodilution.^{12–14} Therefore, the accuracy of serum PSA or fPSA concentration for predicting the TPV may be complicated in obese men.

¹Department of Urology, Catholic Kwandong University International St. Mary's Hospital, Incheon 22711, Korea; ²Department of Urology, Seoul National University Bundang Hospital, Seongnam 13620, Korea; ³Department of Urology, Kangwon National University School of Medicine, Chuncheon 24341, Korea.

Correspondence: Dr. SJ Jeong (urojsj@empal.com)

Received: 09 February 2018; Accepted: 10 July 2018

To overcome the potential limitations caused by hemodilution when determining the TPV using the serum PSA or fPSA concentration, the PSA mass or fPSA mass (the absolute total amount of circulating PSA or fPSA protein, respectively) may be a potential alternative to existing PSA parameters. In this study, we aimed to evaluate the practical role of using PSA mass or fPSA mass versus serum PSA or fPSA concentration to assess the TPV in relation to obesity. To the best of our knowledge, our study is the first report of an investigation into whether these two indicators can improve the accuracy of predicting the TPV in obese men.

PATIENTS AND METHODS

Study population

The medical records of 4886 men who underwent TRUS-guided prostate biopsy at Seoul National University Bundang Hospital (Seongnam, Korea) between May 2003 and May 2012 were reviewed. The patients initially visited our department for evaluation of LUTS or were referred from other hospitals because of a high PSA level. During the evaluation that followed, each underwent multicore (≥ 12) biopsy because of either an elevated serum PSA level (≥ 3 ng ml⁻¹) or an abnormal digital rectal examination (DRE).

Among the 4886 patients, 686 were further selected based on the following inclusion criteria: the patient had undergone the fPSA test prior to biopsy, had a prebiopsy PSA level of ≤ 10 ng ml⁻¹, and had a negative biopsy (*i.e.*, no prostate cancer). The exclusion criteria included were as follows: the patients had just undergone surgical treatment for prostate disease prior to biopsy ($n = 27$); were just taking 5 α -reductase inhibitor or other herbal preparation known to influence serum PSA levels ($n = 32$); met both of the above conditions ($n = 11$); or relevant data were missing ($n = 30$). Thus, data from 586 men were included in the final analyses. If the patient had undergone more than one biopsy, data from the initial biopsy were analyzed. This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (approval number B-1311/226-110) and the requirement for informed consent was waived in this retrospective study.

Clinical data and variable definitions

The serum PSA or fPSA concentration was quantified using ¹²⁵I-PSA immunoradiometric assay (Institute of Isotopes Co., Ltd., Budapest, Hungary). To determine the PSA mass and fPSA mass values in the patients, the body surface area (BSA) and plasma volume were calculated using the following formula: BSA (m²) = body weight (kg)^{0.425} × height (cm)^{0.725} × 0.007184;¹⁵ plasma volume (l) = BSA (m²) × 1.670.¹⁶ The PSA mass (μ g) was calculated by multiplying the serum level of PSA (ng ml⁻¹) with the plasma volume (l).¹² fPSA mass (μ g) was similarly determined using fPSA (ng ml⁻¹) × plasma volume (l).

The TPV was measured at the time of undergoing biopsy via TRUS. The prostate transverse (width), craniocaudal (length), and anteroposterior (height) dimensions were measured, and the TPV was calculated by using the ellipsoid formula (multiplication of the three dimensions × 0.542). In all patients, the PSA parameters and body size (weight and height) were measured only before undergoing biopsy.

All patients were categorized based on the body mass index (BMI), which was determined just before undergoing biopsy. As recommended by the World Health Organization expert consultation,¹⁷ the BMI cut-off points for public health action for the Asian populations that were adopted in the current study

were ≤ 23.0 kg m⁻² (underweight/normal weight), 23.1–27.4 kg m⁻² (overweight), and ≥ 27.5 kg m⁻² (obese).

Statistical analyses

Data are expressed as the mean ± standard deviation (s.d.) or standard error of the mean (s.e.m.). Pearson's correlation test was used to assess the possible associations between PSA concentration, PSA mass, fPSA concentration, and fPSA mass with the TPV. To compare the accuracy in determining the TPV with each of the four parameters, TPV measured via TRUS was divided into two parts with three cut-off points: 30 ml, 40 ml, and 50 ml. Multivariable linear and logistic regression analyses were performed to assess the significance of the association between each PSA-related variable and TPV. For each cut-off value, the area under the receiver operating characteristics curve (AUC) for PSA-related parameters, driven by the predicted probabilities in the logistic regression analyses, were compared using the method described by DeLong *et al.*¹⁸ among all the patients and then within subgroups based on the degree of obesity defined by the BMI for Asian populations. MedCalc[®] software version 12.3.0 (MedCalc Software byba, Ostend, Belgium) and SPSS software package version 20.0 (IBM Corp, Armonk, NY, USA) were used for the correlation analyses, regression analysis, receiver operating characteristics curve, and AUC comparisons. Statistical significance was defined as two-tailed $P < 0.05$.

RESULTS

Table 1 shows the patient characteristics of the study cohort. For 586 men evaluated in the present study, the mean age was 61.96 (s.d.: 0.39) years, mean BMI 24.32 (s.d.: 2.58) kg m⁻², mean TPV 47.73 (s.d.: 0.83) ml, mean PSA 5.41 (s.d.: 0.08) ng ml⁻¹, and mean fPSA 1.12 (s.d.: 0.06) ng ml⁻¹. On the whole, the mean PSA mass and fPSA mass were 15.93 (s.d.: 0.25) μ g and 3.29 (s.d.: 0.09) μ g, respectively.

Correlation coefficients for serum PSA and serum fPSA with the BMI were -0.066 and -0.075 ($P = 0.108$ and 0.068 , respectively), and those for PSA mass and fPSA mass were 0.051 and -0.011 ($P = 0.222$ and 0.783 , respectively). Serum fPSA and fPSA mass were more strongly correlated with the TPV than were the serum PSA and PSA mass (**Table 2**). On the other hand, correlations of PSA mass and fPSA mass with the TPV were not significantly different from those of the serum PSA and serum fPSA with the TPV.

In a linear regression analysis, all the variables were significantly associated with the TPV. The equation for determining the TPV is the following: TPV (ml) = $-30.517 + 0.569 \times (\text{age} [\text{year}]) + 1.091 \times (\text{BMI} [\text{kg m}^{-2}]) + 0.018 \times (\text{PSA} [\text{ng ml}^{-1}]) + 0.457 \times (\text{PSA mass} [\mu\text{g}]) - 3.776 \times (\text{fPSA} [\text{ng ml}^{-1}]) + 4.007 \times (\text{fPSA mass} [\mu\text{g}])$ with $R^2 = 0.746$. The logistic regression analyses with the specific cut-off values

Table 1: Characteristics of all patients (n = 586)

Variable	Value, mean \pm s.d.
Age (year)	61.96 \pm 0.39
BMI (kg m ⁻²)	24.32 \pm 2.58
BSA (m ²)	1.77 \pm 0.01
Plasma volume (l)	2.95 \pm 0.01
TPV (ml)	47.73 \pm 0.83
Serum PSA (ng ml ⁻¹)	5.41 \pm 0.08
PSA mass (μ g)	15.93 \pm 0.25
Serum fPSA (ng ml ⁻¹)	1.12 \pm 0.06
fPSA mass (μ g)	3.29 \pm 0.09

s.d.: standard deviation; PSA: prostate-specific antigen; fPSA: free prostate-specific antigen; BMI: body mass index; BSA: body surface area; TPV: total prostate volume



(30 ml, 40 ml, and 50 ml) of the TPV showed that four PSA-related parameters were associated with the TPV.

The accuracy of serum PSA, PSA mass, serum fPSA, and fPSA mass for assessing the TPV was assessed using AUCs among all the patients (Table 3 and Figure 1). For each of four PSA-related parameters, the accuracy for determining TPV increased with increasing TPV cut-off point. Overall, the AUCs of fPSA and fPSA mass were significantly larger than those of PSA and PSA mass by 8.7%–12.1% at all TPV cut-off points (Table 3). When a TPV of ≥ 40 ml was applied as the cut-off value for a large prostate, the AUCs of each PSA parameter were 0.644, 0.643, 0.745, and 0.749, respectively, and a fPSA of 0.98 ng ml^{-1} and a fPSA mass of $2.18 \text{ }\mu\text{g}$ were identified as the most proper cut-off values (serum fPSA: sensitivity 65.2%, specificity 71.3%; fPSA mass: sensitivity 83.5%, specificity 55.4%).

Pairwise comparisons of the AUCs at each TPV cut-off point showed no significant differences in the accuracy of determining TPV between serum PSA and PSA mass and the differences of the accuracy ranged from only 0.1% to 1.2% (Table 3). When compared with serum fPSA, fPSA mass also did not demonstrate a significantly higher accuracy in determining the TPV, except for the assessment at TPV ≥ 50 ml, where fPSA mass significantly improved the accuracy (by 0.9%) compared with serum fPSA ($P = 0.004$; Table 3). Table 4 shows that neither PSA mass nor fPSA mass enhanced the accuracy of determining the TPV even when combined with serum PSA or serum fPSA, except for the assessment at TPV ≥ 50 ml.

We also assessed the data within subgroups categorized by the degree of obesity (defined by BMI) for Asian populations. We found that, although PSA mass and fPSA mass significantly enhanced the

accuracy by 4.0% and 1.8%, respectively, in determining the TPV of ≥ 30 ml and ≥ 50 ml in obese and overweight men, they did not improve the accuracy in most of the other combinations of the degree of obesity with TPV cut-off points (Table 5).

DISCUSSION

BPH is considered a chronic, progressive disease. Assessment of the TPV is necessary to anticipate the clinical course of BPH and to individualize treatment appropriately for that patient. Based on several large trials including MTOPS study, TPV has a significant role in predicting the progression of the disease and symptoms.^{2,3} For the medical treatment of BPH, TPV also has an important influence on the efficacy of 5α -reductase inhibitors and current guidelines recommend the use of 5α -reductase inhibitors for men with a TPV of ≥ 40 ml.^{4,5} For these reasons, the accurate estimation of TPV is important in selecting the best choice of treatment and in the prediction of outcomes of the treatments among patients with BPH.

DRE is simply performed in daily practice, but it has been reported that it systematically underestimated the TPV when compared with TRUS.¹⁹ Furthermore, DRE underestimated the TPV in men with large prostates and overestimated it in those with small prostates;²⁰ even though, it has been reported to be a modestly accurate tool for measuring TPV.²¹ TRUS has now been accepted as the most accurate method for estimating TPV, except for measurements on surgical specimens from radical prostatectomy. However, TRUS is not available in many primary care facilities and it is costly in most countries. Moreover, men may experience pain during the procedure, particularly if they have anal lesions. Thus, assessment of TPV via a simpler method with acceptable sensitivity and specificity would be more useful in clinical practice.

Till date, many studies have reported a reasonable correlation between the serum PSA concentration and TPV, and have demonstrated the effectiveness of measuring serum PSA concentrations to determine

Table 2: Pearson correlation analyses of serum prostate-specific antigen, prostate-specific antigen mass, serum free prostate-specific antigen, and free prostate-specific antigen mass with the total prostate volume

Variable	Correlation coefficient <i>r</i> (95% CI)	<i>P</i>
Serum PSA	0.268 (0.192–0.342)	<0.001
PSA mass	0.270 (0.193–0.343)	<0.001
Serum fPSA	0.404 (0.334–0.469)	<0.001
fPSA mass	0.412 (0.342–0.477)	<0.001

CI: confidence interval; PSA: prostate-specific antigen; fPSA: free prostate-specific antigen

Table 3: Comparisons of accuracy of four parameters for determining total prostate volume for all patients at different cut-off points using areas under the receiver operating characteristics curve

	TPV cut-off point		
	30 ml	40 ml	50 ml
Serum PSA, mean \pm s.e.m.	0.619 \pm 0.033	0.644 \pm 0.023	0.659 \pm 0.023
PSA mass, mean \pm s.e.m.	0.607 \pm 0.034	0.643 \pm 0.023	0.662 \pm 0.023
Difference (serum PSA - PSA mass), mean \pm s.e.m.	0.012 \pm 0.007	0.001 \pm 0.005	-0.003 \pm 0.005
<i>P</i> (serum PSA vs PSA mass)	0.086	0.726	0.496
Serum fPSA, mean \pm s.e.m.	0.730 \pm 0.030	0.745 \pm 0.020	0.746 \pm 0.020
fPSA mass, mean \pm s.e.m.	0.729 \pm 0.030	0.749 \pm 0.020	0.755 \pm 0.020
Difference (serum fPSA - fPSA mass), mean \pm s.e.m.	0.001 \pm 0.003	-0.004 \pm 0.003	-0.009 \pm 0.003
<i>P</i> (serum fPSA vs fPSA mass)	0.735	0.177	0.004

s.e.m.: standard error of mean; PSA: prostate-specific antigen; fPSA: free prostate-specific antigen; TPV: total prostate volume

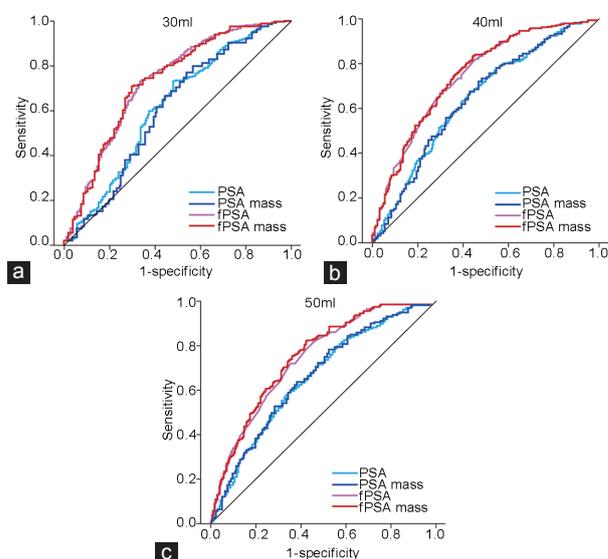


Figure 1: Receiver operating characteristic curves for serum PSA, PSA mass, serum fPSA, and fPSA mass in determining the TPV at (a) 30 ml, (b) 40 ml, and (c) 50 ml of cut-off points. For each of four PSA-related parameters, the accuracy for determining TPV increased with increasing TPV cut-off point. Overall, the AUCs of fPSA and fPSA mass were significantly larger than those of PSA and PSA mass by 8.7%–12.1% at all TPV cut-off points. PSA: prostate-specific antigen; fPSA: free prostate-specific antigen; TPV: total prostate volume; AUCs: areas under the receiver operating characteristics curve.

the TPV.^{8,22-27} One study showed that serum PSA is more accurate than DRE for estimating TPV.⁸ Therefore, the use of serum PSA testing as a marker for TPV is suggested in daily practice for almost all men except those with a high probability of having prostate cancer (presence of a palpable nodule identified by DRE or serum PSA ≥ 4 ng ml⁻¹).

Serum fPSA has been also evaluated as a predictor of TPV in men with LUTS and it has been suggested that the efficacy of serum fPSA testing is equal or superior to that of serum PSA testing for estimating the TPV.^{10,11} Morote *et al.*¹⁰ reported that the serum fPSA concentration could predict the individual TRUS TPV $\pm 10\%$ in 67% of patients and $\pm 20\%$ in 91.2% and that serum PSA concentration could predict TRUS TPV in 63% and 90.9% of patients, respectively. In contrast, Kayikci *et al.*¹¹ concluded that the fPSA concentration had better value than the PSA concentration for predicting the TPV in men with BPH. In their study, the mean AUC for serum PSA at predicting TPV >40 ml was 0.668 (s.d.: 0.022), and it increased to 0.721 (s.d.: 0.021) when using the serum fPSA concentration. The study also showed that the accuracy of the serum fPSA concentration was significantly higher than that of serum PSA concentration (by 8.7%–11.1%) for determining the TPV at all TPV cut-off points.

It is not fully understood why the serum fPSA concentration has a better predictive value than the serum PSA concentration for detecting TPV. One plausible explanation is that the serum fPSA concentration may be more dependent on the amount of prostatic transitional zone or benign tissue volume than is the total serum PSA concentration.^{28,29} fPSA is composed of multiple distinct molecular forms of PSA that can originate from cancerous tissue and benign peripheral and transitional zone tissues. In addition, it has been reported that some PSA isoforms are expressed differentially between the peripheral zone tissue (zone of the most prostate cancers) and transitional zone tissue (zone of BPH).³⁰ Based on the reports, the serum fPSA level may be more dependent on the amount of transitional zone or benign tissue in the prostate,^{28,29}

it may be hypothesized that serum fPSA, compared with serum PSA, is influenced more by changes in the TPV in the presence of BPH, where the increased TPV is mainly attributed to the enlargement of transitional zone nodules. Thus, serum fPSA levels may more accurately represent the TPV than total serum PSA.

Serum PSA and fPSA concentrations are known to be negatively associated with obesity, mainly due to hemodilution.¹²⁻¹⁴ Therefore, the accuracy of the serum PSA or fPSA concentration for determining TPV may be especially complicated in obese men. In the present study, we investigated the accuracy of PSA mass and fPSA mass (the absolute amount of PSA and fPSA protein in the circulation) for determining the TPV to counteract the possible effect of hemodilution on the serum concentrations of PSA and fPSA in obese men. A previous study by Masuda *et al.*³¹ showed that PSA mass was more effective in estimating the TPV than serum PSA, particularly in men ≥ 60 years of age. In their study, however, the use of PSA mass improved accuracy by only 0.8%–2.0% over the serum PSA concentration in determining the TPV ≥ 30 ml or ≥ 40 ml. Moreover, the accuracy of PSA mass depending on the degree of obesity was not compared with that of the serum PSA concentration. In the present study, PSA mass showed no differences in accuracy for determining the TPV compared with serum PSA concentration at all of the TPV cut-off points among all participants. fPSA mass also did not show significantly higher accuracy for determining the TPV than the serum fPSA concentration, except for assessments at TPV ≥ 50 ml, where fPSA mass significantly improved the accuracy over that achieved with serum fPSA despite an increase of only 0.9%. More importantly, although PSA mass and fPSA mass enhanced the accuracy by 4.0% and 1.8%, respectively, in determining TPV of ≥ 30 ml and ≥ 50 ml in obese and overweight men, they did not improve the accuracy in most of the other combinations of the degree of obesity with the TPV cut-off points. We believe that only small

Table 4: Comparisons of the accuracy of determining total prostate volume for four parameters and their combinations using areas under the receiver operating characteristics curve among all the patients

	TPV cut-off point		
	30 ml	40 ml	50 ml
Serum PSA, mean \pm s.e.m.	0.619 \pm 0.033	0.644 \pm 0.023	0.659 \pm 0.023
Serum PSA + PSA mass, mean \pm s.e.m.	0.627 \pm 0.039	0.644 \pm 0.034	0.662 \pm 0.028
<i>P</i> (serum PSA vs serum PSA + PSA mass)	0.281	0.805	0.638
Serum fPSA, mean \pm s.e.m.	0.730 \pm 0.030	0.745 \pm 0.020	0.746 \pm 0.020
Serum fPSA + fPSA mass, mean \pm s.e.m.	0.730 \pm 0.038	0.749 \pm 0.031	0.756 \pm 0.027
<i>P</i> (serum fPSA vs serum fPSA + fPSA mass)	0.707	0.216	0.028

s.e.m.: standard error of mean; PSA: prostate-specific antigen; fPSA: free prostate-specific antigen; TPV: total prostate volume

Table 5: Differences in areas under the receiver operating characteristics curve for pairwise comparisons of accuracy in determining total prostate volume at different cut-off points in relation to obesity defined by the body mass index

	Underweight/normal weight (BMI ≤ 23.0 kg m ⁻² , n=182)			Overweight (BMI: 23.1–27.4 kg m ⁻² , n=343)			Obese (BMI ≥ 27.5 kg m ⁻² , n=61)		
	30 ml	40 ml	50 ml	30 ml	40 ml	50 ml	30 ml	40 ml	50 ml
Serum PSA - PSA mass									
Difference of AUCs, mean \pm s.e.m.	0.010 \pm 0.011	0.004 \pm 0.008	0.002 \pm 0.009	0.022 \pm 0.019	-0.005 \pm 0.016	-0.009 \pm 0.003	-0.040 \pm 0.018	0.027 \pm 0.016	0.018 \pm 0.015
<i>P</i>	0.338	0.606	0.817	0.104	0.501	0.375	0.031	0.093	0.216
Serum fPSA - fPSA mass									
Difference of AUCs, mean \pm s.e.m.	0.003 \pm 0.006	0.006 \pm 0.005	0.005 \pm 0.006	0.001 \pm 0.003	-0.011 \pm 0.004	-0.018 \pm 0.003	0.003 \pm 0.007	0.004 \pm 0.009	0.002 \pm 0.011
<i>P</i>	0.608	0.225	0.364	0.735	0.096	0.003	0.703	0.671	0.846

s.e.m.: standard error of the mean; BMI: body mass index; TPV: total prostate volume; PSA: prostate-specific antigen; fPSA: free prostate-specific antigen; AUCs: areas under the receiver operating characteristics curve. 30 ml, 40 ml, and 50 ml are different TPV cut-off points



improvements in the accuracy (1.8%–4.0%) at certain TPV cut-off points would not provide any meaningful benefits over using serum PSA and fPSA concentration in clinical practice.

The stability of the serum fPSA concentration has been reported to be affected by the method used for sample collection and the storage conditions.³² In our institution, fPSA measurement is routinely performed within 24 h of blood sample collection, ensuring the stability of the serum fPSA concentration and, in turn, not influencing our findings.

The present study may be limited by its retrospective nature. We excluded men with a serum PSA >10 ng ml⁻¹ and enrolled those who underwent a prostate biopsy due to an abnormal PSA or DRE. These could lead to selection bias and further limit the applicability of the study findings to all BPH patients. Inflammation and atrophy are often seen in prostate biopsy specimens and may be a factor contributing to increased PSA. As pathological reports of the biopsies did not include such findings in about one-third of our cohort, we could not evaluate the influence of prostatic inflammation or atrophy on our findings. However, these conditions might be confounding factors. In the analyses within subgroups categorized by the degree of obesity, the number of patients in the obese group was rather small. Thus, further investigation with a larger group of obese patients may be needed to consolidate our findings. Finally, we acknowledge that most of our patients were Asian, so more research is needed to determine whether our findings are applicable to people in different ethnic groups as they may have different baseline levels of PSA, fPSA, or BMI. For instance, the prevalence of obesity in Asian men has been known to be different from those of other races. Compared with their Western counterparts, fewer Asian men are categorized as obese based on the widely accepted BMI-based definition (≥ 30 kg m⁻²).³³

It has been suggested that PSA mass or fPSA mass is an attractive alternative to serum PSA or fPSA concentration for improving the accuracy of predicting the TPV in obese men. Our study, however, demonstrated that PSA mass and fPSA mass showed very limited improvement of the accuracy for predicting the TPV only at certain TPV cut-off points in obese men. Therefore, these indicators may not provide clinical meaningful improvements compared with the serum PSA or fPSA concentration.

CONCLUSIONS

Although PSA mass and fPSA mass might appear to be a potential alternative to the serum PSA and fPSA concentration when predicting the TPV because it avoids the possible hemodilution effect on serum levels, these parameters may not display clinically meaningful improvement in determining the TPV of obese men in the clinical setting.

AUTHOR CONTRIBUTIONS

JWJ and SJJ carried out substantial contributions to conception of the study, data acquisition, statistical analysis, and drafting the manuscript. YDY, YJL, JJK, and HML helped to gather the data and draft the manuscript. JJO, SL, SWL, and SEL helped to interpret the findings and revise the manuscript. SJJ supervised the process and approved the final manuscript. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

ACKNOWLEDGMENTS

The authors would like to acknowledge Dr. Byung Ki Lee (Easyfill Urologic Clinic, Seoul, Korea) for his contributions to this study as advisor for medical writing. This study was supported by a grant from Seoul National University Bundang Hospital Research Fund (No. 06-2014-217).

REFERENCES

- Hald T. Urodynamics in benign prostatic hyperplasia: a survey. *Prostate Suppl* 1989; 2: 69–77.
- Marberger MJ, Andersen JT, Nickel JC, Malice MP, Gabriel M, *et al*. Prostate volume and serum prostate-specific antigen as predictors of acute urinary retention. Combined experience from three large multinational placebo-controlled trials. *Eur Urol* 2000; 38: 563–8.
- Kaplan SA, Lee JY, Meehan AG, Kusek JW; MTOPS Research Group. Long-term treatment with finasteride improves clinical progression of benign prostatic hyperplasia in men with an enlarged versus a smaller prostate: data from the MTOPS trial. *J Urol* 2011; 185: 1369–73.
- Boyle P, Gould AL, Roehrborn CG. Prostate volume predicts outcome of treatment of benign prostatic hyperplasia with finasteride: meta-analysis of randomized clinical trials. *Urology* 1996; 48: 398–405.
- Oelke M, Bachmann A, Descalcaud A, Emberton M, Gravas S, *et al*. EAU guidelines on the treatment and follow-up of non-neurogenic male lower urinary tract symptoms including benign prostatic obstruction. *Eur Urol* 2013; 64: 118–40.
- Bangma CH, Niemer AQ, Grobbee DE, Schröder FH. Transrectal ultrasonic volumetry of the prostate: *in vivo* comparison of different methods. *Prostate* 1996; 28: 107–10.
- McVary KT, Roehrborn CG, Avins AL, Barry MJ, Bruskevicz RC, *et al*. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol* 2011; 185: 1793–803.
- Bohnen AM, Groeneveld FP, Bosch JL. Serum prostate-specific antigen as a predictor of prostate volume in the community: the Krimpen study. *Eur Urol* 2007; 51: 1645–52.
- Stephan C, Lein M, Jung K, Schnorr D, Loening SA. The influence of prostate volume on the ratio of free to total prostate specific antigen in serum of patients with prostate carcinoma and benign prostate hyperplasia. *Cancer* 1997; 79: 104–9.
- Morote J, Encabo G, López M, de Torres IM. Prediction of prostate volume based on total and free serum prostate-specific antigen: is it reliable? *Eur Urol* 2000; 38: 91–5.
- Kayikci A, Cam K, Kacagan C, Tekin A, Ankarali H. Free prostate-specific antigen is a better tool than total prostate-specific antigen at predicting prostate volume in patients with lower urinary tract symptoms. *Urology* 2012; 80: 1088–92.
- Bañez LL, Hamilton RJ, Partin AW, Vollmer RT, Sun L, *et al*. Obesity-related plasma hemodilution and PSA concentration among men with prostate cancer. *JAMA* 2007; 298: 2275–80.
- Grubb RL 3rd, Black A, Izmirlan G, Hickey TP, Pinsky PF, *et al*. Serum prostate-specific antigen hemodilution among obese men undergoing screening in the prostate, lung, colorectal, and ovarian cancer screening trial. *Cancer Epidemiol Biomarkers Prev* 2009; 18: 748–51.
- Chang IH, Ahn SH, Han JH, Kim TH, Kim YS, *et al*. The clinical significance in healthy men of the association between obesity related plasma hemodilution and tumor marker concentration. *J Urol* 2009; 181: 567–72.
- Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. *Nutrition* 1989; 5: 303–11.
- Boer P. Estimated lean body mass as an index for normalization of body fluid volumes in humans. *Am J Physiol* 1984; 247: F632–6.
- WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet* 2004; 363: 157–63.
- DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics* 1988; 44: 837–45.
- Roehrborn CG. Accurate determination of prostate size via digital rectal examination and transrectal ultrasound. *Urology* 1998; 51: 19–22.
- Bosch JL, Bohnen AM, Groeneveld FP, Bernsen R. Validity of three calliper-based transrectal ultrasound methods and digital rectal examination in the estimation of prostate volume and its changes with age: the Krimpen study. *Prostate* 2005; 62: 353–63.
- Stone BV, Shoag J, Halpern JA, Mittal S, Lewicki P, *et al*. Prostate size, nocturia and the digital rectal examination: a cohort study of 30 500 men. *BJU Int* 2017; 119: 298–304.
- Roehrborn CG, Boyle P, Gould AL, Waldstreicher J. Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. *Urology* 1999; 53: 581–9.
- Chung BH, Hong SJ, Cho JS, Seong DH. Relationship between serum prostate-specific antigen and prostate volume in Korean men with benign prostatic hyperplasia: a multicentre study. *BJU Int* 2006; 97: 742–6.
- Hochberg DA, Armenakas NA, Fracchia JA. Relationship of prostate-specific antigen and prostate volume in patients with biopsy proven benign prostatic hyperplasia. *Prostate* 2000; 45: 315–9.
- Roehrborn CG, McConnell JD, Lieber M, Kaplan S, Geller J, *et al*. Serum prostate-specific antigen concentration is a powerful predictor of acute urinary retention and need for surgery in men with clinical benign prostatic hyperplasia. PLESS Study Group. *Urology* 1999; 53: 473–80.
- Di Silverio F, Sciarra A, D'Eramo G, Casale P, Loreto A, *et al*. Relationship among age, prostate-specific antigen, and prostate volume in men with lower urinary tract

- symptoms (LUTS) and in different groups of men with and without benign and malignant prostate diseases. *Prostate* 1998; 36: 1–7.
- 27 Bosch JL, Hop WC, Bangma CH, Kirkels WJ, Schröder FH. Prostate specific antigen in a community-based sample of men without prostate cancer: correlations with prostate volume, age, body mass index, and symptoms of prostatism. *Prostate* 1995; 27: 241–9.
- 28 Collins GN, Alexandrou K, Wynn-Davies A, Mobley S, O'reilly PH. Free prostate-specific antigen 'in the field': a useful adjunct to standard clinical practice. *BJU Int* 1999; 83: 1000–2.
- 29 Mao Q, Zheng X, Jia X, Wang Y, Qin J, *et al*. Relationships between total/free prostate-specific antigen and prostate volume in Chinese men with biopsy-proven benign prostatic hyperplasia. *Int Urol Nephrol* 2009; 41: 761–6.
- 30 Mikolajczyk SD, Millar LS, Wang TJ, Rittenhouse HG, Marks LS, *et al*. A precursor form of prostate-specific antigen is more highly elevated in prostate cancer compared with benign transition zone prostate tissue. *Cancer Res* 2000; 60: 756–9.
- 31 Masuda H, Kawakami S, Sakura M, Fujii Y, Koga F, *et al*. Performance of prostate-specific antigen mass in estimation of prostate volume in Japanese men with benign prostate hyperplasia. *Int J Urol* 2012; 19: 929–35.
- 32 Woodrum D, French C, Shamel LB. Stability of free prostate-specific antigen in serum samples under a variety of sample collection and sample storage conditions. *Urology* 1996; 48: 33–9.
- 33 Ministry of Health and Welfare. Korea Centers for Disease Control and Prevention. In-depth analysis on the 2005 Korea National Health and Nutrition Examination Survey (KNHANES III): nutrition survey. Cheongwon: Ministry of Health and Welfare; 2006.

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

©The Author(s)(2018)