Asian Journal of Andrology (2013) 15, 249–253

www.nature.com/aja

ORIGINAL ARTICLE

Serum prostate-specific antigen as a predictor of prostate volume and lower urinary tract symptoms in a community-based cohort: a large-scale Korean screening study

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The aim of this study is to assess the ability of serum prostate-specific antigen (PSA) to predict prostate volume (PV) and lower urinary tract symptoms (LUTS) represented by the international prostate symptom score (IPSS). From January 2001 to December 2011, data were collected from men who first enrolled in the Korean Prostate Health Council Screening Program. Patients with a serum PSA level of >10 ng ml^{-1} or age <40 years were excluded. Accordingly, a total of 34 857 men were included in our study, and serum PSA, PV and the IPSS were estimated in all patients. Linear and age-adjusted multivariate logistic analyses were used to assess the potential association between PSA and PV or IPSS. The predictive value of PSA for estimating PV and IPSS was assessed based on the receiver operating characteristics-derived area under the curve (AUC). The mean PV was 29.9 ml, mean PSA level was 1.49 ng ml^{-1} and mean IPSS was 15.4. A significant relationship was shown between PSA and PV, and the IPSS and PSA were also significantly correlated after adjusting by age. The AUCs of PSA for predicting PV >20 ml, >25 ml and >35 ml were 0.722, 0.728 and 0.779, respectively. The AUCs of PSA for predicting IPSS >7, >13 and >19 were 0.548, 0.536 and 0.537, respectively. Serum PSA was a strong predictor of PV in a community-based cohort in a large-scale screening study. Although PSA was also significantly correlated with IPSS, predictive values of PSA for IPSS above the cutoff levels were not excellent. Further investigations are required to elucidate the exact interactions between PSA and LUTS and between PSA and PV in prospective controlled studies. Such studies may suggest how PSA can be used to clinically predict PV and the IPSS.
Asian Journal of Andrology (2013) **15,** 249–253; doi:10.1038/aja.2012.132; published online 28 January 2013

Keywords: lower urinary tract symptoms (LUTS); prostate; prostate-specific antigen (PSA); prostate volume (PV)

INTRODUCTION

Clinical benign prostatic hyperplasia (BPH), diagnosed by the presence of benign prostate enlargement and lower urinary tract symptoms (LUTS), has been considered to be a chronic and progressive disease.[1] Because baseline prostate volume (PV) has been linked to the progression of BPH (e.g., acute urinary retention and surgery for BPH), PV has been included as a useful tool in treatment guidelines.[2,3] Prostate-specific antigen (PSA) is a marker for prostate cancer and BPH.[4] The relationship between PSA and PV has been examined frequently in men with BPH, in part to determine how PSA can be used to predict PV. These studies have consistently shown a positive correlation between PSA and PV.[5–11] The Proscar Long-Term Efficacy and Safety Study demonstrated that the strongest predictor of future prostate growth was baseline serum PSA, which was more predictive than baseline PV and age.[10] In the Krimpen study, PSA was used to detect prostate enlargement, and they suggested that the clinical advantage of the formula over PSA alone was only modest, as shown by their analysis among men without prostate cancer.[11] However, most studies of the relationship between PSA and PV have originated from Western countries, and few studies have been conducted in Asia. One Asian study evaluating the relationship between PSA and PV showed Asian-specific criteria for detecting PV by PSA level stratified by age.[12] Although theirs was a multicenter study, the subjects included in this study were limited to patients visiting the hospital with troublesome symptoms.

The treatment indications for male LUTS are defined by symptom severity and associated bother.[13] The International Consultation on BPH agreed to use a symptom index developed by the American Urological Association Measurement Committee as the official worldwide assessment for patients suffering from prostatism. Currently, the International Prostate Symptom Score (IPSS) is widely utilized to characterize and stratify symptom severity and has become a useful tool for determining the appropriate treatment for BPH patients. However, few studies have evaluated the relationship between PSA

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Received: 24 September 2012; Revised: 9 October 2012; Accepted: 31 October 2012; Published online: 28 January 2013

and IPSS. Thus, we performed a study to determine the predictive impact of PSA for PV and the symptoms represented by IPSS in a large-scale Korean screening cohort, including approximately 34 857 people who visited the Korean Prostate Health Council Screening Program.

MATERIALS AND METHODS

After obtaining institutional review board approval, a total of 39 345 men who first enrolled in the Korean Prostate Health Council Screening Program from January 2001 to December 2011 were included in this study. This program was a free medical examination provided to the general community-based population of men. After advertising the program through each public health center, all of the men visiting the program underwent a urologic examination, including serum PSA, PV by using transrectal ultrasonography and some questionnaires including the IPSS.

Serum PSA was assayed using a chemiluminescence method and commercially available kits. Transrectal ultrasonography was conducted using a 7.5 MHz rectal probe. The PV was calculated by substituting the formula for an ellipsoid, i.e., $\pi/6\times$(height)$\times$(length)$\times$(width), with the height, length and width of the prostate measured by transrectal ultrasonography. All patients were routinely asked about their LUTS using the IPSS questionnaire. The IPSS is graded from 0 to 35, with general score classifications of 0–7, 8–19 and 20–35, indicating absent or mild, moderate and severe symptoms, respectively.[14,15,16]

Patients with a serum PSA level of >10 ng ml^{-1} were excluded from the study to reduce the likelihood of including those with occult prostate cancer. Patients who had undergone prior biopsies or surgical treatment of prostate disease were excluded from the study. We also excluded those whose age was <40 years. Accordingly, a total of 34 857 patients were included in our study.

In this study, PV and IPSS were assessed according to the PSA level, and the proportion of men reaching each stratification level was also analyzed. Because IPSS of 13 was the median value, we determined the target IPSSs were >7, >13 and >19. The target levels of PV were >20 ml, >25 ml and >35 ml based on interquartile ranges (IQRs). The proportions of subjects reaching each PV and IPSS target level were observed and evaluated for a relationship with PSA. The relationships between PSA and PV, PSA and IPSS were analyzed using log-linear regression analyses after adjusting for age. Multivariate regression analyses were used to predict PV and IPSS. The predictive value of PSA for each target level was analyzed using the receiver-operating characteristics (ROC)-derived area under the curve (AUC). The AUCs were compared *via* the Mantel–Haenszel test. PV and PSA were analyzed using a regression analysis after logarithmic transformation to ensure a normal distribution. The SPSS software package, version 15.0 (Statistical Package for Social Sciences, Chicago, IL, USA), was used for the statistical analyses. A two-tailed $P<0.05$ was considered significant for all analyses.

RESULTS

The patient characteristics are shown in **Table 1**. A total of 34 857 men were available at baseline with a mean age of 70.1$\pm$9.2 years (IQR: 65–76 years) and a mean PV of 29.9$\pm$14.2 ml (IQR: 21.0–34.1 ml). The mean PSA level was 1.49$\pm$1.50 ng ml^{-1} (IQR: 0.58–1.79 ng ml^{-1}), and the mean IPSS was 15.4$\pm$8.4 (IQR: 9–21).

As shown in **Table 2**, of all 34 857 men analyzed, 51.3% had a PSA level of 0–1.0 ng ml^{-1}, 26.0% a PSA of 1.0–2.0 ng ml^{-1} and 20.8% a PSA >2 ng ml^{-1}. According to PSA level, the proportions of subjects with PVs above 20, 25 and 35 ml were calculated. For men with a PSA level of 0–0.5 ng ml^{-1}, only 4.7% (332/7023) had a PV >35 ml, but for a PSA level above 4.0 ng ml^{-1}, 63.9% (1469/2298) of the men had a large prostate (>35 ml). For the IPSS, men with high PSA level also had a high IPSS, but the trends were not significant (**Table 3**). For example, for men with a PSA level of 0–0.5 ng ml^{-1}, 28.4% (2040/7178) had an IPSS >19, but for those with a PSA level above 4.0 ng ml^{-1}, 38.9% (910/2341) had an IPSS >19.

Table 1 Baseline characteristics

	No. of patients	*Median*	*IQR*	*Mean*	*s.d.*
Age (year)	34 857	71.0	65–76	70.1	9.2
PSA (ng ml^{-1})	34 857	0.98	0.58–1.79	1.49	1.50
PV (ml)	34 200	26.2	21.0–34.1	29.9	14.2
IPSS	34 815	14.0	9–21	15.4	8.4
Stroage symptoms	14 582	7	4–10	7.4	3.9
Voiding symptoms	14 582	8	5–12	8.6	4.6
QoL score	34 811	4	3–4	3.5	1.8

Abbreviations: IPSS, International Prostate Symptom Score; IQR, interquartile range; PSA, prostate-specific antigen; PV, prostate volume; QoL, quality of life.

A linear regression model was used to analyze the relationship between PSA and PV and identified a significant correlation (**Figure 1**, log (PV)$=3.312+0.233\times$log (PSA), $r^2=0.264$, $P<0.001$). The IPSS was also significantly related to PSA after controlling for age in a correlation analysis (IPSS$=15.379+0.718\times$log (PSA), $r^2=0.005$, $P<0.001$). **Table 4** shows the AUCs for the prediction of PV (>20, >25 and >35 ml) and for the prediction of the IPSS (>7, >13 and >19) using serum PSA. For a PV >35 ml, the ROC AUC was 0.779 (95% CI: 0.773–0.785, s.e.: 0.003). For PVs >25 ml and >20 ml, the ROC AUCs were 0.728 and 0.722, respectively. As shown in **Figure 2**, PSA was a better predictor of PV in the higher PV range (larger AUC). However, for an IPSS >19, the ROC AUC was 0.537 (95% CI: 0.531–0.544). For IPSSs of >13 and >7, the ROC AUCs were 0.536 and 0.548, respectively, suggesting that compared to PV, PSA is not a good predictor of IPSS. **Figure 2** shows each AUC under the curves.

Tables 5 and 6 shows the multivariate analyses for predicting PVs >20, 25 and 35 ml and IPSSs >7, >13 and >19 after adjusting for age and IPSS or PV, respectively. The multivariate analysis indicated that PSA was a significant predictor of PV and IPSS. PSA was a significant predictor of a PV>35 ml in the multivariate analysis, with an odds ratio of 3.547 (95% CI: 3.413–3.687, $P<0.001$).

Table 2 Percentage of men with a PV above a specific cutoff value according to various PSA ranges in community-based men in Korean Prostate Health Council Screening Program

PSA level	*No. of patients (%)*	n *(%)*		
		PV>20 ml	*PV>25 ml*	*PV>35 ml*
0–0.5	7023 (20.1)	4044 (57.6)	1867 (26.6)	332 (4.7)
0.5–0.7	5064 (14.5)	3615 (71.4)	2033 (40.1)	435 (8.6)
0.7–1.0	5825 (16.7)	4555 (78.2)	2830 (48.6)	804 (13.8)
1.0–1.5	5821 (16.7)	4945 (85.0)	3525 (60.6)	1296 (22.3)
1.5–2.0	3234 (9.3)	2887 (89.3)	2263 (70.0)	1047 (32.4)
2.0–4.0	4935 (14.2)	4600 (93.2)	3918 (79.4)	2302 (46.6)
4.0–10.0	2298 (6.6)	2193 (95.4)	1967 (85.6)	1469 (63.9)
Missing	657 (1.9)			
Total	34 857			

Abbreviations: PSA, prostate-specific antigen; PV, prostate volume.

Table 3 Percentage of men with a PV above a specific cutoff value according to various PSA ranges in community-based men in Korean Prostate Health Council Screening Program

PSA level	*No. of patients (%)*	n *(%)*		
		IPSS >7	*IPSS >13*	*IPSS >19*
0–0.5	7178 (20.6)	5665 (78.9)	3789 (52.8)	2040 (28.4)
0.5–0.7	5145 (14.8)	4047 (78.6)	2628 (51.1)	1410 (27.4)
0.7–1.0	5915 (17.0)	4637 (78.4)	3003 (50.8)	1602 (27.1)
1.0–1.5	5926 (17.0)	4792 (80.9)	3193 (53.9)	1748 (29.5)
1.5–2.0	3290 (9.4)	2720 (82.7)	1829 (55.6)	1033 (31.4)
2.0–4.0	5020 (14.4)	4283 (85.3)	3001 (59.8)	1736 (34.6)
4.0–10.0	2341 (6.7)	2057 (87.9)	1532 (65.4)	910 (38.9)
Missing	42 (0.1)			
Total	34 857			

Abbreviations: IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen.

DISCUSSION

In the current study, we evaluated the relationships between PSA and PV, PSA and IPSS among 34 857 patients included in a large-scale Korean screening program. As reported by previous studies, PSA had a strong positive correlation with PV, with a 26.4% increased explanatory power for PV in a linear regression model (r^2=0.264). The ability of PSA to predict PV increased with prostate size. The IPSS, which was used to represent LUTS, also had a significant linear correlation with PSA, demonstrating high scores at high PSA levels. After controlling for other factors, including age and PV, PSA was a significant predictor of IPSS. Nevertheless, the accuracy of PSA for predicting IPSS was not excellent in an analysis of the AUC ROC.

Rosenberg[15] first assessed the PSA threshold as a predictor of PV by characterizing the relationship between PV and serum PSA in men with symptomatic BPH in the Proscar Long-Term Efficacy and Safety study. Because PV is strongly related to serum PSA in men with no evidence of prostate cancer, they suggested that serum PSA can be used to estimate the degree of prostate enlargement accurately enough for it was a useful tool in therapeutic decision making.

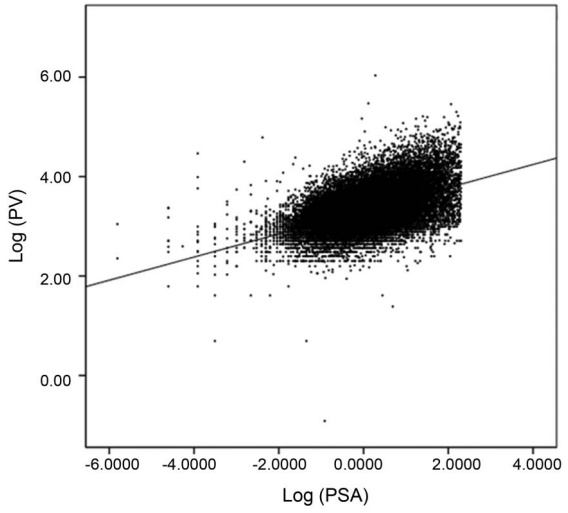

Figure 1 The scatter plots show the relationship between PSA and PV. The line indicates the regression line (log (PV)=3.312+0.233×log (PSA), r^2=0.264, P<0.001). PSA, prostate-specific antigen; PV, prostate volume.

Table 4 Predicting value of prostate-specific antigen for PV and IPSS by measurement of areas under the receiver-operating curve and 95% CI

	AUC	*95% CI*	*Standard error*
PV >20 ml	0.722	0.716–0.729	0.003
PV >25 ml	0.728	0.723–0.733	0.003
PV >35 ml	0.779	0.773–0.785	0.003
IPSS >7	0.548	0.540–0.555	0.004
IPSS >13	0.536	0.530–0.542	0.003
IPSS >19	0.537	0.531–0.544	0.003

Abbreviations: AUC, area under curve; CI, confidence interval; IPSS, International Prostate Symptom Score; PV, prostate volume.

In a study in the Netherlands, Mochtar *et al.*[6] included 1859 patients complaining of LUTS who visited the hospital with a PSA of 0–10 ng ml^{-1}. They demonstrated that PV and serum PSA had an age-dependent log-linear relationship, in which 42% of the variance in PV could be explained by PSA and age. Their predictive accuracy of PSA for PV was 0.82, and the serum PSA cutoff value was 2.0 ng ml^{-1} to detect a PV >30 ml and 2.5 ng ml^{-1} to detect a PV>40 ml. In our study, PSA also had a strong significant correlation with PV, and its explanatory power was 26.4%. In our log-linear correlation analysis, the serum PSA cutoff value was 1.47 to detect a PV>30 ml and 2.8 to detect a PV>35 ml. In the Krimpen study, of all 1524 men analyzed, PSA was shown to be predictive of an enlarged prostate (>30 ml and with a greater accuracy for PVs >40 or >50 ml). The AUC was 0.79 to predict a PV >30 ml, and AUCs of 0.86 and 0.92 denoted a good discrimination of PV >40 ml and PV >50 ml, respectively.[11] In our study, PSA was also an excellent predictor of PV after controlling for other factors and had a strong relationship with PV in a log-linear regression analysis. However, its level of relationship and accuracy of predicting PV was relatively low when compared to previous studies in Western countries. The differences between the results obtained in the Netherlands and our study can be explained in two points. First, our study population included the general population within a prostate screening program. Therefore, the men in our study had small prostates and low PSA levels compared to other studies including men who visited a hospital. Second, a previous study has shown that Asian men typically have smaller prostate and a higher PSA level compared with men in Western populations.[12]

One previous data from Asian have shown that PV and serum PSA have an age-dependent log-linear relationship, the strength of which increases with age.[12] The ROC AUC thresholds to detect PVs >30 ml, >40 ml and >50 ml were 0.755, 0.814 and 0.826, respectively, which are relatively high compared with our results. However, in that study, men who visited a hospital with complaints of troublesome LUTS were included, it had limitation not to show real situation for common men.

Only a few studies have evaluated the relationship between PSA and IPSS. Favilla *et al.*[17] showed that PSA did not have a significant relationship with the IPSS (Pearson correlation coefficient=0.018, P=0.836). Tsukamoto *et al.*[18] also reported in their longitudinal small population study that PSA had no significant correlation with the IPSS (correlation coefficient=−0.13, not significant). However, in our analysis, IPSS did have a significant relationship with PSA after logarithmic transformation in a linear regression analysis. The IPSS also had a significant relationship in a partial correlation test after controlling for age (r=0.041, P<0.001). Because the previous studies were small population studies, they were limited in their ability to explain the relationship between PSA and the IPSS. Although the IPSS

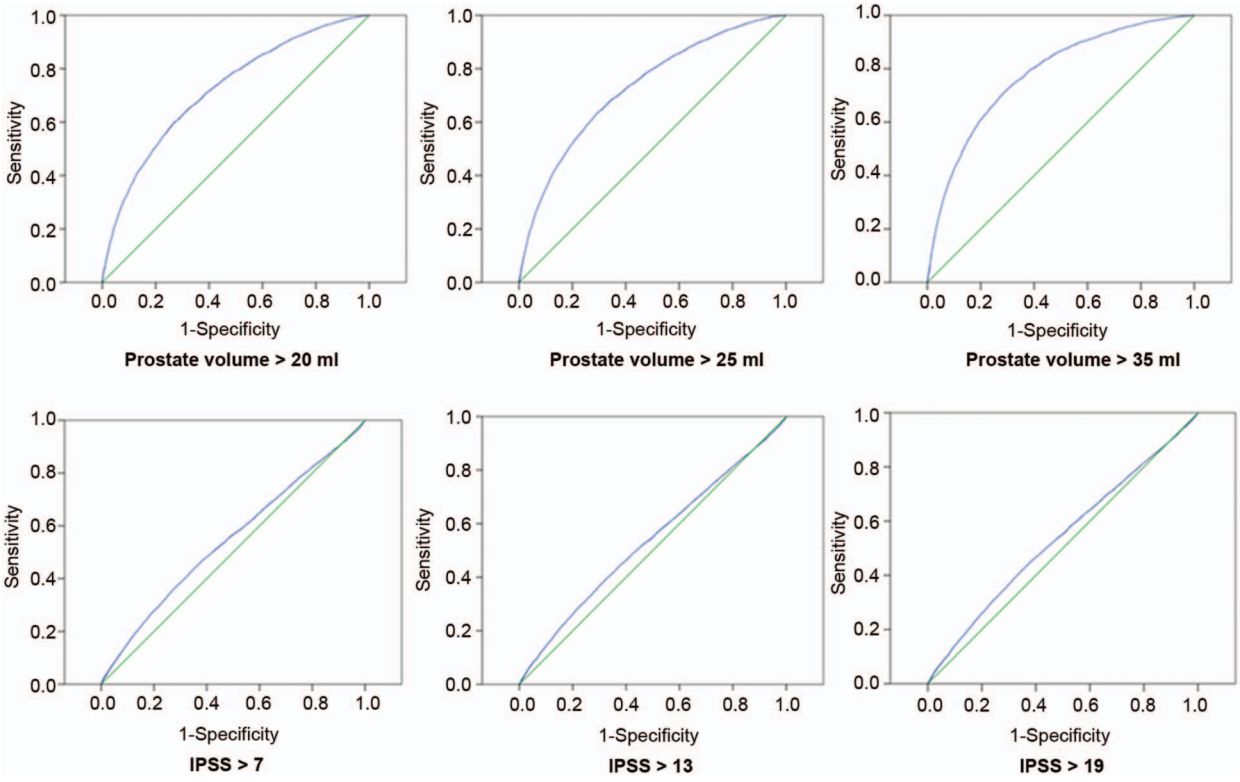

Figure 2 The receiver-operating characteristic curves used to estimate PV and IPSS using PSA. IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; PV, prostate volume.

did not demonstrate a high level of correlation level with PSA in our study, its value was significant because of our large study population. Sciarra *et al.*[13] have reported that symptom scores are weakly correlated with PV (r=0.1966) and that PV has a strong correlation with PSA. Therefore, it is possible that the IPSS was also weakly correlated with PV.

Our study may be limited by its retrospective nature. The history of medication use, which may have affected the PSA level, could not be assessed. Although we excluded men with a PSA level >10 ng ml^{-1}, we could not exclude potential prostate cancer. In general, the difference between the PSA levels in Caucasian and Asian men is due to factors such as obesity and prostate size, our results slightly differed with previous studies in Western countries.[7,12,19] However, this report was a very large-scale study in a country consisting of only one race, and it evaluated PSA, PV and the IPSS in the general population regardless of symptoms. Additionally, the PV cutoff was different from previous studies. Because the mean PV in our cohort of Asian men was determined in the general population and not symptomatic patients, it was less than the PV reported in previous studies; we set the cutoff value using IQRs. If further studies are performed using this cohort, it would be possible to set the cut-off levels to those reported previously (PVs >30 ml, >40 ml and >50 ml) for a more exact comparison. An additional subgroup analysis to evaluate the relationships among other parameters stratified according to age should be performed.

Table 5 Multivariate analysis predicting prostate size. Adjusted PSA value on predicting prostate size in multivariate analysis (age and IPSS were adjusted)

	HR	*95% CI*	P
PV >20 ml			
PSA (ng ml^{-1})	2.824	2.717–2.934	<0.001
Age (year)	1.020	1.017–1.024	<0.001
IPSS	1.001	0.914–1.022	0.235
PV >25 ml			
PSA (ng ml^{-1})	2.874	2.781–2.969	<0.001
Age (year)	1.024	1.021–1.027	<0.001
IPSS	1.049	1.000–1.099	0.050
PV >35 ml			
PSA (ng ml^{-1})	3.547	3.413–3.687	<0.001
Age (year)	1.032	1.028–1.036	<0.001
IPSS	1.161	1.096–1.231	<0.001

Abbreviations: CI, confidence interval; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; PV, prostate volume.

Table 6 Multivariate analysis predicting IPSS. Adjusted PSA value on predicting IPSS in multivariate analysis (age and PV were adjusted)

	HR	*95% CI*	P
IPSS >7			
PSA (ng ml^{-1})	1.060	1.020–1.101	0.003
Age (year)	1.045	1.041–1.048	<0.001
PV (ml)	1.254	1.150–1.368	<0.001
IPSS >13			
PSA (ng ml^{-1})	1.028	1.003–1.060	0.035
Age (year)	1.044	1.041–1.046	<0.001
PV (ml)	1.189	1.113–1.271	<0.001
IPSS >19			
PSA (ng ml^{-1})	1.047	1.014–1.081	0.005
Age (year)	1.044	1.041–1.047	<0.001
PV (ml)	1.149	1.071–1.233	<0.001

Abbreviations: CI, confidence interval; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; PV, prostate volume.

CONCLUSIONS

Our results showed that PSA levels not only have a strong correlation with PV, but that they are also a strong predictor of PV in a large-scale Korean screening cohort. Although PSA also had a significant correlation with IPSS, the correlation power was weak, and the predictive value for IPSSs above the cutoff levels was not excellent. It can therefore be suggested that men with a high PSA level have an increased PV and a high IPSS. Further investigations are required to elucidate the exact interactions between PSA and LUTS and between PSA and PV in prospective controlled studies. Such studies may suggest how PSA can be used to clinically predict PV and the IPSS.

AUTHOR CONTRIBUTIONS

JJO and DSP contributed the study concept and design. JJO wrote the draft of the manuscript under the supervision of DSP, JYH and YKH. DKC, IHG, JHH and SWK conceived of the study, and participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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