The utility of PSA density and free PSA in the prostate biopsy decision-making process in a South African population

By

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Declaration

I, Dr Ashfaaq Abdullah Maher, declare that:

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Dedication

I would like to dedicate this research project to my wife, children and parents; who showed patience while I carried out this research.

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List of abbreviations

4K score	4 Kallikrein score
A2M	α2-macroglobulin
ACT	α1-antichymotrypsin
API	α1-protease inhibitor
AUC	Area Under the Curve
BPH	Benign Prostatic Hyperplasia
BRCA	BReast CAncer gene
BREC	Biomedical Research Ethics Committee
cPSA	complexed Prostate Specific Antigen
DRE	Digital Rectal Examination
EAU	European Association of Urology
ERSPC	European Randomized study of Screening for Prostate Cancer
fPSA	free Prostate Specific Antigen
hK3	Human kallikrein 3
ISUP	International Society of Urological Pathology
MP-MRI	Multi-Parametric Magnetic Resonance Imaging
MRI	Magnetic Resonance Imaging
NPV	Negative Preditive Value
PCA3	Prostate Cancer Antigen 3
PHI	Prostate Health Index
PLCO	Prostate, Lung, Colorectal and Ovarian
PPV	Positive Predictive Value
PSA	Prostate Specific Antigen

PSAD	Prostate Specific Antigen Density
PSAV	Prostate Specific Antigen Velocity
ROC	Receiver Operator Curve
SD	Standard Deviation
SPSS	Statistical Package for the Social Sciences

Abstract

Background:

Controversy around the role of PSA screening for prostate cancer still exists because evidence has not yet shown that it saves lives. Additional tests used in conjunction with PSA, can improve the sensitivity and specificity after screening when deciding which patients should be biopsied (-during screening), thus potentially reducing the number of unnecessary prostate biopsies and reducing the number of clinically insignificant prostate cancers that are detected.

Methods:

A retrospective chart review was undertaken on a heterogeneous group of South African men from a private urology practice in Johannesburg, South Africa. PSA, prostate volume, PSA density (PSAD), free PSA (fPSA) and prostate histopathological diagnosis were assessed.

Results:

Of the 227 patients included, 59.9% were diagnosed with prostate cancer and 40.1% with benign pathology. The mean age was 60.5 years. The mean PSA ($p<0.001$), fPSA ($p=0.043$) and PSAD ($p<0.001$) were significantly different between the cancer and the benign groups. The area under the ROC curve for PSA was 0.83 ($p<0.001$) with an ideal cutoff of greater than 4.87ng/mL to detect cancer, for fPSA was 0.66 ($p=0.036$) with a cutoff of <12.25% and for PSAD was 0.86 ($p<0.001$) with a cutoff of > 0.11 ng/mL/cm^3. In the prostate biopsy decision-making process, using a PSAD > 0.1ng/mL/cm^3 or a percentage fPSA <= 12% in addition to the standard indication of PSA >= 4ng/mL as an indication for biopsy would have prevented 21.1% of biopsies and 16.7% of clinically insignificant prostate cancer diagnoses but would have missed 8.6% of clinically significant cancers. There is a trend toward increasing PSA and PSAD and decreasing fPSA with increasing Gleason score.

Conclusions:

If PSA screening for prostate cancer is undertaken, the addition of PSAD and fPSA, both of which can be obtained in resource-constrained state hospitals, can reduce the number of clinically insignificant prostate cancer detected and the number of unnecessary prostate biopsies.

This, however, runs the risk of a small reduction in the detection of clinically significant prostate cancer. Further investigation is required to minimise this risk. Patients with equivocal PSA values, but with PSAD > 0.1ng/mL/cm^3 or fPSA <= 12% should be referred for further assessment.

Chapter 1

Introduction

Introduction

The diagnosis of prostate cancer is made on histopathology obtained at prostate biopsy. Biopsy of the prostate is an invasive procedure and carries a number of risks, including bleeding and infection. Identifying which patients need to undergo prostate biopsy is essential to correctly identify clinically significant prostate cancer while avoiding the side effects and complications of unnecessary biopsies. Currently, serum prostate-specific antigen (PSA) and digital rectal examination (DRE) are the main triggers for prostate biopsy. In addition, ethnic background and family history are taken into account. Several additional parameters can be considered before deciding to proceed to a prostate biopsy. These include PSA velocity, PSAD, free PSA, (-2) pro-PSA, prostate health index (PHI), multiparametric magnetic resonance imaging (MP-MRI) and the ‘‘“4K score”’’. PSAD is calculated using the serum PSA and the measured prostate volume on imaging. It can be calculated easily in the urology clinic by performing a bedside trans-rectal ultrasound and utilising the patient’s presenting PSA. Unlike the other parameters, it does not require any additional blood testing or referral for additional imaging and can be calculated without any additional cost to the patient or health system. It is thus an attractive parameter to include in the decision-making process for prostate biopsy in a resource-constrained state healthcare system. Furthermore, a blood test to measure the percentage of unbound PSA (free PSA) is also available at many tertiary centres and this can also be used to predict the risk of a patient having prostate cancer. The value of the percentage of free PSA can then be used in the prostate biopsy decision-making process. There is currently no data to assess the performance of PSAD and free PSA to predict prostate cancer in a South African population. The purpose of this study will be to assess whether PSAD and free PSA can play a role in assessing the likelihood of patients actually having prostate cancer, thereby potentially reducing the number of biopsies that are performed.

Literature review

Prostate cancer is the most common malignancy and the second most common cause of cancer-related deaths in men in the United States[1]. It is also the most common solid neoplasm in European men[2]. In South Africa, prostate cancer is the most common cancer in men excluding non-melanoma skin cancer[1]. It has been well described that prostate cancer incidence rates and mortality rates are higher among African-American men than Caucasian men[3]. Prostate cancer is the most common cancer in Sub-Saharan Africa, with a mortality rate of more than five times that of African Americans[4,5]. African-American men also present with more aggressive disease as supported by higher rates of intermediate- and high-risk prostate cancer[6]. In a South African population at a regional hospital in KwaZulu-Natal, black South African men were presented late with advanced disease[7].

Prostate-specific antigen (PSA), also known as human kalikrein 3 (hK3), is an antigen secreted by epithelial cells of the prostate gland. The main physiological function of PSA is that it cleaves proteins in the seminal fluid allowing liquefaction of the coagulum of seminal fluid[8]. PSA can be found in seminal fluid and serum and circulates in bound (complexed, cPSA) and unbound forms (free, fPSA). Three main proteins known to bind to PSA and these are α1-antichymotrypsin (ACT), α2-macroglobulin (A2M), and α1-protease inhibitor (API)[9]. About 70% of PSA in serum is bound to a protein, with the remainder being unbound, i.e. free PSA[12]. Measurement of PSA in serum is used to detect prostate cancer, and sequential measurements are used to monitor the progress of the disease and treatment response.[11,13,14].

Serum PSA becomes detectable at puberty with increases in luteinising hormone and testosterone[13]. Provided there is no prostate cancer, serum PSA levels can vary with race, age and prostate volume. PSA may be raised in both benign and malignant lesions of the prostate[8]. It is thought that PSA levels increase in serum due to disruption of the cellular architecture within the prostate gland[10,15]. Disruption of the normal cellular architecture can occur secondary to prostate diseases such as benign prostatic hyperplasia (BPH), prostatitis and prostate cancer[15]. Disruption may also occur with prostate manipulation due to prostate massage or prostate biopsy[15]. Prostatic

inflammation (acute and chronic) and urinary retention have also been shown to cause PSA elevations[15]. Trauma to the prostate, which occurs after a prostate biopsy, can cause a temporary spike in serum PSA that can last for approximately 4 weeks before returning to baseline values[16]. Ejaculation has also been shown to increase PSA levels causing a spike for about 24 hours before returning to baseline[17]. Long-distance cycling is another potential cause of PSA elevation and this should be ruled out when taking a history from the patient[15].

Even though these factors can slightly increase PSA levels, the most notable and important factors that cause levels to be elevated are due to the presence of prostate disease (prostate cancer, BPH and prostatitis). The impact of BPH and prostatitis on PSA levels confounds the accuracy of PSA in the detecting prostate cancer by utilising PSA alone. Thus, the use of PSA alone in screening for prostate cancer has been challenged upon.

PSA has been used since the 1990's' to screen for prostate cancer[8]. The widespread use of PSA as a screening tool for prostate cancer has led to an increase in detecting more histologically confirmed indolent prostate cancer, which is unlikely to result in potentially aggressive disease in the patient's lifetime. This has resulted in the over-diagnosis and over-treatment of prostate cancer, and thus it has been suggested that PSA alone should be abandoned as a screening tool[18]. The European Randomised Study of Screening for Prostate Cancer (ERSPC) showed an 8.2% incidence of prostate cancer in the routine PSA screening arm, whereas the disease incidence of the disease in the control arm was 4.8 percent after thirteen years of follow-up[19]. To put this into context, 1410 men would need to be screened with PSA for prostate cancer to diagnose 48 cases of the disease to prevent one death[20]. The findings of a Swedish prostate cancer screening trial called the 2010 Goteborg Prostate Screening Trial were comparable with the ERSPC trial. In this trial, at fourteen years of follow-up, 293 men needed to be screened with 12 new diagnoses of prostate cancer to prevent 1 death from the disease[21]. Another trial, the Prostate, Lung, Colorectal and Ovarian (PLCO) trial, did not demonstrate any significant reduction in mortality related to prostate cancer and thus, till today, prostate cancer screening remains a controversial subject[20]. However, a recent review of data of the ERSPC and PLCO trials which used mean lead time estimations, also taking into account the differences in implementation and setting, revealed that both these studies provided adequate evidence that screening does reduce prostate cancer mortality[22].

Despite the findings of the trial mentioned above, prostate cancer screening using a PSA based approach may still not be indicated for the general male population. ‘“‘The risk of a 50-year-old male with a 25-year life expectancy of having microscopic prostate cancer is 42%, of having clinically significant cancer 9.5% and of dying from prostate cancer 2.9 percent”’’[23]. However, a male in his forties with a family history of prostate cancer in which 3 close relatives are diagnosed with the disease (e.g. brother, father, uncle) has a 30-40% lifetime risk of developing clinically significant disease[23]. Therefore it has been suggested that prostate cancer screening should be directed to men deemed at high risk for prostate cancer. In the European Association of Urology Guidelines (EAU) of 2021, there is a strong recommendation that the following populations should be offered screening provided that they have been well counselled of the pros and cons of screening and have a life expectancy of at least 10 – 15 years:

- Men over the age of 50 years
- Men over the age of 45 years with a family history of prostate cancer
- Men over the age of 45 years and of African descent
- Men over the age of 40 years who carry the BRCA2 mutation

An alternative recommendation by the EAU guidelines 2021 is to do a PSA at the age of 40 and/or 60 years. If the PSA is >1ng/mL at 40 years or >2ng/mL at 60 years, patients should be followed up every 2 years with a repeat PSA and DRE. If PSA levels in their blood are less than those then they can be re-screened after 8 years[36].

The need for criteria of which subgroups qualify for a biopsy is important as prostate biopsy is not an innocuous procedure[18, 23]. Two common complications of prostate biopsy are sepsis and hematuria which have rates of 1-7% and 2-34% respectively[23].

It is important to note that PSA is prostate-disease specific and not prostate cancer-specific and it can be raised in other conditions such as infections, instrumentation and prostate cancer itself. Furthermore, PSA may not be raised at all and lie within the normal range in poorly differentiated prostate cancer or prostate cancer of variant histology. All these factors make PSA being used alone not ideal.

The normal range of PSA is between 0-4ng/mL but in patients with more advanced ages a slightly higher cutoff of PSA of 6.5ng/mL is accepted[24]. A study by Neal et al. of 332 men who were >50

years with serum PSA between 2.6 – 4 ng/mL and had a prostate biopsy showed that 22% of those patients had histologically proven cancer[23]. Oesterling, however, showed that a PSA range of 0 – 4.5 ng/mL is appropriate in men aged 60 – 69 years while PSA of 0 – 6.5 ng/mL should be considered normal for men aged 70 – 79 years[8]. Hence, it is safe to omit biopsies in men whose PSA lies in that range provided they have a normal digital rectal exam[8]. However, a retrospective review of prostate biopsies contradicted this revealing that if that protocol is followed we could miss up to 60% of aggressive prostate cancers[24]. Thus, it would be ideal not to use PSA alone as a screening tool, and other modalities should be explored.

Furthermore, specific subgroup populations are known to be at greater risk of developing prostate cancer. This is often due to predisposing genetic factors, lack of awareness of the disease or a mix of these factors. One such subgroup, which makes up the bulk of our population, are men of African ancestry. Due to the increased risk in this subgroup of developing the disease, which tends to be more aggressive, may benefit from PSA-based screening.

As depicted above, it is apparent that using the absolute serum PSA level as a screening test has a number of flaws which include, firstly, some men with normal or low absolute serum PSA levels have been found to have prostate cancer and secondly, many men with high absolute PSA levels do not have prostate cancer and, have instead BPH[25]. Thus, serum PSA alone has the potential of false-positive and false-negative results when used as a screening test for prostate cancer. Additional parameters that improve the test's diagnostic accuracy are likely to be beneficial, hence the development and use of additional parameters such as PSA velocity, PSAD and percentage free PSA[26].

PSA density (PSAD) was first developed by Benson et al. to improve cancer detection rates when PSA ranged between 4 – 10 ng/mL[27]. It is calculated by a formula and is used to help differentiate benign versus malignant disease of the prostate. It is calculated by dividing the PSA value in ng/mL by the prostate gland volume in cubic centimetres[27].

$$\textbf{PSAD}\ (ng/mL/cm^3) = \textbf{PSA}\ (ng/mL) / \textbf{Prostate vol}\ (cm^3)$$

Prostate gland volume is measured either via trans-rectal ultrasound or MRI. A high PSA density indicates a higher risk of prostate cancer and PSAD values greater than 0.15 ng/ml/cm^3 are considered to be significant, strengthening the case for performing a prostate biopsy. Lower PSAD values (<0.15 ng/ml/cm^3) are less likely to be associated with malignancy and favour observation rather than biopsy[27].

There have been many studies done internationally to study the performance of PSAD but none in South Africa. In a study done by Catalona et al. in 2000, they found high cancer detection performance (95% sensitivity) when they used a PSAD cutoff of 0.078 in men whose PSA was between 4 – 10 ng/mL[28]. This group found that 40% of cancer cases would not be missed with a cutoff of 0.15ng/mL[28]. There is another study which was done recently to predict the accuracy of PSAD to detect clinically significant prostate cancer by Aminsharifi et al. His group found the using a PSAD cutoff of 0.08 ng/mL could have avoided 273 of 2162 biopsies (13%), missing 48 of 622 non clinically significant prostate cancers (ISUP grade group 1) (8%) and 10 of 499 clinically significant cancers (2%)[29].

Nordrom et al. found that using PSAD cutoff of 0.1 and 0.15 ng/mL could result in a missing detection rate of 23% and 51% respectively[30]. However, when they set a cutoff of 0.07ng/mL, they could avoid 20% of biopsies while only missing about 7% of clinically significant disease[28]. To further test the performance of PSAD another study set a cut-off of PSAD of 0.15 and this value gave them the highest sensitivity (70%) and specificity (70%) for the detection of any clinically significant prostate cancer[31]. To summarise, all these studies show that PSAD with PSA is a better predictor of prostate cancer than PSA alone of biopsy outcomes in patients undergoing prostate biopsies.

Most of the serum PSA is found complexed to proteins. However, up to 45% of PSA exists as free PSA (fPSA)[32], found in the serum in an unbound form. In the conventional serum PSA test it measures total PSA taking into account both fPSA and cPSA. In patients with prostate cancer there is a lower percentage of fPSA[33]. Thus, the percentage of fPSA has been explored and used in prostate cancer screening and can aid in the prostate biopsy decision-making process. The measurement of fPSA is then used to calculate the % of fPSA, and this is used as a diagnostic

index for detection of prostate cancer in men whose PSA ranges from 4 to 10 ng/mL[34]. The lower the value of % of fPSA the greater the likelihood that an elevated PSA represents a cancer and not BPH.

fPSA is calculated as follows:

***% fPSA** (%) = **free PSA** (ng/mL) / **total PSA** (ng/mL) x 100*

There is no absolute cutoff that can confidently differentiate prostate cancer from BPH but it has been shown that fPSA levels below 15% have been shown to significantly improve the ability to distinguish between patients with and without cancer compared to the use of PSA alone[25]. For example, in one study of men with PSA between 4 and 10 ng/mL the probability of cancer in men with a % fPSA below 10% was 56%, compared with only 8% of men with a value >25%[25].

fPSA has also been explored for use in the risk stratification of men with prostate cancer. It has been shown that men with a lower % fPSA may be associated with more aggressive disease. This was shown in a study of 20 men with prostate cancer[35]. In this study, all the 8 men with aggressive cancers (T3 disease, N1 or M1 or Gleasons >7) had a %fPSA of ≤14%, compared with only 2 of 6 (33%) with non-aggressive cancer[35].

<u>Research question</u>

What is the utility and performance of PSA, free PSA and PSAD in predicting the risk of prostate cancer in a South African population and if these measures can improve the prostate biopsy decision-making process.

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Chapter 2

The utility of PSA density and free PSA in the prostate biopsy decision-making process in a South African population

Introduction

Prostate cancer is the commonest cancer in South African men, excluding skin cancer[1]. Serum prostate specific antigen (PSA) testing of asymptomatic men has been used since the late 1980s[2] as a screening test for prostate cancer, to detect prostate cancer while still being amenable to cure. However, the controversy around this practice has intensified recently because evidence has not shown that screening for prostate cancer saves lives[3,4]. Moreover, prostate cancer screening is associated with potential harm including complications from biopsies and treatment of clinically insignificant disease[5]. Ultimately, the diagnosis of prostate cancer is made on histopathology obtained at prostate biopsy. This is an invasive procedure and carries risks including bleeding, infection, urinary retention and rarely death[6].

International guidelines now recommend against systematic or population-based PSA screening[7]. Patients with limited life expectancy, either due to age or poor functional status, who present with lower urinary tract symptoms, or patients requesting screening require shared decision making with a doctor, especially regarding the implications of screening. Men, especially those with a high risk of prostate cancer (such as those of African descent or with a family history of prostate cancer), may, based on their values and expectations, choose screening[7]. On the other hand, after considering the implications of screening, lower risk men may decide against screening.

Identifying which patients should undergo prostate biopsy is essential to accurately detect clinically significant prostate cancer while avoiding the negative consequences of biopsy in clinically insignificant disease. Currently, elevated total serum PSA and abnormal findings on digital rectal examination (DRE) are the main triggers for prostate biopsy, but the performance of South African doctors who are not urologists in assessing patients at risk of prostate cancer is poor[8]. There are additional parameters that can be considered before deciding to proceed to a prostate biopsy. These include PSA velocity (PSAV), PSA density (PSAD), percentage unbound PSA (free PSA) (fPSA), (-2)pro-PSA, urine Prostate Cancer Antigen 3 (PCA3), multiparametric

magnetic resonance imaging (MP-MRI) of the prostate, the prostate health index (PHI), and the ‘‘‘‘4K score”’’. Many of these are not cost-effective for or readily available to all patients, particularly in resource-constrained state hospitals.

There is currently no data from South Africa assessing the performance of the available tests to predict the risk of a patient with an elevated PSA having prostate cancer. Serum PSA, free PSA and PSAD can be obtained relatively easily and cost-effectively with a blood test and an imaging investigation of the prostate. Trans-rectal ultrasound, which is available in most urology clinics, and trans-abdominal ultrasound, which is available in most regional and some district-level hospitals, can be used to measure the prostate volume required to calculate PSAD. The purpose of this study is to assess whether the use of PSA, free PSA and PSAD can be used in the prediction of the risk of a patient having prostate cancer, as well as in assessing whether the use of these parameters may be useful in the decision-making process, when deciding to biopsy a patient with an elevated PSA in the South African population.

Methods

A retrospective review of patients who had a PSA test and prostate histopathology, either from biopsy or after surgery, was conducted between 01 July 2018 and 30 June 2019 at a private urology practice in Johannesburg, South Africa. The practice sees a wide range of insured patients from the greater Johannesburg area, representing all age and demographic groups. Prostate volume, PSA, fPSA, histopathological diagnosis and Gleason score were collected. fPSAs were only reported for patients with a PSA between 2.5 and 10ng/mL. Prostate volumes were recorded from trans-rectal ultrasound, trans-abdominal ultrasound, multi-parametric MRI or computed tomography (CT) scan measurements depending on which investigations had been performed. Percentage fPSA was calculated as follows:

$$\textbf{\% fPSA}\ (\%) = \textbf{free PSA}\ (ng/mL) / \textbf{total PSA}\ (ng/mL) \times 100$$

Prostate volume was calculated according to the ellipsoid formula as follows[9]:

$$\textbf{Volume}\ (cm^3) = \textbf{Length}\ (cm) \times \textbf{Width}\ (cm) \times \textbf{Height}\ (cm) \times \pi / 6$$

An example of prostate volume measurement on trans-abdominal ultrasound is shown in Figure 1.

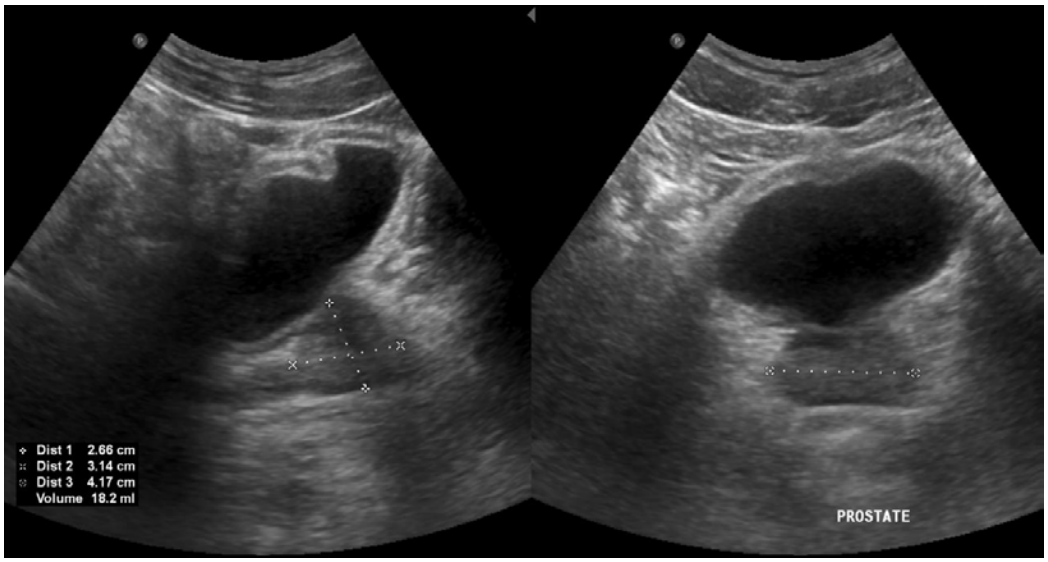

Figure 1: Example of ultrasound measurement of prostate volume on trans-abdominal ultrasound in a 40-year-old man. Source: Image obtained from patient records with permission.

PSAD was calculated as follows:

$$\textbf{PSAD}\ (ng/mL/cm^3) = \textbf{PSA}\ (ng/mL) / \textbf{Prostate vol}\ (cm^3)$$

Prostate cancer was graded using the modified Gleason scoring system[10]. Ethics approval for this study was granted by the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal (BE459/18).

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 24 (IBM, USA). Comparison of means was performed using the t-test for equality of means in independent samples. Sensitivity and specificity of tests were calculated using two-by-two tables. Receiver operating characteristic (ROC) curves were drawn for PSA, fPSA and PSAD

using easyROC[11,12], an online ROC tool that provided more flexibility than SPSS. The area under the curve (AUC) was calculated and the optimal cutoff value was selected by identifying the variable value with the highest sensitivity and specificity using the Youden Index. The significance of the AUC was reported compared to the null hypothesis. Pearson's χ^2 test with Yates'' correction for continuity[13] was used to compare categorical variables. If the projected frequency, assuming a true null hypothesis, in a cell of a two-by-two table was less than five observations, Fisher's exact test was applied using double the one-tailed exact probability[13]. A p-value of <0.05 (5%) was considered statistically significant.

Results

Two hundred and twenty-seven patients were included in the analysis. The mean age at presentation was 60.5 years (SD 8.65 years; range 40-84 years). The mean prostate volume was 52.7cm^3 (SD 32.8; range 6-300cm^3).

Prostate cancer vs benign histology

Of the 227 patients reviewed, 136 (59.9%) were diagnosed with prostate cancer and 91 (40.1%) were found to have benign pathology. The mean PSA, fPSA and PSAD differentiated into patients with prostate cancer and benign histology is outlined in Table 1.

	Prostate Cancer (n=136)	**Benign Histology (n=91)**	**p-value**
PSA	11.45ng/mL (SD 16.38; range 1.5-175.0ng/mL)	4.37ng/mL (SD 4.82; range 0.3-32ng/mL)	<0.001*
fPSA	15.1% (SD 9.0; range 2.4-46.3%)	20.0% (SD 9.9; range 8.9-47.1%)	0.043*
PSAD	0.24ng/mL/cm^3 (SD 0.19; range 0.04-1.31ng/mL/cm^3)	0.09ng/mL/cm^3 (SD 0.09; range 0.01-0.66ng/mL/cm^3)	<0.001*

Table 1: Comparison of mean PSA, fPSA and PSAD in patients with prostate cancer and benign histology.

** Indicates a significant finding.*

Predicting prostate cancer

The ROC curves for PSA, fPSA and PSAD are shown in Figure 2. The AUC for PSA was 0.83 (95% CI 0.77-0.89; p<0.001) and the optimum PSA cutoff for predicting cancer was a PSA greater than 4.87ng/mL. The AUC for percentage fPSA in patients with PSA between 2.5 and 10ng/mL was 0.66 (95% CI 0.53-0.79; p=0.036) and the optimum percentage fPSA for predicting cancer was a percentage fPSA less than 12.25%. The AUC for PSAD was 0.86 (95%CI 0.80-0.91; p<0.001) and the optimum PSAD cutoff to exclude prostate cancer was less than 0.11ng/mL/cm^3.

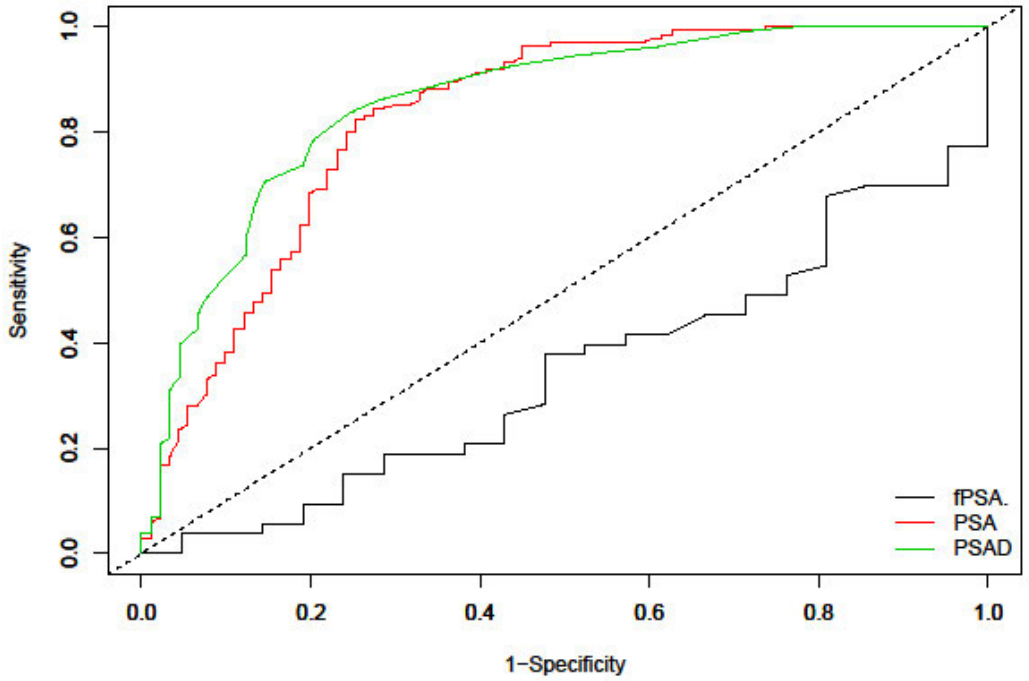

Figure 2: ROC curve for PSA, fPSA and PSAD. The fPSA curve is inverted compared to the PSA and PSAD curves as the more negative the fPSA, the more significant the result.

In the prostate biopsy decision making process, using a PSAD > 0.1ng/mL/cm^3 or a percentage fPSA <= 12% in addition to the standard indication of PSA >= 4ng/mL as an indication for biopsy would have prevented 21.1% of biopsies. It would have missed 12.5% (n=17) of prostate cancers, including preventing the diagnosis of 16.7% (n=11) of clinically insignificant and missing 8.6% (n=6) of clinically significant prostate cancers.

The sensitivities, specificities, positive predictive values (PPVs) and negative predictive values (NPVs) for the detection of prostate cancer are summarised in Table 2.

Parameter	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
PSA >= 4 ng/mL	93.4% (87.8-96.9%)	57.1% (46.3-67.5%)	76.5% (71.9-80.6%)	85.3% (75.0-91.8%)
fPSA <= 12%	49.1% (35.1-63.2%)	76.2% (52.8-91.8%)	83.9% (69.8-92.1%)	37.2% (29.3-45.8%)
PSAD > 0.1ng/mL/cm^3	83.7% (76.2-89.6%)	75.3% (65.0-83.8%)	83.1% (77.2-87.7%)	76.1% (67.9-82.3%)
PSA >=4 and one of fPSA <= 12% or PSAD >0.1ng/mL/cm^3	80.9% (73.3-87.1%)	76.9% (66.9-85.1%)	84.0% (78.1-88.5%)	72.9% (65.2-79.5%)

Table 2: Sensitivities, specificities, PPVs and NPVs for PSA, fPSA, PSAD and the combination of parameters for the detection of prostate cancer.

Differentiating between clinically significant and clinically insignificant prostate cancer

The breakdown of mean PSA, fPSA and PSAD by cancer grade is summarised in Table 3. The mean PSA (p=0.009) and PSAD (p=0.001) were significantly higher and the mean fPSA (p=0.01) was significantly lower in patients with clinically significant disease (Gleason > 6). There was a trend toward increasing PSA and PSAD and declining fPSA with increasing Gleason Score.

	Gleason 6 (n=66; 48.5%)	Gleason 7 (3+4) (n=35; 25.7%)	Gleason 7 (4+3) (n=16; 11.8%)	Gleason 8 (n=12; 8.8%)	Gleason 9-10 (n=7; 5.2%)
PSA (ng/mL)	7.76	9.96	10.50	33.93	17.23
fPSA (%)	17.3	13.1	6.1	8.7	6.7
PSAD ($ng/mL/cm^3$)	0.18	0.22	0.23	0.53	0.37

Table 3: Mean PSA, fPSA and PSAD broken down by grade of prostate cancer diagnosed.

Discussion

Due to the complexities surrounding PSA screening for prostate cancer[3,4] and the availability of surveillance rather than treatment for certain patients with low-grade prostate cancer, careful consideration is necessary at a primary care level of which patients to screen and subsequently, which to refer to a specialist. Additional tests that are easy to perform and are cost-effective can assist primary healthcare providers in making this decision. Furthermore, with knowledge of the risks associated with prostate biopsy, these tests can assist doctors working in urology units with the prostate-biopsy decision making and counselling process.

In South Africa, there is little data describing the performance of PSA and related parameters in the detection of prostate cancer. In a study assessing the utility of PCA3 in a heterogeneous sample of 105 South African men, Adam et al. reported the area under the ROC curve for PSA to be 0.844[14], very similar to the finding of 0.83 in our study. There is no South African data on the performance of fPSA or PSAD. We were able to show that both PSA and PSAD perform similarly in detecting prostate cancer with AUCs of 0.83 and 0.86. In patients with PSA between 2.5 and 10ng/mL, fPSA can detect prostate cancer but performs less well than PSA and PSAD, with an AUC of 0.66.

Since the development of PSA testing, the reference range for normal serum total PSA has been standardised at <4ng/mL[15]. We found an optimal cutoff for PSA to detect prostate cancer of >4.87ng/mL in the South African population. Although there is no standardised reference range

for fPSA, a cutoff of <25% is associated with a 95% sensitivity for detecting prostate cancer[16], but with low specificity and a high risk of unnecessary biopsy. We found a more useful cutoff of <12.5% to detect prostate cancer with optimum sensitivity and specificity in the South African population. The commonly used cutoff for PSAD is >0.15ng/mL/cm^3 to detect prostate cancer, although this was found to have a low sensitivity by Catalona et al.[16], who found a cutoff of >0.078ng/mL/cm^3 was associated with the highest sensitivity. We found a PSAD cutoff of >=0.11ng/mL to be associated with the optimum sensitivity and specificity in the South African population.

In a study by Nordström et al., PSAD was added to PSA in the prostate cancer diagnostic algorithm[17]. This study found better discrimination for clinically significant prostate cancer with the use of PSAD than PSA alone. We found that PSAD provided the best combination of sensitivity and specificity to detect prostate cancer in the South African population. Furthermore, in patients with elevated PSA, using the finding of a fPSA <=12% or a PSAD >0.1ng/mL/cm^3 as part of the prostate biopsy-decision making process had good sensitivity and specificity. It was able to avoid 21.1% of biopsies at the cost of missing 8.6% of clinically significant prostate cancers. Nordström et al. similarly found a cost to improving specificity of the prostate cancer diagnostic algorithm by adding PSAD[17]. They would have avoided 19.7% of biopsies and missed 6.9% of clinically significant prostate cancers using a PSAD cutoff of 0.07ng/mL/cm^3.

Recently, the idea of potential harm from diagnosis and subsequent treatment of clinically insignificant prostate cancer has been recognised. We found a trend toward increasing PSA and PSAD and decreasing fPSA with increasing Gleason score and, hence increasing clinical significance. The future of prostate cancer screening will focus on tests that can discriminate between clinically insignificant and aggressive disease[18]

We chose to investigate PSAD and fPSA because we felt they represented the most minor increase in cost to the prostate cancer detection process and could be obtained in both state hospitals[19] and the private sector. PSAD requires the prostate volume to be calculated. This can be done with ultrasound, which is generally available in most South African hospitals. Either supra-pubic or trans-rectal measurements are sufficient, as they have been shown to correlate well[20]. On the other

hand, tests such as MP-MRI, PCA3 and PHI are more costly and less likely to be available in state hospitals.

This study, as well as the study by Adam et al.[14], investigated a heterogeneous South African population. It is well known that black South African men present with higher PSA levels and more aggressive prostate cancer[21-23]. We did not have a reliable source of demographic data in this retrospective study, and were unable to assess the impact of race on the performance of PSA, fPSA and PSAD in the prostate cancer diagnostic algorithm. This would be a useful future investigation to further understand the role of screening for prostate cancer in South Africa, and improve the sensitivity and specificity of screening tests. Furthermore, the risk associated with missing 8.6% of clinically significant prostate cancers is concerning, and further investigation is required to minimise this risk.

Conclusion

Screening tests perform well at detecting prostate cancer. However, they have not been shown to save lives and are associated with potential harm from complications of unnecessary prostate biopsy and overtreatment of clinically insignificant prostate cancer. Currently, PSA screening in men with symptoms or who request it should follow a shared decision-making process between the patient and the doctor, with adequate counselling on the implications. If PSA screening is undertaken, the addition of PSAD and fPSA, both of which can be obtained in resource-constrained state hospitals, can reduce the detection of clinically insignificant prostate cancer and the number of unnecessary prostate biopsies. This, however, runs the risk of a small reduction in the detection of clinically significant prostate cancer. Further investigation is required to minimise this risk. Patients with equivocal PSA values, but with PSAD > 0.1ng/mL/cm^3 or fPSA <= 12% should be referred for further assessment.

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Appendix 1: Study Protocol

Degree: MMED Urology

Title: The utility of PSA density and free PSA in the prostate biopsy decision making process in a South African population.

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Title of study

The utility of PSA density and free PSA in the prostate biopsy decision making process in a South African population.

Motivation of study

The diagnosis of prostate cancer is made on histopathology obtained at prostate biopsy. This is an invasive procedure and carries a number of risks including bleeding and infection. Identifying which patients need to undergo prostate biopsy is essential to correctly identify clinically significant prostate cancer while avoiding unnecessary biopsy's side effects and complications. Currently, serum prostate-specific antigen (PSA) and digital rectal examination (DRE) findings are the main triggers for prostate biopsy. In addition, ethnic background and family history are taken into account. A number of additional parameters can be considered before deciding to proceed to a prostate biopsy. These include PSA velocity, PSAD, free PSA, (-2)pro-PSA, prostate health index (PHI), multiparametric magnetic resonance imaging (MP-MRI) and the "4K score". PSAD is calculated using the serum PSA and the measured prostate volume on imaging. It can be calculated easily in the urology clinic by performing a bedside trans-rectal ultrasound and utilising the patient's presenting PSA. Unlike the other parameters, it does not require any additional blood testing or referral for additional imaging and can be calculated without any additional cost to the patient or health system. It is thus an attractive parameter to include in the decision-making process for prostate biopsy in the resource-constrained state healthcare system. Furthermore, a blood test to measure the percentage of unbound PSA (free PSA) is also available at many tertiary centres and this can also be used to predict the risk of a patient having prostate cancer. There is currently no data to assess the performance of PSAD and free PSA to predict prostate cancer in a South African population. The purpose of this study will be to assess whether PSAD and free PSA can play a role in assessing the risk of prostate cancer and improve the prostate biopsy decision-making process.

Research hypothesis

PSA, PSAD and free PSA combined with DRE has better diagnostic accuracy than PSA and DRE alone to predict the presence of prostate cancer.

Aim of study

1. To determine the sensitivity, specificity, positive predictive value and negative predictive value for PSAD and free PSA in a South African population.
2. To assess the diagnostic accuracy of PSAD and free PSA combined with DRE and PSA compared to DRE and PSA alone.
3. To determine the utility of PSAD and free PSA in resource-constrained urology centres to assist in decision making to perform a prostate biopsy**.**

Specific objectives

1. Identify a South African population where prostate cancer is diagnosed commonly, where prostate volume is measured routinely and where there is a high standard of record keeping.

2. Perform a chart review of patients having undergone prostate biopsy with either prostate cancer or without prostate cancer in this population.

3. Record the following variables:
    a. Patient demographics (age and race).
    b. Prostate volume on imaging.
    c. Presenting PSA and free PSA
    d. Presenting clinical findings on DRE (benign vs malignant, clinical stage).
    d. Histopathology (diagnosis, grade, tumour extent on biopsy).

4. Tabulate the data.

5. Analyse the data to determine the diagnostic accuracy of PSAD and free PSA in a South African population.

Background and Literature

Prostate cancer is the most common malignancy and the second most common cause of cancer-related deaths in men in the United States[1]. It is also the most common solid neoplasm in European men[2]. In South Africa, prostate cancer is the most common cancer in men excluding non-melanoma skin cancer[3]. It has been well described that prostate cancer incidence rates and mortality rates are higher among African-American men than Caucasian men[4]. Prostate cancer is the most common cancer in Sub-Saharan Africa, with a mortality rate of more than five times African Americans[5,6]. African-American men also present with more aggressive disease as supported by higher rates of intermediate- and high-risk prostate cancer[7]. In a South African population at a regional hospital in KwaZulu-Natal, black South African men present late with advanced disease[8].

Men with larger prostates will have more prostate cells and, consequently, produce more PSA, regardless of whether they have cancer or not. Using the absolute serum PSA level as a screening test has a number of flaws. Firstly, some men with normal or low absolute serum PSA levels have been found to have prostate cancer[9]. Secondly, many men with high absolute PSA levels do not have prostate cancer and, have instead benign prostatic hyperplasia (BPH)[9]. Thus, serum PSA alone has the potential of false-positive and false-negative results when used as a screening test for prostate cancer. Additional parameters that improve the test's diagnostic accuracy are likely to be beneficial, hence the development and use of additional parameters such as PSA velocity, PSAD and percentage free PSA[10].

PSA density (PSAD) is calculated by a formula and is used to help differentiate benign versus malignant disease of the prostate. It is calculated by dividing the PSA value in ng/mL by the prostate gland volume in cm cubed[11]. Prostate gland volume is measured either via trans-rectal ultrasound or MRI. A high PSA density indicates a higher risk of prostate cancer and PSAD values greater than 0.15 ng/ml/cm^3 are considered to be significant, strengthening the case for

performing a prostate biopsy. Lower PSAD values (<0.15 ng/ml/cm^3) are less likely to be associated with malignancy and favour observation rather than biopsy[11].

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Study design

Retrospective observational descriptive study.

Study population

The study population will be made up of patients attending a private urology practice at Netcare Waterfall City Hospital in Johannesburg, South Africa. This practice sees a wide range of insured patients from the greater Johannesburg area, representing all age and demographic groups.

Sampling strategy

All patients meeting the inclusion criteria in the study population over the study period will be included in the study

Statistical planning (variables / confounders)

Possible confounding factors include:

1. The presence of additional diagnoses such as acute or chronic prostatitis may falsely elevate the PSA level, even in small prostates.
2. There is potential for cross-over from the non-cancer to the cancer group if a patient is subsequently diagnosed with cancer after an initial negative biopsy. This may not be known to the investigators and may result in inaccurate results or incorrect conclusions being drawn.

The demographics of the study population, being mostly insured patients, may not accurately reflect the demographics of the country.

Sample size

The total sample size will be 227 patients, with a target of 136 patients with prostate cancer and 91 patients without prostate cancer.

Reliability and Validity

Validity will be achieved by completing the objectives of this proposal which are structured to answer the research question. The two arms of the study, one population with histopathologically diagnosed prostate cancer after biopsy and the second without, will allow assessment of the diagnostic accuracy and performance of the PSAD as an additional screening tool to assess for the risk of prostate cancer.
Reliability will be achieved by ensuring a sufficiently large sample size to obtain a meaningful result.

Inclusion / exclusion criteria

Once the study population is identified, the following criteria will be applied:

1. Inclusion criteria: men between the ages of 40 and 90 who have been assessed by DRE, had a serum PSA test and free PSA, undergone imaging of the prostate with prostate volume calculated and whom have undergone prostate biopsy.
2. Exclusion criteria: Men whom have not had a DRE, serum PSA test, free PSA, prostate imaging with prostate volume calculation and whom have not undergone prostate biopsy.

Data collection methods and tools

See appendix 2.

Data analysis techniques

Data will initially be captured and stored in tabular format in a Microsoft Excel spreadsheet. This will be password protected and only accessibly to the investigators. The raw data from the data capture sheets will be filed and stored in a locked cupboard for reference. No patient identifying data will be recorded, and each patient in the study will be allocated a study number for reference. Once data capture is complete, the data will be imported into statistics software.

Statistical analysis

Demographic and clinical characteristics will be analysed descriptively.
Categorical data will be described by frequency and percentages.
Diagnostic accuracy will be calculated for the DRE alone, PSA alone, PSAD alone, DRE and PSA, and DRE, PSA, free PSA and PSAD. The test's diagnostic accuracy will be assessed using standard measures: sensitivity, specificity, positive and negative predictive values where biopsy result is the gold standard. A ROC analysis will be used to establish whether alternative cut-points improve the predictive power of the test.
Frequency distributions of continuous data will be examined for normality using Shapiro-Wilk tests and means (SD) and medians (interquartile ranges) used as appropriate.
Subgroup comparisons of demographic/clinical factors associated with cancer will be performed using Chi-Square, t-test or Wilcoxon rank-sum test. Factors associated at the bivariate level will be included in a logistic model to determine independent risk factors. Odds ratios and 95% confidence levels will be reported.
Data will be analysed using Stata V13.1.

Study location

A private urology practice at Netcare Waterfall City Hospital in Johannesburg, South Africa**.**

Study period

01 July 2018 to 30 June 2019

Ethical considerations

Data will be collected retrospectively from hospital outpatient records. Patients will be assigned numbers and that will be recorded in the database. There will be no direct patient contact nor additional investigations as a result of this study. All data collected during the study will be stored in a password-protected database that will only be available to the investigators. The database will be stored in a password protected computer which will stay in a locked office with an alarm system. There are no other ethical considerations.

Appendix 2 – Data collection sheet

Reference Number	Age	Race	Prostate volume	PSA	Free PSA	Benign or Malignant on DRE	Clinical stage	Histology diagnosis	Histology Grade	Histology Tumour Extent
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										