CAVEATS OF PROSTATE CANCER DIAGNOSIS: DIAGNOSTIC UTILITY STUDY OF DIGITAL RECTAL EXAMINATION, PROSTATE VOLUME AND PROSTATE SPECIFIC ANTIGEN

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ABSTRACT

Objective: To investigate the diagnostic utility of prostate specific antigen (PSA), digital rectal examination (DRE) and prostate volume (PV) in arriving at diagnosis of prostate cancer (PCa) in a cohort of elderly male patients presenting with lower urinary tract symptoms (LUTS).

Methodology: This was a descriptive study of 120 elderly (> 50-years-old) male patients who presented with complaints of LUTS or were referred for further specialist management. All patients were s subjected to DRE on clinical examination, PV assessment on ultrasonography and a PSA screen. Prostate biopsy reports were recorded (positive or negative for PCa) once the patient underwent prostatectomy (transvesical prostatectomy-TVP, transurethral resection of prostate-TURP or transrectal prostate biopsy-TRPB).

Results: There were 120 patients with overall mean age of 71.03 ±9.19 years. Combining the three test variables, namely DRE, PV and PSA, the sensitivity was 61.8%, specificity was 70.8%, positive predictive value was 64.1% and negative predictive value was 68.7%. The most effective single test was DRE if applied alone, and the most ineffective was PSA if considered alone for diagnosing PCa. Patients with a positive DRE had 5.45 while raised PSA had 1.01 times higher odds to exhibit PCa as those having a negative DRE or a lower PSA. However, an increasing PV had no significant effect on the likelihood (OR =0.96, 95% CI, 0.928 to 1.008) of having a diagnosis of PCa.

Conclusion: A combination of the DRE, PV and PSA has good diagnostic capacity and should be used to better identify prostate cancer patients.

Key Words: Prostate cancer, Prostate specific antigen, Digital rectal examination, Prostate volume

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INTRODUCTION

Prostate cancer (PCa) has become one of the most common malignancy among men in the U.S. with a prevalence of 2,219,280 persons during 2009 and is the second leading cause of cancer mortality with a projected rate of 219,360 in 2020. For the year 2015, in U.S., it is estimated that 221,000 new cases will be diagnosed and 27,500 of these patients will be dying of prostate cancer[1,2]. These figures indicate the need for increased vigilance regarding diagnosis and management of these patients.

After approval from the U.S. food and drug administration (FDA) regarding PSA as a screening tool, PCa detection rates have plummeted from 1986 until recently when large meta-analyses have shown that PSA alone for screening purposes gives high rates of false positives and unnecessary investigation and overtreatment[3]. However, epidemiological studies have shown that there is variability of normal and abnormal PSA ranges according to geographic and ethnicity differences . It is also notable that prostate cancer differs in its mortality rates and invasiveness according to race and geographic location. GLOBOCAN 2012 has shown that PCa incidence is highest in Western societies as compared to Asia . The drawbacks of PSA screening combined with epidemiological variations of PCa worldwide have stimulated a robust research to identify other compounding tests for early and accurate detection of PCa in the high

risk populations[6,7]. Some of the most commonly combined clinical and radiological parameters in combination to PSA testing are DRE and ultrasonographically determined prostate volume (PV)[7-9]. These parameters have long been favoured as having compounding diagnostic impact for PCa diagnosis and initial decision making regarding further investigation and treatment[10].

Various risk-based and clinical parameter guided nomograms and calculators have also been introduced in order to better predict the chances of occurrence of PCa[11,12]. Ethnic and geographical variations in the incidence of PCa are also of note when taking into consideration the predictive factors and their clinical utility[13,14]. In this study we aimed to determine the diagnostic utility of combining serum PSA, DRE findings and prostate volume in arriving at the diagnosis of PCa, with an emphasis on answering the concern of clinicians worldwide as to how to determine the best possible algorithm in diagnosing PCa in light of the above mentioned parameters.

METHODOLOGY

This was a descriptive study conducted between January to December 2016 (12 months) at the Department of Urology, Lady Reading Hospital, Peshawar, Khyber Pakhtunkhwa, Pakistan. The data were collected prospectively. Approval of the institute's ethical committee was obtained and consent was obtained from all patients enrolled in the study. Data was collected about DRE, prostate volume, PSA and final histopathologic diagnosis once the patient underwent transurethral prostate resection, radical prostatectomy or transrectal prostate biopsy.

A DRE was regarded positive if prostate consistency was found to be hard, with obliteration of median sulcus, immovability or nodularity on palpation. A prostate volume of 35cc on trans-abdominal ultrasonography was regarded as cut-off limit for including cases of enlarged prostate along with finding hypoechoic regions . A PSA value was regarded as normal if it was 4 ng mL[7,15]. Prostate volume was calculated from the ultrasound findings of antero-posterior (AP), transverse (T) and cranio-caudal (CC) dimensions and putting these values in the ellipsoid formula (AP T CC 6)[16]. Inclusion criteria were patients above the age of 50 years, those who presented with complaints of lower urinary tract symptoms (LUTS) and those with any or a combination of the following three findings; positive DRE on clinical examination; or increased prostate volume (PV) on trans-abdominal ultrasonography. A prostate volume of 35 cc or above was included; or elevated prostate specific antigen (PSA). Prostate biopsy report was obtained. Exclusion criteria were patients who underwent preoperative therapies, such as active surveillance, hormone therapy and radiation therapy; and patients with incomplete records.

All descriptive statistics were presented as mean ± standard deviation (SD) for the continuous variables while for categorical variables the data were presented in frequency and percentages. A linear regression analysis model was developed which included DRE, PV, PSA in order to determine the utility of the combination of these tests in correctly predicting a positive tissue diagnosis. Receiver operating characteristic (ROC) analyses were performed for the different tests and individual curves were obtained taking the histopathology diagnosis as the final state variable. The linear regression classification table was used to determine sensitivity, specificity, positive predictive value and negative predictive value of the model which combined the three test variables (DRE, PV and PSA) in correctly predicting the occurrence of PCa on histopathology examination. A p value of <0.05 was considered statistically significant. All tests were 2-tailed and all analyses were performed using IBM SPSS statistics version 22.0 (SPSS Inc. Chicago, IL).

RESULTS

120 patients with overall mean age of 71.03 ±9.19 years, mean PSA value of 38.68 ±23.14 ng mL and a mean prostate volume of 60.55 ±9.69 cc. Clinically DRE was rated positive in 59 (49.2%) patients while histopathological PCa diagnosis was established in 55 (45.8%) specimens. The frequency distribution of the above clinical parameters classified according to positive or negative PCa diagnosis is presented in Table 1. Individual ROC curve analysis for DRE showed a sensitivity of 67.3% and specificity of 66.2% with area under the curve (AUC) value of 66.7%. For PV, the sensitivity of 78.2% and a specificity of 35.4% and AUC of 57.4% while for PSA, the sensitivity of 54.5% and a specificity of 58.5% with an AUC of 50.6%.

A logistic regression analysis was performed to ascertain the effects of DRE, PV, and PSA on the likelihood that patients have a positive biopsy for PCa. The logistic regression model was statistically significant, 2(3) =17.66, p =0.001. The model explained 18.3% (Nagelkerke R2) of the variance in PCa diagnosis and correctly classified 66.7% of cases with an AUC of 71.3% (Table 2 & Figure 1). Combining the three test variables, the sensitivity was 61.8%, specificity was 70.8%, positive predictive value was 64.1% and negative predictive value was 68.7% (Table 2 & Figure 1). Of the three predictor variables only one was statistically significant: DRE (as shown in Table 1). Patients with a positive DRE had 5.45 while raised PSA had 1.01 times higher odds to exhibit PCa as compared to those having a negative DRE or a lower PSA. However, an increasing PV had no significant effect on the likelihood (OR =0.96, 95% CI, 0.928 to 1.008) of having a diagnosis of PCa (Table 3).

Table 1: Distribution of variables according to histopathologic diagnosis

Variables	Positive Histopathology (n =55)	Negative Histopathology (n =65)
Age	Mean: 70.44 ± 8.72 years	Mean: 71.54 ± 9.62 years
Prostate volume	Mean: 61.80 ± 9.75 cc	Mean: 59.49 ± 9.58 cc
PSA	Mean: 39.40 ± 25.25 ng mL	Mean: 38.08 ± 21.37 ng mL
DRE	Positive 37 (67.3%)	Positive 22 (33.8%)
	Negative 18 (32.7%)	Negative 43 (66.2%)

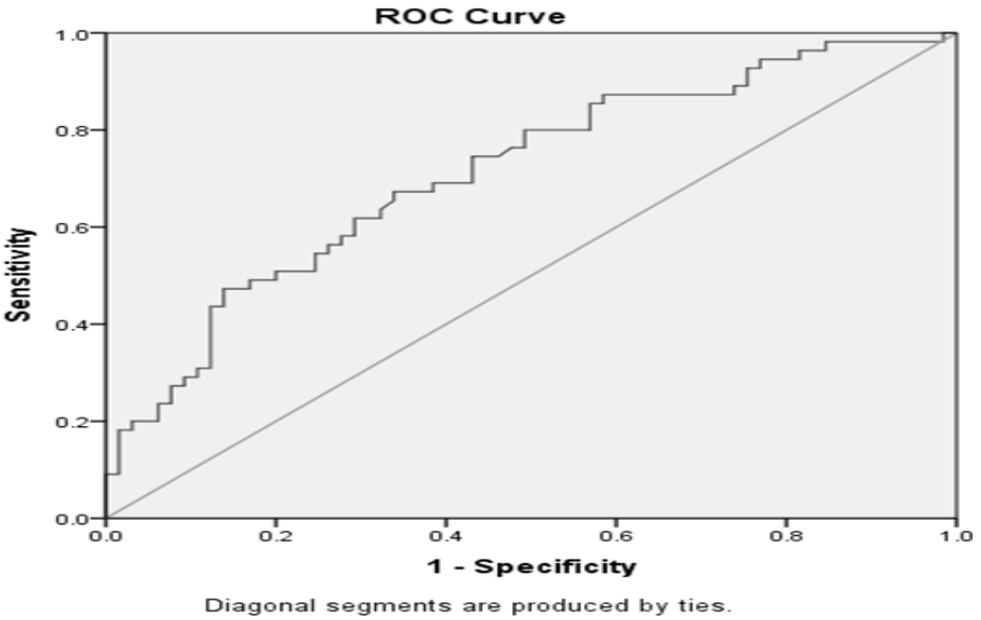
Table : Classi cation table for test predictability

Observed		Predicted		
		Histopathology		Percentage Correct
		Positive	Negative	
Histopathology	Positive	34	21	61.8
	Negative	19	46	70.8
Overall Percentage				66.7
Sensitivity: 61.8%, Speci city: 70.8%, Positive predictive value: (34 34 19) x 100 = 64.1% Negative predictive value: (46 46 21) x 100 = 68.7%				

Table 4: Linear regression analysis for study variables

Linear Regression Analysis		B	S.E.	Sig.	Exp(B)	95% CI for EXP(B)	
						Lower	Upper
Step 1[a]	PSA1	.014	.010	.152	1.014	.995	1.034
	Prost_vol	-.033	.021	.115	.967	.928	1.008
	DRE(1)	1.695	.453	.000	5.447	2.242	13.236
	Constant	.795	1.296	.539	2.215		

Figure 1: The Receiver operating characteristic curve for predictability of the clinical tests co ined (digital rectal exa ination, Prostate volu e and prostate speci c antigen)



DISCUSSION

Over the last twenty years various clinical and laboratory parameters have been studied in order to improve the correct diagnosis of PCa and to timely institute treatment strategies[11,17-19]. When taken individually for predicting the presence of PCa in screened populations, the commonly used tools such as DRE, PV and PSA have been known of weaknesses in one or many aspects due to which their utility is reduced and cannot be relied upon individually[2,7,15]. However, it has been shown that prostate volume was the most significant factor for the detection of prostate cancer with a sensitivity and specificity were 61.1% and 73.1% respectively[20]. Furthermore, combining multiple clinical, laboratory and radiological parameters increases the sensitivity and specificity of these factors and can be predictably relied upon[2,7,12].

Walsh et al in a prospectively collected data has investigated the diagnostic value of DRE as a screening method for PCa and has shown that DRE alone has a sensitivity of 80% and a specificity of 40%. It was observed that 76% of patients who were investigated further on the basis of an abnormal DRE were having high grade PCa . Our findings are in close agreement with this study where we noted a sensitivity of 67.3% and specificity of 66.2% with AUC value of 66.7%. These findings show that DRE is an effective way to screen patients on clinical examination and to investigate them further for PCa. However, despite its effectiveness, ease of performance and virtually no financial cost of the test itself, the results also show that it cannot be relied upon individually as it does have false positive and negative rates. In our study we noted that 33.8% of patients were classified as false positive while 32.7% as false negative.

Ahn et al[19] have developed a nomogram using the clinical, radiologic and laboratory parameters from the Korean population in order to better predict the high risk patients for prostate cancer in the below 10 ng mL PSA level. They have shown that age, PV and PSA were significant individually as well as when combined to make a clinical scale. Regarding prostate volume, they have shown that an increased volume is independently associated with higher clinical risk for prostate cancer. In a multivariate analysis, PV has been shown to be significant in predicting PCa when combined with patient age and PSA levels ($p < 0.001$)[19]. In our study, however, we found that individually PV is not a reliable indicator of the risk of PCa. In the studies by Ahn et al[19] and Kim et al[20], only patients with raised PSA were included. So in patients with raised PSA, PV was found to be significant in detecting Pca. While in our study, patients with a combination or any of 3 factors were included i.e with raised PSA or raised PV or abnormal DRE. In a ROC curve analysis, we found a sensitivity of 78.2% and a specificity of 35.4%. Higher sensitivity and lower specificity means that if PV is used individually, a high number of false positives will be encountered. False positive in cancer diagnosis are associated with unnecessary investigations and treatment, some of which may be invasive and bear adverse effects, therefore, on the basis of our study we recommend not to use PV individually as a sole screening measure.

In a large case control study from Sweden, Holmström B et al[21] has evaluated the diagnostic utility of PSA in early detection of PCa. Like many other studies[3,15,22] they have concluded that PSA has poor predictive power especially in younger age patients when the PSA is low and a quarter of these patients are later found of having PCa. Additionally, they have failed to provide a definitive cut-off value for PSA which is capable of predicting of a high grade PSA[21]. We found that in our patients 9.1% had a PSA level of below 10 ng mL who were found to have a positive prostate histopathology for PCa while in 51.67% patients the PSA levels were above 10 ng mL and negative histopathology for PCa. In a ROC curve analysis, we noted that with a mean PSA of 38.7%, a sensitivity of 54.5% and a specificity of 58.5% was attained which is a very poor test characteristic in order to better predict truly positive and negative patients. However, in a combined model with the overall sensitivity of 61.8% and a specificity of 70.8%, these three clinical parameters can identify true positive PCa in nearly 65% of patients (positive predictive value = 64.1%). On the basis of our findings, we recommend to utilise combination of these clinical, laboratory and radiological tests to better identify the high risk patients.

LIMITATIONS

The weaknesses of our study are its lower sample size and no external control groups. These weaknesses can be alleviated by conducting large randomised studies, which can give us better results in identifying the clinical tests required for positively identifying true PCa patients. An external control group will help us ascertain as to what reference levels of these clinical parameters should be consulted in our population.

CONCLUSION

Prostate cancer diagnosis is better established if clinical, laboratory and radiological tests are combined. The application of any of these tests individually have high rates of false positive results which themselves have negative impact in terms of unnecessary alarm for patient and doctor as well as overtreatment and unnecessary investigative studies .

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CONTRIBUTORS

AUR conceived the idea, planned the study, and drafted the manuscript. IUK and BA helped acquisition of data, did literature search and statistical analysis. MAJ critically revised the manuscript and supervised the study. All authors contributed significantly to the submitted manuscript.