Redefining Serum PSA Cut-off in Indian Population to Avoid Unnecessary Biopsies - A Descriptive Study

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Research Article

Abstract

INTRODUCTION:

Prostate cancer is the second most common cancer diagnosed in men with an estimated 1.2 million diagnoses worldwide. The incidence of Prostate cancer is higher in western countries and low in Asian countries. The need for prostate biopsy is based on PSA levels. The general cut off PSA value for the Indian population is 4.0 ng/mL. The reported cancer detection rate of TRUS-guided biopsies is around 30 percent in western countries and lesser in Asian countries, including India, particularly for serum PSA values less than 20 ng/mL indicating that many of the Indian patients are subjected to unnecessary biopsy which adds up to distress to these patients.

PURPOSE:

To determine the cancer detection rate of TRUS-guided prostate biopsy in the Indian population at different serum Prostate-Specific Antigen levels and determine a PSA cut-off level to avoid unnecessary biopsies.

MATERIALS AND METHODS:

All symptomatic patients who underwent TRUS guided biopsy for raised serum PSA levels between 4 - 20 ng/mL were included. The patients were categorized into four groups corresponding to the PSA levels ranging between 4-6 ng/mL, 6- 8 ng/mL, 8-10 ng/mL, and 10-20 ng/mL respectively, and cancer detection rate in each group were statistically analyzed.

RESULTS:

The sensitivity, specificity, and positive predictive value of TRUS guided biopsy are 75%, 95%, and 98% respectively in our study. The overall cancer detection rate of TRUS biopsy in our series was 18.4%. The PSA cut-off to do biopsy was derived by ROC curve as 8.9 ng/ml for all the men.

CONCLUSION:

The PSA cut-off of 4.0 ng/mL is currently used as an indication for biopsy among men of all ages in the Indian population. We recommend a raise in cut-off to 8.9 ng/mL to avoid unnecessary TRUS-guided biopsies in the Indian population.

Background:

Prostate cancer is the second most commonly diagnosed cancer in men worldwide with an estimated 1.1 million diagnoses accounting for 15% of cancers diagnosed [1]. The incidence of autopsy detected Prostate Cancer (PCa) is roughly equal worldwide. However, there is a wide variation in the incidence of

PCa diagnosis between geographical areas being higher in Australia, North America and Europe countries mostly due to the use of prostate-specific antigen (PSA) screening tests and the aging population. The incidence of is low in the Asian countries[2]. India is the second most populous country in the world with an estimated population of 51 million men above 60 years of age [3]. Although the incidence of prostate cancer is increasing in the developed world, it remains under-diagnosed in the developing world where it often presents late. Serum Prostate specific antigen (PSA) is used as a diagnostic as well as prognostic marker of PCa since its discovery. biopsy of the prostate forms the cornerstone in establishing the diagnosis of PCa. The cancer detection rates in India have been lower than the western world for serum PSA values that fall in the grey zone: 4–10 ng/dL, implying that PSA levels vary with race and ethnicity. However, a strict PSA screening protocol has not been adopted in India owing to the lower incidence of PCa. The reported cancer detection rate of Trans-Rectal Ultrasonography (TRUS) guided prostate biopsies ranges between 30–40 percent in western countries and about 20 percent in Asian countries, including India[2]. This study was conducted to find out the cancer detection rate of TRUS guided prostate biopsy in Indian population in the standard grey zone levels of serum PSA and to re-evaluate the need for TRUS guided biopsies in the same setting to curb the burden of prostate biopsies in Indian population. MEASUREMENT of serum prostate-specific antigen (PSA) is widely used as an aid in the early detection of prostate cancer.[1] A limitation of PSA testing has been its relative lack of specificity within the 4.0- to 10.0-ng/mL range, a diagnostic gray zone in which prostate cancer is present in only 25% of patients. Most patients with prostate cancer and a PSA level less than 10.0 ng/mL have early-stage disease, whereas more than half of the patients with PSA levels above 10.0 ng/mL have advanced disease.[1] Thus, the detection of prostate cancer in its potentially curable stages requires the use of low PSA cutoffs for screening, which leads to many unnecessary biopsies.

Materials And Methods:

The study population included a total of 125 men between 45 to 80 years with elevated serum PSA in a single institution. All patients who were subjected to TRUS and TRUS guided biopsy for serum PSA levels between 4 ng/mL and 20 ng/mL, irrespective of digital rectal examination (DRE) findings from August 2017 to August 2020 were included. Patients with recent history of urinary tract infection, urinary retention, per-urethral instrumentation or catheterisation, serum PSA levels of more than 20 ng/dL and patients who were taking 5-alpha reductase inhibitor were excluded from this study. Final HPE report suggestive of chronic prostatitis were also excluded from this study.

Serum PSA levels, TRUS findings and TRUS guided biopsy data were prospectively collected, on a standardised proforma at the time of biopsy and combined with the histological findings. Only patients with complete data sets were included in the study. Clinical parameters included patient demographics including age, volume of prostate, Total PSA value, and findings on TRUS.

Absolute PSA values were recorded and subsequently subdivided for the purposes of analyses into four groups: A, B, C and D corresponding to the PSA levels ranging between 4–6 ng/mL, 6–8 ng/mL, 8–10

ng/mL, and 10–20 ng/mL respectively and cancer detection rate in each group were statistically analysed.

TRUS was performed using a Mindray DP-50 diagnostic ultrasound machine with a 7.5-MHz transrectal probe. Informed consent was obtained. All patients were given tablet bisacodyl (10 mg) along with tablet ciprofloxacin (500 mg) one night prior to biopsy. Post-biopsy, oral antibiotics were continued for three days. Majority of the patients received local anaesthesia with either intrarectal instillation of 20 mL of 2% lignocaine jelly or periprostatic needle infiltration of local anaesthesia.

The findings on TRUS were documented for both the right and left lobe as follows: the presence of hypoechoic areas and/or calcifications in the periphery and the centre of the glands as well as the presence of capsular distortion. The prostate gland was assessed in the axial plane where the transverse and antero-posterior measurements were taken at the point of maximum diameter, followed by a paramedian longitudinal measurement in the sagittal plane.

The volume was calculated using a standard pre-programmed formula *{π/6 × (transverse diameter) × (antero-posterior diameter) × (superior−inferior diameter)} based on an ellipsoid shape.*

The biopsies were taken using 17 mm tip Bard biopsy gun and sent for histopathological examination and reports were duly collected.

STATISTICAL ANALYSIS:

The data were compiled with the help of Microsoft Excel® application and statistical analysis was performed by a biostatistician. SPSS-28 statistical software was used to calculate the sensitivity, specificity, positive predictive value, negative predictive value and receiver operating characteristic curve was plotted to find the optimal cut-off value. The age, prostate size and grey zone PSA levels between benign and malignant disease patients were compared using Mann-Whitney test. A p-value less than 0.05 was considered to be significant.

Results:

A total of 125 patients were included in the study. 21 patients were diagnosed with carcinoma prostate.

Table 1
Demography and PSA, TRUS and Biopsy correlation in our study.

Observation	All Patients	Malignant Disease	Benign Disease	p-value
Total patients	125	21	104	-
Age (years)	65(48−90)	64.5(45−80)	65(48−90)	> 0.05
Prostate Size (grams)	55.16(25−110)	43.38(25−70)	57.40(35−110)	< 0.001
Total PSA (ng/mL) (median)	09.67(4.2−19.59)	15.05 (9.41−19.59)	7.715 (4.2-18.57)	> 0.05

Mean age of the study participants was 66 ± 8.9 with minimum age 48 and maximum age 90 years. There was no significant difference in the age group of patients with benign and malignant disease. Patients with malignant disease had significantly smaller prostate gland size than patients with benign disease (40 vs 50; p = < 0.001)[Table 1]. The sensitivity, specificity, positive predictive value and negative predictive value of TRUS guided biopsy are 75%, 95%, 98% and 100% respectively in our study. The number of PCa in category A, B, C, and D were 0,0,1 and 26[Figure 1]. The overall cancer detection rate of TRUS biopsy in our series was 18.4%. Out of 79 patients in the grey zone (4−10 ng/mL), only one patient had malignancy. The cancer detection rate in the grey zone (4−10 ng/ml) was 1.27%. The overall cancer detection rate of TRUS biopsy in our series was 18.4%. The cancer detection rates in groups A, B, C, and D were found to be 0%, 0%, 4.76%, and 43.47% respectively [Table 2], implying that 49.43% of the patients underwent unnecessary biopsy in our study. The PSA cut-off to do biopsy was derived by ROC curve as 8.9 ng/ml for all men [Figure 2].

Table 2
– The Cancer detection rate in each category of our study.

GROUP	PSA range (ng/mL)	Total patients	Benign	Cancer Prostate	Cancer Detection Rate (Percent)
A	4 to 6	35	35	-	-
B	6 to 8	23	23	-	-
C	8 to 10	21	20	1	4.76%
D	10 to 20	46	26	20	43.47%

Discussion:

The highest incidence of PCa is reported in Australia/New Zealand, Northern & Western Europe and North America (79.8-111.6 per 1,00,000 population)[3]. In Africa (10.6−61.7 per 1,00,000 population), the southern African nations have higher incidence of PCa than north African nations, with highest incidence reported in Nigeria[3]. Among Asian countries (4.5−10.5 per 1,00,000 population), the incidence varies with

lowest rates being in Iran and highest rates in Philippines[3], with India falling in-between the two extremes[4]. The incidence of PCa in India has been reported to be ranging between 2 and 11.1 per 1,00,000 population in various population-based cancer registries all over India[5].

Our study shows low positive predictive value for PCa in the grey zone range (4–10) ng/mL of serum PSA. Our study proves that patients can be counselled and reassured regarding higher probability of benign outcome at serum PSA range (4–10) ng/mL.

Major studies conducted in India analysed the PSA levels between grey zone and PSA levels above 10 ng/mL. Agnihotri et al., had an overall cancer detection rate of 34.6% and for serum PSA ranges of (4–10) was 15.2% irrespective of DRE findings[6]. They had suggested raising the serum PSA cut off in symptomatic men with negative DRE for TRUS biopsy in India to 5.4 ng/mL to avoid 10% unnecessary biopsies. Agarwal et al., had a overall cancer detection rate of 34.6 % with 28.3 % detection rate in the grey zone levels. They suggested an increased sensitivity and specificity of biopsy yield for a cut off of 6 ng/mL[7]. Chavan et al., had an overall cancer detection rate of 8.7% with 2.3% detection rate in the grey zone levels. Furthermore, they suggested raising the cut-off level to 20 ng/mL in Indian population for biopsy[9]. These reports reflect the low cancer detection rates of TRUS biopsy in grey zone PSA levels in Indian population which correlates with our study. In our study we have further stratified the grey zone levels into 4 categories and analysed each category statistically.

Many studies from other countries all over Asia have reported wide variations in the TRUS biopsy yield. Yu et al., from Taiwan a cancer detection rate of 14.6% in patients with serum PSA between (4.1–20) ng/mL [9]. Narayanaswamy et al., from Kuwait reported lower yield for serum PSA ranges of (4–10) and (10–20) ng/mL [10].

A large retrospective study from China by Na R et al., reported lower yield for patients with serum PSA less than 10 ng/mL and (10–20) ng/mL despite overall high yield[11]. Two studies from Singapore by Lee et al., and Teo et al., confirmed the lower yield for serum PSA below 10 ng/mL which was less than 21% [12,13]. In contrast to other Asian studies, the study by Lee et al., reported higher yield of 38.4% for serum PSA range of (10–20) ng/mL [12]. Another large study by Teoh et al., from Hong Kong reported lower yield for symptomatic men with normal DRE with serum PSA below 20 ng/mL (22%)[14]. Two studies from Japan by Miyoshi et al., and Imazu et al., were the only studies from Asia showing much higher TRUS biopsy yield in contrast to all other Asian studies [15,16].

The European studies showed much higher yield of TRUS biopsy as compared to Asian studies. Two studies from North America showed high TRUS biopsy yield more than 35%. The largest study was reported by Orozco et al., from the Unites States, showing higher overall yield despite performing 6-core biopsies[17].

Hence, other than few exceptions, Asian population (including India) have a lower TRUS biopsy yield as compared to other continents, especially for serum PSA values less than 20 ng/mL. Our study has

confirmed the above findings. Hence the traditional serum PSA cut off of 4 ng/mL followed in western countries gives lower TRUS biopsy yield for Indian population. The current cut offs for PSA have high sensitivity and low specificity. Hence adjusting or raising the serum PSA cut offs for Indian population can increase the TRUS biopsy yield without increasing the false negative rate, thus avoiding unnecessary biopsies. Our study has a very low rate of post-biopsy complications requiring admission indicating that the procedure is safe if performed with accurate technique under antibiotic cover.

Limitations:

The limitation of our study is that repeat biopsies were not done in patients with high serum PSA and had negative initial biopsy. Also, all the patients with serum PSA below 4 ng/mL were not subjected to TRUS biopsy.

Conclusion:

Currently, a single demarcation between normal and elevated PSA values, 4.0 ng/mL, is used as an indication for biopsy among men of all ages in the Indian population. Our study concludes that using the PSA cut-off value of 4 ng/mL derived from western literature has a lower positive predictive value in the Indian population as compared to western counterparts. Hence, we recommend that the cut-off be raised to 8.9 ng/mL to curb the burden of unnecessary TRUS guided biopsies in the Indian population.

Declarations

Ethical approval has been obtained from the Institutional ethical committee, Stanley medical college. We also declare that there are no competing interests.

Abbreviations

TRUS
Trans-rectal ultrasonography
PSA
Prostate specific antigen
PCa
Prostate cancer
ng/mL
nanogram per millilitres
MHz
Mega Hertz
mm
milimetres
DRE

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Figures
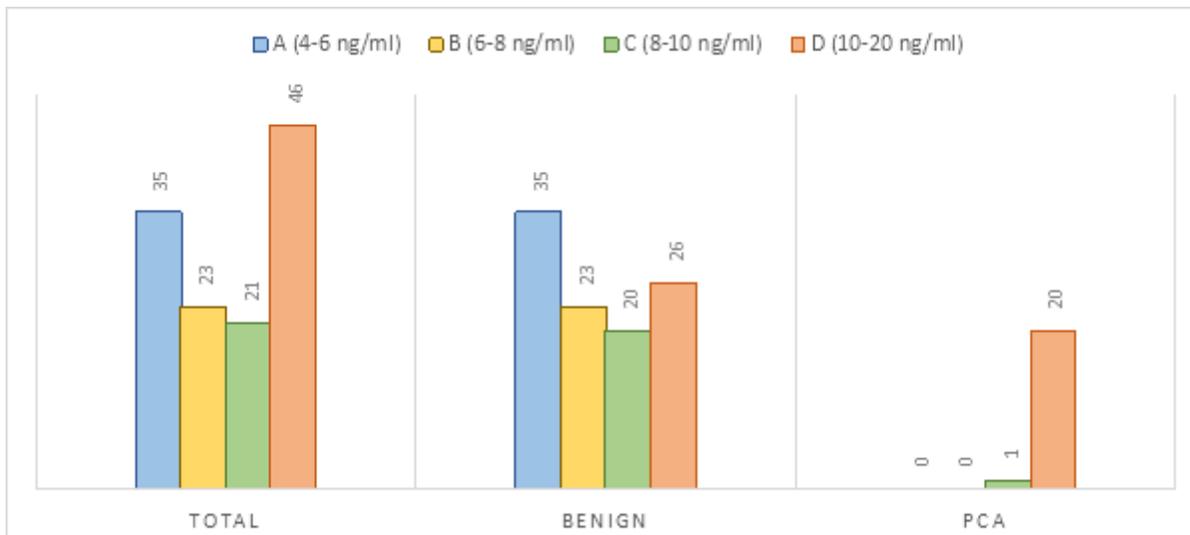
Figure 1

The incidence of benign and PCa in each category of PSA levels
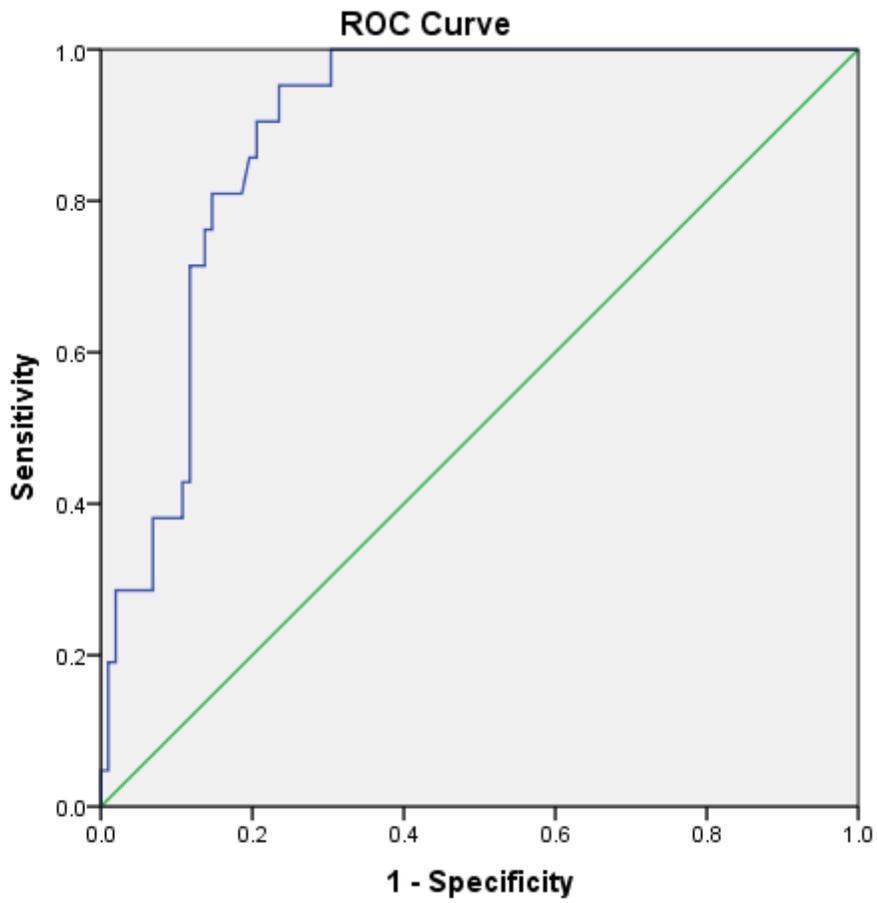
ROC Curve

Diagonal segments are produced by ties.

Figure 2

PSA cut-off of 8.9 ng/ml derived from ROC curve