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AGE SPECIFIC PROSTATE - SPECIFIC ANTIGEN AND PROSTATE VOLUME IN NON-PROSTATIC CARCINOMA MEN – A CROSS-SECTIONAL STUDY

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ABSTRACT

Introduction: A common biomarker for the early identification of prostate diseases, including prostate cancer, is prostate-specific antigen (PSA) testing. But benign disorders like benign prostatic hyperplasia (BPH) can also cause an increase in PSA levels, which can result in diagnostic conundrums and needless biopsies. A PSA cutoff of 4.0 ng/mL is widely utilized worldwide, although not all age groups or demographics may benefit from this set level. Since PSA levels are known to be influenced by age and prostate volume, a number of studies indicate that setting age-specific PSA reference ranges may improve diagnostic precision and lower overdiagnosis. Redefining PSA rules to suit local demography is becoming more and more necessary in the Indian setting, where there is a lack of population-based and region-specific data. This study aimed to establish age-specific PSA reference ranges and examine their

association with Prostate Volume (PV) in a North Karnataka population to enhance diagnostic accuracy and minimize unnecessary biopsies.

Methodology: Conducted in a tertiary care hospital, 130 non-malignant BPH cases were analyzed.

Results: The mean PSA increased with age, with 95th percentile values ranging from 1.03 ng/mL (41–50 years) to 5.2 ng/mL (81–90 years). Compared to other Indian and global studies, our findings reinforce the need for region-specific PSA thresholds.

Notably, a strong and highly significant positive correlation was found between prostate volume and PSA levels, indicating that prostate size substantially contributes to PSA elevation in men without prostate cancer.

Conclusion: Age and prostate volume significantly influence PSA levels in men without prostate cancer. Establishing age-specific, region-based PSA reference ranges can improve diagnostic accuracy. This approach may help reduce unnecessary biopsies in benign prostate conditions. Prostate volume-adjusted PSA reference ranges might enhance clinical judgment.

Keywords: Prostate-Specific Antigen (PSA), Prostate Volume, Benign Prostatic Hyperplasia (BPH), Age-specific reference range, Non-malignant prostate conditions, Indian population

INTRODUCTION

As per the Global Cancer Statistics, Prostate Cancer (PCa) is one of the most common forms of Cancer worldwide **[1]**. Prostate cancer is becoming increasingly prevalent in India. It ranks as the third most common cancer in Indian men **[2]**. While it is historically less common compared to Western countries, the incidence is rising, possibly due to improved diagnostic practices and changing lifestyles **[3]**. Prostate cancer frequently grows slowly, and symptoms might not appear until the disease has progressed **[4]**. Close to 14% of (PCa) are diagnosed at the metastatic stage **[5]**. Hence, early detection of PCa and differentiation from non-carcinoma conditions such as Benign Prostatic Hyperplasia (BPH) is essential to improve treatment efficacy and increase survival rates. Benign Prostatic Hyperplasia (BPH) is a non-malignant enlargement of the prostate gland commonly seen in aging men and is a leading cause of lower urinary tract symptoms.

Prostate Biopsy is still the gold standard for confirmation of diagnosis. Despite its limitations, Prostate Specific Antigen (PSA) testing is an important and accepted diagnostic tool for PCa early diagnosis, especially in asymptomatic men with earlier negative biopsy and also in BPH patients **[6, 7, 8]**. Due to the consequences of regional

and cultural diversity; each community has its own reference range. Indian studies highlight that PSA levels and the prevalence of prostate conditions may differ from those in Western populations, indicating the need for tailored screening guidelines **[9, 10]**.

Age is one of the main risk factors and it increases the chance of prostate cancer **[11, 12]**. In a healthy person without PCa, the blood PSA concentration increases by around 3.2% (0.04 ng/mL) per year **[13]**. Since age and serum PSA levels correlate, it is necessary to have a single reference range for men across all age groups to guide the clinicians **[14]**.

Currently, PSA values of 4.0 ng/mL are regarded as normal in most of the clinical setups. However many with higher PSA levels between 4 and 10 ng/mL do not have prostate cancer. This has necessitated a debate and initiated several studies to develop age-specific reference ranges. Adjusted PSA thresholds are suggested for Indian men to optimize early detection of prostate cancer to avoid "Unnecessary" biopsies. As the prostate enlarges, it can lead to elevated Prostate-Specific Antigen (PSA) levels, which complicates the differentiation between benign and malignant conditions. Prostate volume (PV), therefore, becomes a crucial parameter in evaluating PSA levels and guiding clinical decisions **[15, 16, 17]**. Hence, the present study aimed to determine the Age-Specific PSA and Prostate Volume in BPH patients in North Karnataka population.

MATERIALS AND METHODS

The present study was conducted in a tertiary care hospital in North Karnataka. All adult men aged 40-80 years visiting the Urology Department at the Hospital and willing to participate in the study and to undergo serum PSA determination, transrectal ultrasound (TRUS) examination, and potential prostate biopsy were included in the study. Although agreements to participate were received from all patients through informed consent, all the participants had these tests done at their own expense. The confirmed cases of Prostate Cancer were excluded from the study and all other participants with BPH were included. A patient information sheet detailing the entire protocol of the study was handed over to the participants. Specimens were measured for PSA using Roche Cobas Pro automated immunoassay instrument. The electrochemiluminescence immunoassay method was used for measurements.

For analysis, the variable "age" was divided into various groups. Simple descriptive statistical analyses were carried out in SPSS Version 20.0 and quartiles and 95th percentiles were calculated for each age group. Prostate volume (PV) was measured using transrectal ultrasonography (TRUS) and analyzed across age groups. To assess the relationship between age, PSA levels,

and prostate volume, Pearson's correlation coefficient (r) was used. A p-value of less than 0.05 was considered statistically significant.

RESULTS

All the patients included in the study were from North Karnataka. Of the 202 men who underwent PSA and Biopsy 130 men fulfilled the inclusion criteria as they were confirmed cases of BPH. About 79% of the participants belonged to the age group of >60 years old and accounted for the study cohort. This cohort was categorized into five age groups 41–50, 51–60, 61–70, 71–80, and 81-90 years. The mean PSA of our study cohort was 1.9 ng/mL (SD ± 1.37) and the median PSA was 1.66 ng/mL. With the increase in the age for each decade, a statistically significant increase in the PSA values was observed till 80 years of age. The mean age-specific PSA increased with age and was 0.61, 1.77, 1.84, 2,04, and 2.58 for ages ≤40, 41–50, 51–60, 61–70 and 71–80 It is depicted.

The cutoff age-specific PSA, which is defined as the 95th percentile PSA, was 1.03 ng/mL for men 41-50 years. The 95th percentile PSA in the fifth decade was 3.91 ng/mL and further increased to 4.00 ng/mL in the sixth decade and 4.74 ng/mL in men between 71- 80 years and 5.2 in men between 81-90 years of age. The 95th percentile for the overall study cohort was 3.78 ng/mL, and given in **Table 1**.

As mentioned in **Table 2**, Prostate volume increased progressively with age. Correlation analysis revealed a weak but statistically significant positive correlation between age and prostate volume ($r = 0.194$, $p = 0.027$). A weak positive correlation was also observed between age and PSA levels, though it did not reach statistical significance ($r = 0.161$, $p = 0.067$). Notably, a strong and highly significant positive correlation was found between prostate volume and PSA levels ($r = 0.629$, $p < 0.001$), indicating that prostate size substantially contributes to PSA elevation in men without prostate cancer.

Table 1: Age-Specific Distribution of PSA Across Percentiles

Age Group	Mean	Percentile 05	Percentile 25	Percentile 75	Percentile 95	Percentile 99
41-50	.61	.09	.30	.81	1.03	1.03
51-60	1.77	.55	.70	2.90	3.91	3.99
61-70	1.84	.40	.78	2.75	4.00	6.90
71-80	2.04	.23	1.01	3.00	4.74	7.92
81-90	2.58	.27	.31	3.85	5.20	5.20

Table 2: Correlation between Age, PSA and PV

Variables Compared	Pearson Correlation (r)	p-value	Interpretation
Age vs Prostate Volume (PV)	0.194	0.027	Weak positive correlation ($p < 0.05$), statistically significant
Age vs PSA	0.161	0.067	Weak positive correlation, not statistically significant
PV vs PSA	0.629**	< 0.001	Strong positive correlation, highly significant ($p < 0.01$)

DISCUSSION

PSA levels are typically considered normal if they are between 0 and 4.0 ng/mL, but cancer can still occur within this range, and also intermediate ranges between 4ng/ml to 10 ng/ml and >10 ng/ml is still debatable **[18, 19, 20]**.

Many benign illnesses, such as prostatitis and benign prostatic hyperplasia, which are said to occur more frequently beyond the age of fifty do raise the PSA levels **[21, 22]**. The present study is a cross-sectional study where all men clinically evaluated and non-malignant confirmed cases were included in the study. This can be contrasted with the large retrospective study reported for healthy Indian men published in 2023 **[23]**. However it should be warranted that Prostate Cancer is asymptomatic. Hence, in such men, Prostate Cancer cannot be ruled out. Our study on the other hand can be justified as these subjects are clinically proven non-malignant BPH cases. This could be the reason for the small sample size when compared to other Indian studies, which were either observational, data-based or studies conducted on healthy subjects. Our study also has shown lower values for the age group 81-90 and this may be attributed to the fact that there were very few participants. Below are some of the Indian studies tabulated below comparing their mean PSA which show variation within the same ethnicity **[10, 23-27]**.

The present study can also be compared with various studies **(Table 4)** conducted for other Asian groups which reveal the 95th percentile PSA value for a specific age group **[13, 28-33]**.

Given that, prostate cancer predominantly affects older individuals, with PSA levels typically rising with age, this would enhance diagnostic accuracy for non-malignant conditions and help prevent unnecessary and often unwelcome biopsies. This study therefore highlights the necessity of reevaluating the serum PSA cut-off to account for a person's age and race for any clinical setup. When the age and race-specific reference interval for PSA is taken into account, it becomes a more powerful biomarker for identifying people with early-stage cancer. However, variations within the same ethnicity necessitate the need to reevaluate and establish reference intervals for each clinical setup.

Prostate volume (PV) and blood levels of prostate-specific antigen (PSA) were shown to be strongly and significantly positively correlated in males without prostate cancer. This result demonstrates that, even in benign diseases like benign prostatic hyperplasia (BPH), prostate size significantly contributes to elevated PSA. Serum PSA concentrations naturally rise with gland growth because PSA is produced by the prostate's epithelial cells. This physiological increase in PSA can make it more difficult

to interpret elevated readings clinically because it frequently resembles those observed in prostate cancer and may result in needless biopsies. These findings provide credence to the idea that measuring prostate volume in addition to PSA testing can improve diagnostic precision **[34, 35, 36]**.

The significant link found in this study is consistent with previous research as depicted in **Table 5**, highlighting the value of Prostate Volume **[37, 38, 39]** as a more accurate indicator for assessing prostate illness. Overdiagnosis and overtreatment may result from relying just on absolute PSA results, particularly when using a fixed threshold such as 4.0 ng/mL, without taking individual anatomical variances into account. Prostate volume may help prevent false-positive cancer referrals and improve the ability to distinguish between benign and malignant diseases in routine evaluations. According to our research, setting age-specific and prostate volume-adjusted PSA reference ranges might enhance clinical judgment and risk assessment, especially for Indian men.

Table 3: Comparison of mean prostate-specific antigen in the current study with other Indian studies

Age cohort	Current study	Ganpule *et al.*	Gupta *et al.*	Agrawal *et al.*	Malti *et al.*	Addla *et al.*	Shenoy *et al*
Study cohort	137	1899	1253	1772	583	86,728	5199
Mean PSA (overall)	1.89	-	1.12	1.76	1.4	1.213	-
41–50 years	0.61	1.0	0.78	1.22	1.14	0.798	1.33
51–60 years	1.77	1.2	1.03	1.97	1.31	1.1196	1.84
61–70 years	1.84	1.5	1.31	2.08	1.41	1.7052	2.74
71–80 years	2.04	1.9	1.63	-	1.67	2.3952	3.28
>80 years	2.58	-	1.89	-	2.02	3.0836	4.16

Table 4: Comparison of mean prostate-specific antigen in the current study with other worldwide studies

Age cohort	Current study	Oesterling *et al*	Zhi-Yong Liu *et al*	Young Deuk Choi *et al*	Tsung-Hsun Tsai *et al*	Lee *et al*	Yuan *et al*	Kao *et al*
Study cohort	137	537	9 374	120,439	213,986	5805	11 150	414
41–50 years	1.03	2.0	2.15	1.92	2.0	2.0	2.19	1.88
51–60 years	3.91	3.0	3.20	2.37	3.2	2.4	2.88	2.37
61–70 years	4.00	4.0	4.10	3.56	5.6	3.9	4.42	4.82
71–80 years	4.74	5.0	5.37	5.19	7.4	6.3	6.52	5.86

Table 5: Comparison of Prostate Volume in the current study with other worldwide studies

Various Studies	Pearson Correlation (r)	p-value
Deori R *et al*	0.93	<0.001
Mosli HA *et al.*, and Abdel-Meguid TA *et al.*	0.44	<0.001
Park DS *et al.*	0.26	<0.001
Our study	0.629	< 0.001

CONCLUSIONS

This study is the first to establish age-specific PSA reference ranges for the North Karnataka population, enhancing diagnostic accuracy. Conducted at a major tertiary care hospital, it highlights the need for refined PSA screening to improve early detection. Despite its limitations, PSA remains the most widely accepted biomarker. Tailored PSA ranges can improve screening accuracy and disease management. Given the rising BPH and PCa incidence, further large-scale validation studies are essential to develop robust age-specific PSA thresholds, optimizing screening strategies and minimizing unnecessary biopsies.

This cross-sectional study confirms a clear relationship between age, prostate volume, and PSA levels in men without prostate cancer. The strong correlation between prostate volume and PSA highlights the influence of BPH on PSA elevation. Establishing age- and volume-adjusted PSA reference ranges is crucial for improving diagnostic accuracy and reducing unnecessary biopsies. Our findings underscore the need for region-specific guidelines tailored to the Indian population, warranting further validation through larger, diverse studies.

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