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**Original Research Article**

# Serum testosterone to prostate specific antigen ratio as predictor of prostate cancer: a diagnostic test evaluation

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## ABSTRACT

**Background:** Prostate cancer is suspected by an increase in serum PSA level, and the diagnosis is confirmed with a systematic biopsy. There is no established cutoff value of PSA levels for recommending biopsy and it shows a lack of specificity when PSA levels are in the "gray zone". The objectives are to study the diagnostic ability and effectiveness of serum testosterone-PSA ratio in predicting prostate cancer and its severity in patients with normal DRE and serum PSA level of 4-20 ng/ml.
**Methods:** Patients more than 40 years of age with normal DRE and elevated serum PSA (4-20 ng/ml) admitted in the Department of Urology, Government medical college Kozhikode will be included. The sTT-PSA ratio will be calculated with sTT and PSA in ng/ml. 12 core prostate biopsy is performed. The HPR results will be depicted as benign and malignant, with malignancy as grade groups (1-5) based on Gleason scoring.
**Results:** In our study cancer detection rate is 20.8%. Mean PSA and testosterone levels are 10.01ng/ml and 4.84 ng/ml in benign group, 15.45 ng/ml and 4.03ng/ml in cancer group. Mean T-PSA ratio are 0.52 and 0.27 in benign and cancer group respectively. Based on ROC curve with a cut off 0.336, T-PSA has the diagnostic ability for Ca prostate with sensitivity of 79.17% and specificity of 89.01%. There is a positive correlation between T-PSA ratio and grade group but it is statistically not significant.
**Conclusions:** The present study suggests that the sTT/PSA ratio might beconsidered a predictor of the risk of prostate cancer.

**Keywords:** Testosterone, PSA, Ratio, Prostate

## INTRODUCTION

Prostate cancer is the second most common cancer in men worldwide, and established risk factors for prostate cancer are age, race and a family history of the disease.[1,2] Prostate cancer is normally suspected by an increase in the serum PSA level, and the diagnosis is made after histological confirmation through a systematic biopsy of the prostate gland. Although the serum prostate-specific antigen (PSA) level has been used as an index in screening for PCa, it has no established cutoff value for recommending biopsy and shows a lack of specificity, especially in patients whose PSA levels are within the "gray zone".[3] A serum PSA level of between 4 and 10 ng/mL is considered to fall within the diagnostic gray zone, and PCa is detected in only 25% of patients whose PSA levels are within thisinterval.[4] Thus, other diagnostic tools, such as the free-to-total PSA ratio, PSA density, PSA velocity, and other PSA parameters, have been proposed to improve the PCa screening performance and avoid unnecessary biopsies in men with gray- zone PSA levels.[4-6] Given the pathologic and therapeutic significance of the androgen axis and the fact

that the secretion and production of PSA are under androgenic control, it has been suggested that the detection of serum testosterone may be useful for the evaluation of PCa risk in clinic practice. The potential clinical applications of serum total testosterone (sTT) determination in patient screening, diagnosis and the management of prostate cancer have been evaluated in the literature.[7] Currently, the association of serum testosterone with prostate cancer is incompletely understood. Studies comparing circulating male sex hormone levels between subjects with and without prostate cancer have produced widely varying results.[8,9] The usefulness of using the sTT/PSA ratio as a predictor of prostate cancer risk was recently suggested by Karamanolakis et al, Rhoden et al confirmed its usefulness in hypogonadal men with low levels of serum PSA.[10,11] Morote et al however, failed to confirm that it is a useful tool to increase the specificity of PSA in eugonadal or hypogonadal men.[12]

### *Objectives*

The objectives are to study the diagnostic ability of serum testosterone PSA ratio in predicting prostate cancer in patients with normal DRE and serum PSA level of 4-20 ng/ml and to evaluate how effective this ratio is in predicting severity of prostate cancer in terms of Gleason score and grade group.

## METHODS

### *Study design and duration*

Hospital-based prospective study for diagnostic test evaluation was conducted for a period of 12 months from April 2022 to April 2023.

All patients more than 40 years of age with normal DRE and elevatedserum PSA (4-20 ng/ml) admitted in the department of urology in Government medical college Kozhikode will be included for evaluation. Informed consent will be obtained from all eligible patients. All demographic data and perioperative information will be tabulated. Blood samples for PSA and serum testosterone will be obtained between 08:00and 10:00 hours and processed immediately. Mohit et al supported need of testosterone levels in ca prostate and evidence indicates maximal androgen stimulated prostatic cancer growth at relatively low testosterone levels.[13,14]

The sTT to PSA ratio will be calculated after transforming sTT levels into ng/mL, the units in which PSA is normally expressed. Biopsy procedure will be performed with acceptable12 core prostate biopsies (from right and left lateral rightand left paramedian regions in base, mid zone and apical region of prostate). The 12 core biopsy specimen should be sent to histopathological examination. After discharging the patients, they were told to review with histopathology report (takenas reference standard for diagnosing ca prostate).[15]

The results will be depicted as benign and malignant, if malignant, it willbe presented as grade groups (Grade group 1 to garde group 5) based on Gleason scoring.[16] This will help to assess severity of malignancy and find out any relationship with S. testosterone-PSA ratio.

### *Sample size*

The sample size was calculated as shown below, According to a study conducted by Gurbuz et al.[13]

$$n = 4\,x\,specificity\,x\,(100 - specificity) \div (precision)2\,x\,(1 - overall\ cancer\ detection\ rate).$$

Hence sample size is calculated as 113.

### *Inclusion criteria*

The study includes patients who are more than 40 years of age with normal DRE, who were willing to participate in the study and with elevated serum PSA (4- 20 ng/ml).

### *Exclusion criteria*

Men on medications known to lower PSA, such as finasteride or dutasteride will be excluded. Patients receiving anticoagulant therapy, who had an indwelling Foley catheter, a symptomatic or asymptomatic urinary tract infection, bleeding disorders, acute prostatitis before prostate biopsy and Previous prostatic biopsy or prostate surgery will also be excluded from the study.

### *Statistical analysis*

All statistical procedures were performed using Statistical Package for Social Sciences (SPSS) 20.0. Calculations for power (80%) of study was performed before the commencement of the study. All quantitative variables expressed in mean and standard Deviation. Qualitative variables will be expressed in percentages. Shapiro-Wilk test was used for testing the normality assumption ofthe quantitative data. Independent t test was used for comparison between two groups. ROC curve analysis was done using MedCalc software sensitivity specificity PPV NPV were calculated. Probability value ($p<0.05$) was considered statistically significant.

### *Relevance*

Although the serum prostate-specific antigen level has been used as an index in screening for PCa, it has no established cutoff value for recommending biopsy and shows a lack of specificity, especially in patients whose PSA levels are within the "grey zone. As we know the pathological and therapeutic significance of androgen axis, serum testosterone determination is not currently used in determining prostate cancer risk. There is lot of controversy regarding the role of testosterone in assessing risk of prostate cancer and also literature is

showing contradicting results. There is very few articles regarding the topic in Indianpopulation. So, conducting a study for assessing testosterone PSA ratio in predicting prostate cancer in Indian population is relevant.

## RESULTS

### *Age*

Out of 115 patients, the number of patients in age group 45-55 years were 12 (10.4%). The number of patients in age group 56-65 years were 41 (35.7%). The number of patients in age group 66-75 years were 41 (35.7%). The number of patients in age group >76 years were 21 (18.3%).

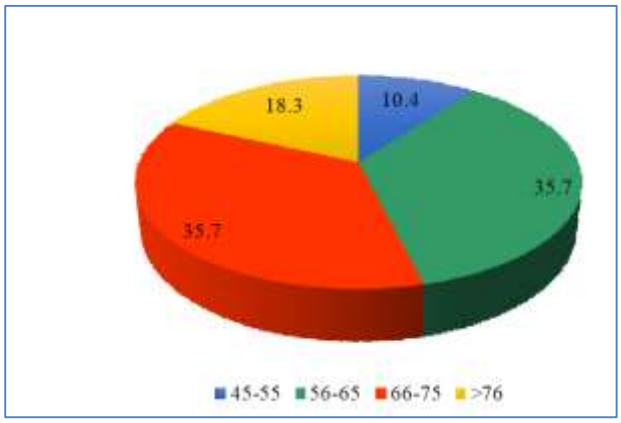


**Figure 1: Age based distribution.**

### *Serum PSA and testosterone*

The mean value of PSA is 11.14 with a Standard Deviation (SD) of 4.23. The mean value of Testosterone is 4.67 with a Standard Deviation of 1.19. The mean value of T/PSA ratio is 0.47 with a Standard Deviation of 0.17.

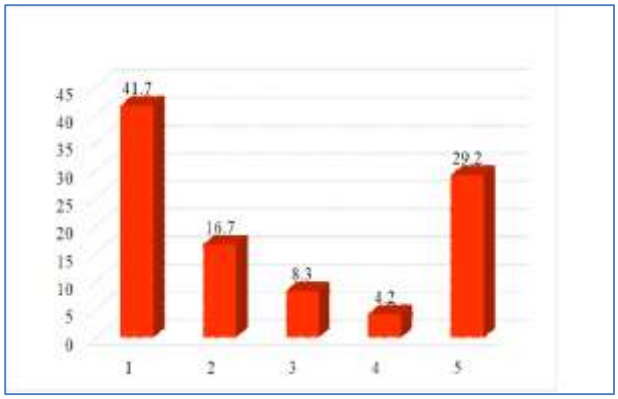


**Figure 2: Gleason grade.**

### *Comparison of PSA*

The mean PSA in the benign group is 10.01 with a SD of 3.44 whereas in the cancer group, it is 15.45 with a SD of 4.25. The 95% confidence interval of the difference has an upper limit of -7.09 and a lower limit of -3.79. The T value is -6.54. The p value is 0.001 (p value <0.05 is statistically significant and <0.001 is statistically highly significant).

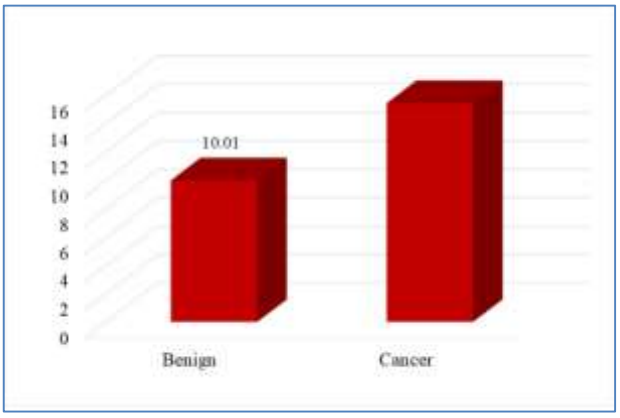


**Figure 3: Comparison of PSA.**

### *Comparison of testosterone*

The mean value of testosterone in the benign group is 4.84 with a SD of 1.13while in the cancer group, it is 4.03 with a SD of 1.20. The 95% confidence interval of the difference has an upper limit of 0.29 and a lower limit of 1.33. The T value is 3.09. The p value is 0.002 (p value <0.05 is statistically significant and <0.001 is statistically highly significant).

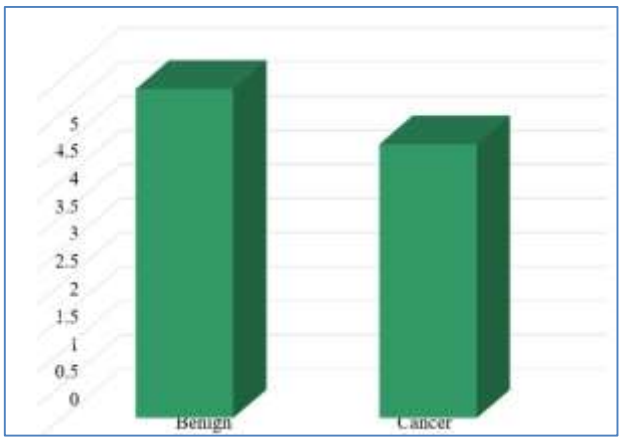


**Figure 4: Comparison of testosterone.**

### *Comparison of T/PSA ratio*

The mean value of T/PSA ratio in benign group is 0.52 with a SD of 0.15. However, in the cancer group is 0.27 with a SD of 0.10. The 95% confidence interval of the difference has an upper limit of 0.17 and a lower limit of 0.30. The T value is 7.27. The p value is 0.001 (p value <0.05 is statistically significant and <0.001 is statistically highly significant).

***ROC curve***

The cutoff value is ≤0.336. The sensitivity is 79.17 with 95% CI of 57.8-92.9. The specificity is 89.01 with 95% CI of 80.7-94.6. The positive predictive value is 65.5 with 95% CI of 50.6-77.9. The negative predictive value is 94.2 with 95% CI of 88.1-97.3.

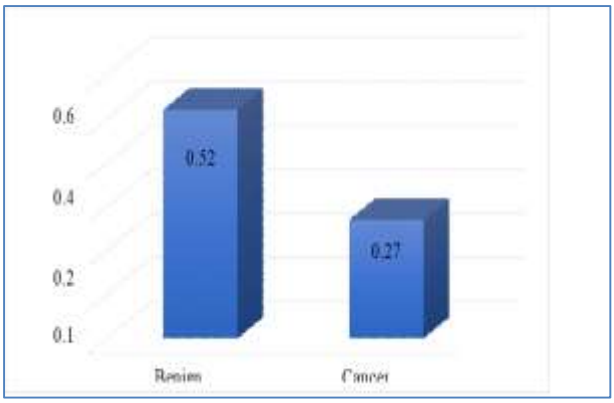


**Figure 5: Comparison of T/PSA ratio.**

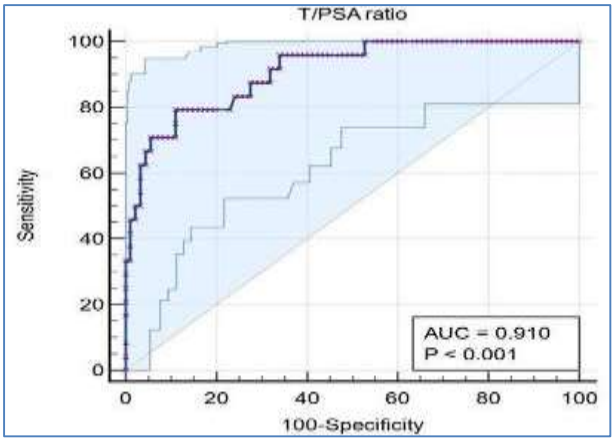


**Figure 6: ROC curve.**

***Correlation of T-PSA ratio with grade group***

In Grade group 1, the mean value of T-PSA ratio is 0.25 with a SD of 0.09 and Standard error of 0.031. The 95% CI is 0.18-0.32. (N=10). In Grade group 2, the mean value of T-PSA ratio is 0.30 with a SD of 0.07 and Standard error of 0.038. The 95% CI is 0.18-0.42. (N=4). In Grade group 3, the mean value of T-PSA ratio is 0.25 with a SD of 0.11 and Standard error of 0.078. The 95% CI is -0.73-1.24. (N=2). In Grade group 4, the mean value of T-PSA ratio is 0.30. (N=1). In Grade group 5, the mean value of T-PSA ratio is 0.30 with a SD of 0.13 and Standard error of 0.05. The 95% CI is 0.18-0.43. (N=7), p value is 0.84.

***Correlation of T-PSA ratio with grade group***

The area under the curve is 0.910 with a Standard error of 0.0322. Asymptotic significance is <0.0001. Z statistic is 12.707. Asymptotic 95% CI is 0.842-0.955.

## DISCUSSION

As we know the pathological and therapeutic significance of androgen axis,serum testosterone determination is not currently used in determining prostatecancer risk. There is lot of controversy regarding the role of testosterone in assessing risk of prostate cancer. In our study cancer detection rate is 20.8%. Mean PSA and testosterone levels are 10.01 ng/ml and 4.84 ng/ml in benign group, 15.45 ng/ml and 4.03ng/ml in cancer group. Mean T-PSA ratio are 0.52 and 0.27 in benign and cancer group respectively. Based on ROC curve with a cut off 0.336, T-PSA has the diagnostic ability for Ca prostate with sensitivity of 79.17% and specificity of 89.01%. There is a positive correlation between T-PSA ratio and grade group but it is statistically not significant. Karamanolakis et al analyzed a group of 97 patients with a serum PSA level of 3-10 ng/ml who underwent a sextant transrectal ultrasound-guided biopsy.[10] They observed significantly lower sTT levels and significantly lower sTT/PSA ratios in patients with prostate cancer than in those who provided biopsies that were free of any sign of cancer. The 0.95 threshold suggested by Karamanolakis et al offered increased 84% specificity but at the cost of greatly decreasing sensitivityto 43%. In a study by Cenk et al analysed 104 patients with a cancer detection rate of 17.3%.[13] The probability of detecting ca prostate was significantly higher in hypogonadal men comparing with eugonadal men. The median sTT/PSA ratio in these groups was 0.55 and 0.74, respectively (p value=0.035). The receiver operator characteristic (ROC) method was used to evaluate the properties of the sTT/PSA ratio, with testosterone and PSA as predictors of prostate cancer risk. Theaccuracy of the sTT/PSA ratio in prostate cancer diagnosis, represented by the areaunder the curve (AUC), was 0.739 (95% CI 0.640-0.823, p<0.05). Optimizing thesensitivity and specificity of the sTT/PSA ratio using the ROC provided a cutoff point of 0.60, which corresponded to 82% sensitivity and 62% specificity. Rhoden et al studied 184 patients, 154 patients with benign biopsy and 30patients with malignancy with a cancer detection rate of 16.3%.[11] Testosterone concentrations were similar in the prostate cancer and noncancer groups, although mean prostate specific antigen was higher in the prostate cancer group. The testosterone-to-prostate specific antigen ratio was inversely related to prostate cancer risk (OR 0.49, 95% CI 0.33-0.74). An ROC for the testosterone-to-prostate specific antigen ratio suggested that a ratio of below 1.8 was diagnostic for prostate cancer, while values below this threshold were associated with an OR of 3.17 (95% CI 1.17-8.59) for prostate cancer Xu et al reviewed 92 patients with benign prostatic hyperplasia (BPH) and 164 patients with PCa. In their study, BPH and PCa groups had similar serum total testosterone (median, 15.8 versus 16.3 nmol/l). Compared with the BPH group, the PCa group had higher PSA (16.8 versus 5.1 ng/ml) and T/PSA (1.37 versus 4.69) ROC curve analysis yielded an AUC of 0.712; for the optimal cutoff of 4.43, specificity and sensitivity were 52% and 97% respectively. Above mentioned studies are comparable with our results. and it shows sTT/PSA may improve the

accuracy of PCa diagnosis in patients with a PSA level ≤20 ng/ml. Morote et al reviewed 439 patients with PSA value between 4-20 ng/ml.[12] The overall cancer detection rate was 42.1%. The median sTT level was 469 ng/dl in men with cancer and 499 ng/dl in those without (p=0.521). The median sTT/PSA was 0.68 and 0.74, respectively (p=0.215). These results do not support the use of sT/PSA for predicting the risk of prostate cancer. Gurbuz et al stated gleason grade group is inversely related to serum testosterone. The frequency of high-grade cancer (Gleason score >6) was reported as 28% (2/7) and 36% (4/11) in hyopogonadal and eugonodal patients, respectively (p=0.648). In our study, there is statistically insignificant correlation between T-PSA ratio and Gleason grade group, probably due to small sample size in cancer group.

***Limitations***

Major limitation of study is that sTT/PSA ratio between eugondal and hypogonadal men was not compared (serum testosterone <300 ng/dl). This is because we got only 10 patients in hypogonadal state in our study.

## CONCLUSION

In the literature, there is worrisome relationship between testosterone and prostate cancer risk. Most of the studies showed conflicting results. In our study Prostate cancer risk is related to testosterone concentration and sTT/PSA ratio. With the cutoff of 0.336, sTT/PSA has the diagnostic ability of predicting prostate cancer with a sensitivity of 79.17% and specificity of 89.01%. So, the present study suggests that the sTT/PSA ratio might be considered a predictor of the risk ofprostate cancer.

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*Ethical approval: The study was approved by the Institutional Ethics Committee*

## REFERENCES

1. Ferlay J, Bray F, Pisani P, Parkin DM. Cancer incidence, Mortality and Prevalence worldwide. France: IARC Press; 2004.
2. Bostwick DG, Burke HB, Djakiew D, Euling S, Ho SM, Landolph J et al. Human prostate cancer risk factors. Cancer. 2004;101(10):2371-490.
3. Polascik TJ, Oesterling JE, Partin AW. Prostate specific antigen: a decade of discovery--what we have learned and where we are going. J Urol. 1999; 162(2): 293-306.
4. 893-4. Fang J, Metter EJ, Landis P, Carter HB. PSA velocity for assessing prostate cancer risk in men with PSA levels between 2.0 and 4.0 ng/ml. Urology. 2002;59(6):889-93.
5. Chen CS, Wang SS, Li JR, Cheng CL, Yang CR, Chen WM, et al. PSA density as a better predictor of prostate cancerthan percent-free PSA in a repeat biopsy. J Chin Med Assoc. 2011;74(12):552-5.
6. Yang CR, Su CK, Chiu KY, Ho HC, Ou YC, Cheng CL, et al. Free/total prostate specific antigen ratio for prostate cancer detection: a prospective blind study. Anticancer Res. 2005;25(3):2439-43.
7. Schulman CC, Irani J, Morote J, Schalken JA, Montorsi F, Chlosta PL, et al. Testosterone measurement in patients with prostate cancer. Eur Urol. 2010;58(1): 65-74.
8. Gann PH, Hennekens CH, Ma J, Longcope C, Stampfer MJ. Prospective study of sex hormone levels and risk of prostate cancer. J Natl Cancer Inst. 1996;88(16): 1118-26.
9. Heikkilä R, Aho K, Heliövaara M, Hakama M, Marniemi J, Reunanen A, Knekt P. Serum testosterone and sex hormone-binding globulin concentrations and the risk of prostate carcinoma: a longitudinal study. Cancer. 1999;86(2):312-5.
10. Karamanolakis D, Lambou T, Bogdanos J, Milathianakis C, Sourla A, Lembessis P, et al. Serum testosterone: A potentially adjunct screening test for the assessment of the risk of prostate cancer among men with modestly elevated PSA values (> or =3.0 and <10.0 ng/ml). Anticancer Res. 2006; 26(4):3159-66.
11. Rhoden EL, Riedner CE, Morgentaler A. The ratio of serum testosterone-to- prostate specific antigen predicts prostate cancer in hypogonadal men. J Urol. 2008;179(5):1741-4.
12. Morote J, Planas J, Ramirez C, Gómez E, Raventós CX, Placer J, et al. Evaluation of the serum testosterone to prostate-specific antigen ratio as a predictor of prostate cancer risk. BJU Int. 2010;105(4):481-4.
13. Ferguson, R.S. Prostatic Neoplasms: Their Diagnosis by Needle Puncture and Aspiration. Am J Surg. 1930;9:507-11.
14. Gurbuz C, Canat L, Atis G, Guner B, Caskurlu T. The role of serum testosterone to prostate-specific antigen ratio as a predictor of prostate cancerrisk. Kaohsiung J Med Sci. 2012;28(12):649-53.
15. Wild J, Reid J. Fourth Annual Conference in Ultrasound Therapy. BJU Int. 1955.
16. Watanabe H, Kato H, Kato T, Morita M, Tanaka M. Diagnostic applicationof ultrasonotomography to the prostate. BJU Int. 1968;59(4):273-9.
17. Hodge KK, McNeal JE, Stamey TA. Ultrasound guided transrectal core biopsies of the palpably abnormal prostate. J Urol. 1989;142(1):66-70.
18. Xu L, Hu X, Zhu Y, Lu J, Xu Y, Wang G, et al. Additional value of the ratio of serum total testosterone to total prostate-specific antigen in the diagnosis of prostate cancer in a Chinese population. Andrologia. 2018;50(2):34-7.

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