

# Association of Pre-Treatment Serum Testosterone Levels with Prostate Cancer: A Prospective Study

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**Ethical guidelines:** Ethical guidelines of the Declaration of Helsinki and its amendments were followed. Written informed consents were obtained from all the patients regarding the study and the procedures involved.

## Abstract

**Introduction:** It has been widely accepted that prostate cancer (PCa) growth is related to serum testosterone (ST). A direct correlation between pre-treatment ST level and PCa growth and progression has been reported. However, recent studies have shown that pre-treatment ST levels have a negative correlation with PCa. Thus, the literature is, at best, conflicting. In this study, we examined the pre-treatment serum total testosterone (ST) levels in PCa.

**Methods:** In this prospective observational study, suspected cases of PCa underwent digital rectal examination, routine blood investigation, Prostate-Specific Antigen (PSA) measurement, and prostate biopsy. Diagnosed cases of PCa without any risk factors affecting testosterone levels were included. Their pre-treatment total ST levels were measured. All patients underwent staging evaluation with either Magnetic Resonance Imaging (MRI) & Bone scan or Ga-68 Prostate Specific Membrane Antigen Positron Emission Tomography (PSMA PET). ST levels were also measured in patients with Benign Prostatic Hyperplasia (BPH) and compared with those in PCa patients. ST levels were also assessed according to Gleason Score (GS) and clinical stage in PCa.

**Results:** 110 cases and 54 patients with BPH were included in the study. The median ST level in PCa patients was significantly lower as compared to BPH patients [352.28 ng/dL (Interquartile Range (IQR) 224.99-563.17) vs. 448.29 ng/dL (IQR 400.97-596.42) ( $p = 0.004$ )]. The median ST level in metastatic PCa was significantly lower than the localized PCa group [298.20 ng/dL vs. 452.30 ng/dL ( $p = 0.0001$ )]. Moreover, the median ST level was also significantly lower in patients with Gleason Score  $\geq 8$  than those with Gleason Score  $\leq 7$  [285.92 ng/dL (149.97-560.40) vs. 425.13 ng/dL (320.43-571.46) ( $p = 0.002$ )].

**Conclusion:** This study shows lower ST levels in patients with PCa compared to patients with BPH, thus supporting a potential association as described in previous studies. ST levels may have prognostic value since a low pre-treatment ST level is associated with a higher clinical stage and aggressive PCa.

**Keywords:** Prostate Cancer, Serum Testosterone, Gleason Score, Hypogonadism

## Introduction

The traditional serum testosterone (ST) dependent view of prostate cancer, first postulated in 1949 by Huggins *et al.*, stood for more than 65 years [1-3]. Studies found that castration resulted in prostate cancer regression, whereas testosterone administration caused rapid prostate cancer growth. These studies have suggested a direct correlation between circulating levels of testosterone with relation to PCa progression and proved that both progression and regression of PCa are ST-dependent. These findings led to the prevailing hypothesis that elevated androgen levels increase the risk of PCa. On the other hand, some studies have found negative or no association between ST and the risk of PCa [4-9]. Since 1990, research findings started suggesting this inverse relationship of ST level with prostate cancer [6,10-14]. Some findings correlated low ST level to worse clinical and pathological outcomes of prostate cancer including an increased risk of prostate cancer, worse disease-free survival, increased positive cores on biopsy, a high Gleason score, poor pathological stage, and increased risk of positive margins after radical prostatectomy [6,10-14]. Meanwhile, Mikkola *et al.* showed no significant difference in pre-treatment ST levels between patients with and without metastases [7]. The data is therefore at best conflicting. Moreover, data regarding the association of pre-treatment serum testosterone and prostate cancer in the Indian population is scarce [15]. Thus, the primary objective of this study is to examine the association of serum testosterone levels with PCa and correlate it with the Gleason score and clinical stage of PCa.

## Methodology

This prospective observational study included patients diagnosed with prostate cancer (PCa) from July 2017 to December 2018 after obtaining IEC approval (INT/IEC/002049). Ethical guidelines of the Declaration of Helsinki and its amendments were followed. Since it was an exploratory

study, no formal sample size calculation was performed. Written informed consents were obtained from all the patients regarding the study and the procedures involved. Patients who present lower urinary tract symptoms with PSA > 4 ng/mL and/or abnormal digital rectal examination underwent Multiparametric Magnetic Resonance Imaging (MRI) and TransRectal Ultrasound Scan (TRUS)-guided biopsy. Patients with locally advanced disease on clinical evaluation underwent TRUS-guided biopsy directly. All patients with biopsy-proven PCa and age > 40 years were included as cases. Exclusion criteria included patients on hormone replacement therapy (medical or surgical castration), anti-androgens, or exogenous testosterone supplements, those with a history of Chronic Liver Disease (altered liver function tests), a Body Mass Index (BMI) > 30 kg/m<sup>2</sup>, a diagnosis of hypogonadism, as well as those with chronic kidney disease (serum creatinine > 2 mg/dL), diabetes or any known disease of the hypothalamic-pituitary axis. PCa patients underwent staging evaluation, which included either contrast-enhanced MRI prostate with a bone scan or PSMA PET scan. An age-matched comparator arm of BPH patients, defined as patients with lower urinary tract symptoms and with normal digital rectal exam and serum prostate-specific antigen (PSA), were included as controls.

Total serum testosterone (ST) was measured by Electrochemiluminescence immunoassay before the treatment. A morning 8:00 am fasting blood sample (2 mL) was collected in an ethylenediamine tetraacetic acid EDTA vial and sent to the Endocrinology laboratory. The ST level was reported in ng/dL. ST levels were assessed from this lab only, to ensure standardization. An ST level <300 ng/dl, as defined by the Food & Drug Administration, was considered hypogonadism [16]. Serum PSA levels were measured exclusively at the Biochemistry lab of the institute.

The normality of continuous variables was initially checked using Kolmogorov-Smirnov and Shapiro tests for normality. Normally distributed data were expressed as mean

with standard deviation and statistical significance was checked using an independent sample t-test. Non-parametric data were expressed as median with range and statistical significance checked using the Wilcoxon rank sum test or Mann-Whitney test wherever applicable. For analysis of two or more variables for continuous data, analysis of variance (ANOVA) and Kruskal-Wallis test were used for parametric and non-parametric data respectively. A p-value of  $< 0.05$  was considered statistically significant. All the statistical analyses were performed using SPSS v22 software. We confirm the availability of all original data reported in this study and access to the same data can be provided when required.

## Results

A total of 164 patients were enrolled in the study. Of these, 110 patients belonged to the prostate cancer (PCa) group, and 54 patients were in the benign prostatic hyperplasia (BPH) group. The mean age for PCa patients was  $67.29 \pm 8.65$  years and for the BPH group, it was  $64.57 \pm 7.99$  years. The median PSA was 60.19 ng/ml (IQR 16.48-292.75) and the median serum testosterone (ST) was 352.28 (IQR 224.99 - 563.17). In the Pca group, the patients were distributed across the following clinical stages: Localised (n=42), Locally advanced (n=13), and Metastatic (n=55). The localized group included patients stratified as stage T1 and T2 without nodal involvement and no metastasis as per AJCC TNM staging. The locally advanced group included patients with Clinical stage T3, T4, or any T with pelvic lymph node-positive disease but no metastasis. The metastatic group included any T and any N with visceral, skeletal, or distant lymph nodal involvement. Based on the Gleason score, they were distributed as 7 or less (n=47), and 8 or greater (n=63). In the BPH group, the median PSA levels were 0.97 ng/ml (IQR=0.7 - 2.0) and the median serum T was 448.29 ng/dl (IQR 400.97-596.42) (Table 1). BPH patients were categorized into different age groups to examine whether there was any change in ST with increasing age.

ST levels were not significantly different among the different age groups in both cases and controls (Table 2). The mean age of the BPH patients was comparable to the PCa group (64.59 vs 67.29 years,  $p=0.067$ ) and the mean age across the groups of PCa was also comparable. Median ST level of PCa patients was significantly low compared to BPH patients [352.28 ng/dL (224.99 - 563.17) vs 448.29 ng/dL (400.97 - 596.42)], ( $p=0.007$ ) (Figure 1). The median ST level in the localized PCa group was 452.30 ng/dL (363.69 - 653.74), the locally advanced PCa group was 352.70 ng/dl (118.97 - 586.98), and in the metastatic PCa group was 298.20 ng/dl (161.30 - 476.10). As noted, the ST level in locally advanced and metastatic PCa was lower than the localized PCa patients and the difference was statistically significant between the localized and metastatic group [298.20 ng/dl vs. 452.30 ng/dl ( $p = 0.0001$ )].

Based on the Gleason score on the histopathology, PCa patients were categorized into two groups. Patients in both groups were comparable in terms of age (mean- 66.83 vs. 67.63 in years). Median ST level was significantly lower in patients with a Gleason score  $\geq 8$  than in patients with a Gleason score  $\leq 7$  [285.92 ng/dL vs. 425.13 ng/dl ( $p = 0.002$ )] (Figure 2). Out of 55 patients with Metastatic prostate cancer, 13 patients had low or intermediate Gleason scores whereas 42 patients had high Gleason score for prostate cancer. Median ST in the metastatic PCa group of patients with  $GS \geq 8$  was significantly low compared to metastatic PCa patients with  $GS \leq 7$  [255.40 ng/dl vs 346.10 ng/dl, ( $p=0.033$ )].

On further analysis of the patients based on hypogonadism level of ST (i.e.  $< 300$  ng/dl), 40 (36.4%) prostate cancer patients and 4 (7.4%) control patients had ST levels  $< 300$  ng/dl. Most of the patients (82.5%) in the low ST group ( $T < 300$  ng/dl) had high Gleason score prostate cancer compared to the normal ST group ( $p=0.014$ ).

## Discussion

Data are scarce regarding the relationship between ST and PCa in the Indian population [15]. In our study, we evaluated

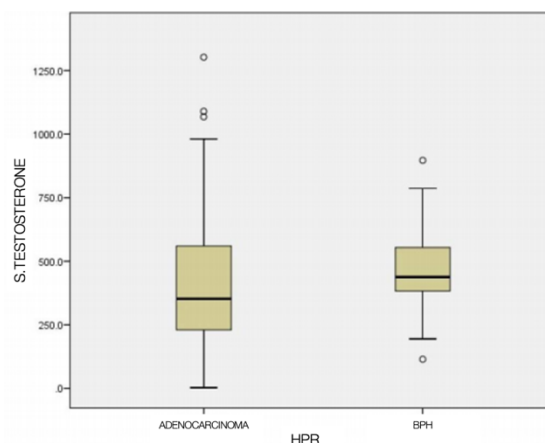
**Table 1: Baseline comparative parameters among the groups**

|  | BPH (control)          | Prostate Cancer        | Prostate cancer groups (n=110) |                        |                        |
|--|------------------------|------------------------|--------------------------------|------------------------|------------------------|
|  |                        |                        | Localised                      | Locally advanced       | Metastatic             |
| Patients (n)                               | 54                     | 110                    | 42                             | 13                     | 55                     |
| Mean age (years)                           | 64.57 ± 7.99           | 67.29 ± 8.65           | 66.88 ± 8.07                   | 66.92 ± 10.34          | 67.69 ± 8.81           |
| PSA (ng/ml)<br>Median (IQR)                | 0.97 (0.7-2.0)         | 60.19 (16.48-292.75)   | 18.62 (10.49-47.75)            | 30.00 (12.6-178.5)     | 202.00 (64-530)        |
| Serum Testosterone (ng/dl)<br>Median (IQR) | 448.28 (400.96-596.42) | 352.28 (224.99-563.17) | 452.30 (363.69-653.74)         | 352.70 (118.97-586.98) | 298.20 (161.30-476.10) |

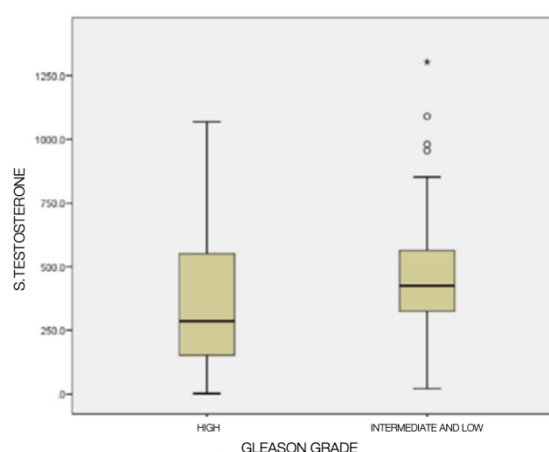
**Table 2: Age distribution of Prostate cancer and control groups**

| Age Group | Prostate Cancer Number (Percent) | Benign Prostate Hyperplasia Number (Percent) |
|-----------|----------------------------------|--|
| 41-50     | 4(3.6)                           | 4(7.4)                                       |
| 51-60     | 22(20.0)                         | 12(22.2)                                     |
| 61-70     | 45(40.9)                         | 25(46.2)                                     |
| 71-80     | 33(30.0)                         | 12(22.2)                                     |
| 81-90     | 6(5.4)                           | 1 (1.8)                                      |

the levels of pre-treatment ST values in patients with PCa and compared them with those of patients with BPH (control group). In our study cohort, the median value of ST in BPH patients was 448.29 ng/dl (IQR 400.97- 596.42) and there was no significant change in ST value with increasing age. Five control patients (8.2%) had ST levels less than 300 ng/dl (lower normal range of ST). Iwamoto T et al., in a much larger cohort, studied the total and free ST levels among 1172 adult males in Japan and concluded that the influence of aging on total ST level was negligible in male subjects older than 50 years old [17]. However, our cohort study was much smaller, and it consisted of BPH patients and not of healthy individuals. When comparing the median ST values between PCa and BPH patients, the PCa patients had significantly lower median ST levels than BPH patients [352.28 ng/dl vs 448.29 ng/dl, (p=0.007)]. A similar finding was reported by



**Figure 1: Box plot of median testosterone levels in Benign prostatic hyperplasia and Prostate cancer group.**



**Figure 2: Box plot of median serum testosterone levels among prostate cancer patients based upon Gleason score (High is Gleason score ≥8 and Low & Intermediate is ≤7).**

Luigi Mearini *et al.* in their Italian population [18]. In their study, they compared age-matched 103 PCa patients with 103 BPH patients and found significantly low median ST level in PCa patients compared to control patients [336 ng/dl vs. 444 ng/dl, ( $p < 0.0001$ )]. Saturation theory and suppression theory have been proposed to examine this inverse relationship [6,19-21]. The saturation theory of prostate growth was supported by Song W *et al.* in their *in vitro* study on PCa cell lines, where they concluded that when testosterone is below an appropriate level, the PCa cell lines showed abnormal proliferative growth [19].

Another possible explanation is that the prostate cancer cell inhibits the synthesis of ST through negative feedback by secreting some inhibitory substance (i.e., suppression theory). This theory was studied by Zhang *et al.* and Miller *et al.* in their radical prostatectomy cohort. They found an increase in ST levels after radical prostatectomy and suggested that one or more factors in prostate cancer cells inhibit ST levels [20,21]. Whether low ST levels lead to PCa or PCa leads to low ST levels remains a dilemma. The Baltimore longitudinal study incriminated an age-dependent relation between PCa and ST values. They concluded that the likelihood of high-risk PCa was inversely related to free testosterone index (FTI) for patients <65 years but for patients >65 years it was directly related [22].

When comparing the median ST values among PCa groups, we found that localized PCa patients had significantly lower ST levels than the metastatic PCa group [298.20 ng/dl vs. 452.30 ng/dl ( $p=0.0001$ )]. Similar findings were also reported by Massengill *et al.* who concluded that patients with lower ST levels had an increased likelihood of non-organ confined disease [13]. The results of our study were also supported by Perez Marquez *et al.* who reported that patients with low ST levels are at increased risk of metastatic disease and at heightened risk of tumor progression [23]. Our study supports this evidence that PCa is associated with low ST levels compared to

BPH patients.

We also found that high Gleason score PCa patients have significantly low median ST levels [285.92 ng/dl Vs 425.13 ng/dl, ( $p = 0.002$ )]. A study by Hoffman *et al.* also demonstrated that patients with lower free ST were more likely to display a Gleason score of 8 or more [12]. However, they noted no significant differences based on total ST. Another study by Schmaltz *et al.* on a cohort of 156 cases, reported similar findings. They suggested a tumor-mediated suppression of the hypothalamic-pituitary gonadal hormone axis particularly in men with high Gleason score tumors [24]. Moreover, another study by this group demonstrated that low ST in men with newly diagnosed prostate cancer was associated with higher Gleason scores, higher microvessel density, and higher androgen receptor density [25]. Hence, low ST levels are a sign of aggressive disease and may have prognostic value.

Arunprasad *et al.* earlier in their study on 100 Indian patients found that the patients with hypogonadism (< 250 ng/dl) had more aggressive tumors [15]. Similarly in our cohort, patients with ST < 300 ng/dl, had a significantly higher number of high Gleason score prostate cancer. However, unlike our study, they did not have BPH patients and used arbitrary cut-off levels to seek this association.

The exact association of serum testosterone and prostate cancer is still ambiguous. Contrary to our study, many studies have found either a linear association of serum testosterone with prostate cancer aggressiveness and grade of the tumor [22,26,27] or no association [28,29]. Therefore, there is currently no clear answer about the relationship between serum testosterone and prostate cancer.

### Strengths and Limitations

Our work is a prospective exploratory study in the Indian sub-population comparing ST levels between prostate cancer (PCa) patients and benign prostatic hyperplasia (BPH) patients. However, it is limited by the small cohort size; therefore, the study

requires validation in a larger size.

## Conclusion

PCa is associated with low ST levels compared to BPH patients. ST level may have a prognostic value since a low pre-treatment ST level is associated with a higher clinical stage and more aggressive prostate cancer. However, there is still ambiguity in the literature about the association and the results of our study require validation in a larger cohort size.

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