Original Article

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# Histomorphologic Correlation of PSA Levels in Prostatic Pathology

Pathology Section

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## ABSTRACT

**Introduction:** Nodular Prostatic Hyperplasia (NPH) and carcinoma of the prostate are increasingly frequent with advancing age. Early detection of these lesions can significantly reduce the patient mortality and morbidity. Prostate Specific Antigen (PSA) level estimation has become a popular method for screening prostatic lesions as it is easy to perform and is cost effective.

**Aim:** To evaluate the role of PSA as a screening tool in different prostatic pathology including prostate cancer. Also, to assess the accuracy of PSA at a cut off 4 ng/ml and to correlate Gleason's score with PSA levels.

**Materials and Methods:** A total number of 170 prostatic biopsies from June 2012 to June 2016 received at the Central Diagnostic Laboratory, A.J Institute of Medical Sciences and Research Centre (AJIMS&RC), Mangaluru, India, was taken for the study. Paraffin embedded sections were stained with routine haematoxylin and eosin stain. The PSA levels were estimated in our Biochemistry Department. These values were correlated with histopathological diagnosis.

**Results:** Out of 170 cases, there were 125 (73.5%) cases of NPH, 31 (18.2%) cases of prostatic adenocarcinoma, 5(2.8%) cases of prostatitis, 3 (1.76%) cases of urothelial carcinoma, 3 (1.76%) cases of low grade Prostatic Intraepithelial Neoplasm (PIN), 1 (0.58%) case of basal cell hyperplasia, 1 (0.58%) case of retention cyst, 1 (0.58%) case positive for small cell carcinoma metastasis. Based on the available PSA values 25 out of 31 cases of prostatic adenocarcinoma had a PSA value >10 ng/ml and 2 cases of prostatic adenocarcinoma had PSA value between 4 and 8 ng/ml. Correlation between Gleason's score with age or PSA was not statistically significant.

**Conclusion:** PSA is a valid, sensitive and early marker for the diagnosis of prostate cancer. With a cut off value of 4ng/ml the diagnostic accuracy is 56%, sensitivity was 96.67% and specificity was 38.5%. There was no correlation between Gleason's score with age or PSA levels.

**Keywords:** Inflammation, Nodular prostatic hyperplasia, Prostate, Prostatic adenocarcinoma

## INTRODUCTION

PSA is used widely as a screening tool for prostatic carcinoma. Even though considerable efforts have been taken to improve the diagnostic quality of prostatic carcinoma, screening and staging parameters are still in the primitive stage [1]. Curative treatments are available only for early stage lesions ofthe disease. There comes the role of an efficient, easy to perform and cost effective method for screening prostatic carcinoma [2].

There has been an on going search for a tumour marker more sensitive and specific for prostate cancer than Prostate Acid Phosphatase (PAP). Due to simplicity and cost effectiveness which are the essential characteristics of a screening test, PSA remain essential for prostate cancer diagnosis and management [3].

PSA is a protein which is found exclusively in prostatic tissue [4]. Although, increased PSA levels have been found to be closely associated with prostate cancer, there can be different reasons for an elevated PSA level, including benign prostatic hyperplasia, prostatitis, prostatic trauma, and prostatic infarction [5]. This study is conducted to correlate PSA levels in different prostatic pathology.

## MATERIALS AND METHODS

The present study was undertaken at the Central Diagnostic Laboratory of A.J Institute of Medical Sciences and Research Centre, Mangaluru, India, and is a prospective and retrospective study. Three-year retrospective study from June 2012 to June 2015 and one-year prospective study from July 2015 to July 2016. The study was done after obtaining patient consent and approval from institutional ethical committee. The demographic group selected for the present study include the rural population of Mangaluru, the Dakshina Kannada district of Karnataka. All the prostate biopsy specimens referred to the Central Diagnostic Laboratory for histopathological evaluation was enrolled in the study. Inadequate biopsy material, follow-up cases, post

therapeutic and recurrent tumours were excluded from the present study.

Out of the 170 cases included in the study 167 were Transurethral Resection of the Prostate (TURP) specimens and 3 were radical prostatectomy specimens. The PSA levels were estimated in our Department of Biochemistry, The PSA levels were estimated using the CIBA-CORNING automated chemiluminescence system which estimates PSA by sandwich assay utilizing a constant amount of 2 antibodies-labelled polyclonal sheep antibody and monoclonal mouse antibody. The PSA level in serum is estimated and correlated with histopathological diagnosis. Paraffin embedded sections were stained with routine haematoxylin and eosin stain.

## STATISTICAL ANALYSIS

Statistics was done using SPSS 10.5 version software system. Results were expressed in numbers and percentages. The sensitivity, specificity, the positive predictive value and the negative predictive value was calculated for PSA value.

## RESULTS

A total number of 170 cases were studied. The cases were distributed in the age group of 30 to 90 years as shown in [Table/Fig-1]. The maximum number of patients were in the age group of 60-70 years consisting of 90 cases. Above the age of 70 years, there were 48 cases and below 60 years 32 cases were present. The mean age of the patients was 65.58 years.

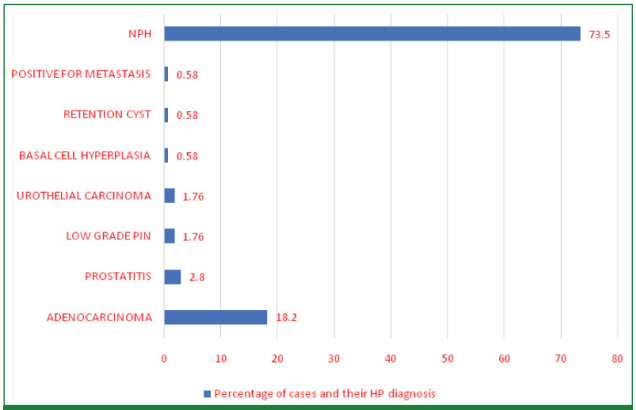
| Age Interval (in years) | Frequency | Percentage (%) |
|---|---|---|
| 30-40 | 02 | 1.18 |
| 40-50 | 0 | 0 |
| 50-60 | 30 | 17.65 |
| 60-70 | 90 | 52.94 |
| 70-80 | 45 | 26.47 |
| 80-90 | 03 | 1.76 |
| Total | 170 | 100 |

**[Table/Fig-1]:** Frequency of cases in different age groups.

Out of 170 cases, there were125 (73.5%) cases of NPH, 31 (18.2%) cases of prostatic adenocarcinoma, 5 (2.9%) cases of prostatitis, 3 (1.76%) cases of urothelial carcinoma, 3 (1.76%) cases of low grade PIN, 1 (0.58%) case of basal cell hyperplasia, 1 (0.58%) case of retention cyst, 1 (0.58%) case positive for small cell carcinoma metastasis [Table/Fig-2].

Among 125 cases of NPH, maximum number of cases (71) were in the age group of 60-70 years. Maximum incidence of prostatic adenocarcinoma (15) was in the age group of 70-80 years. There were 2 cases of urothelial carcinoma in the age group of 50-60 years. In the present study, mean age of prostatic adenocarcinoma is 68.8 years and the mean age for NPH is 65.7 years [Table/Fig-3].

As shown in [Table/Fig-4] among the 125 cases of NPH, 3 cases (2.4%) showed features of fibromuscular hyperplasia

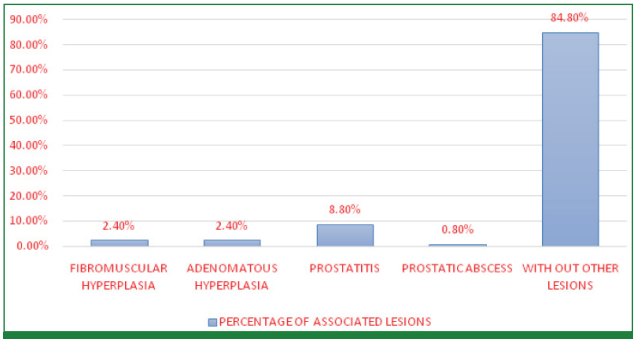



**[Table/Fig-2]:** percentage of cases and their HP diagnosis.

| Histopathological diagnosis | Age interval in years | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | 30-40 | 40-50 | 50-60 | 60-70 | 70-80 | 80-90 | |
| NPH | 1 | 0 | 22 | 71 | 28 | 3 | 125 |
| Adenocarcinoma prostate | 0 | 0 | 4 | 12 | 15 | 0 | 31 |
| Low grade PIN | 0 | 0 | 1 | 1 | 1 | 0 | 3 |
| Prostatitis | 0 | 0 | 0 | 5 | 0 | 0 | 5 |
| Urothelial carcinoma | 0 | 0 | 2 | 1 | 0 | 0 | 3 |
| Basalcell hyperplasia | 0 | 0 | 0 | 0 | 1 | 0 | 1 |
| Retention cyst | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Postivefor metastasis | 0 | 0 | 1 | 0 | 0 | 0 | 1 |
| Total | 2 | 0 | 30 | 90 | 45 | 3 | 170 |

**[Table/Fig-3]:** Number and percentage of cases in different age groups.

and 3 cases (2.4%) revealed features predominantly of adenomatous hyperplasia. There were 11 cases (8.8%) of NPH with prostatitis and 1 case (0.8%) of NPH with prostatic abscess. Remaining 106 cases (84.8%) showed features only that of NPH [Table/Fig-4].




**[Table/Fig-4]:** Features seen in NPH.

PSA values were present for only 101 of the total 170 cases. Among the 101 cases 29 cases had PSA value between 0 and 4 ng/ml, 34 cases had PSA value between 4 and 8 ng/ml, 3 cases had PSA between 8 and 10 ng/ml. Based on the available PSA values 25 out of 31 cases of prostatic adenocarcinoma had a PSA value >10 ng/ml and 2 cases of prostatic adenocarcinoma had PSA value between 4 and 8 ng/ml [Table/Fig-5].

| PSA range in ng/ml | Adeno carcinoma prostate | Urothelial carcinoma | NPH | Low grade PIN | Prostatitis | Basalcell hyperplasia | Suspicios of malignancy | Positive for metastasis | Total |
|---|---|---|---|---|---|---|---|---|---|
| <4 | 0 | 1 | 27 | 0 | 0 | 0 | 0 | 1 | 29 |
| 4 - 8 | 2 | 2 | 29 | 0 | 1 | 0 | 0 | 0 | 34 |
| 8-10 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | 0 | 3 |
| 10-20 | 11 | 0 | 2 | 1 | 1 | 0 | 1 | 0 | 16 |
| 20-30 | 3 | 0 | 1 | 0 | 1 | 1 | 0 | 0 | 6 |
| >30 | 11 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 13 |
| Total | 27 | 3 | 62 | 2 | 4 | 1 | 1 | 1 | 101 |

**[Table/Fig-5]:** PSA range in different prostatic pathology.

| | |
|---|---|
| Sensitivity | 96.67% |
| Specificity | 38.57% |
| Positive predictive value | 40.28% |
| Negative predictive value | 96.43% |
| Diagnostic accuracy of test | 56.00% |

**[Table/Fig-6]:** Probability of PSA in detecting malignancy.

When serum PSA levels were estimated to calculate the probability of malignancy in patients. A cut-off point of 4 ng/ml was taken. Values under 4 ng/ml were considered as negative for malignancy and values over the threshold were considered as positive for malignancy. The results from the test were compared with the histopathology report. The sensitivity and specificity were calculated. The positive and negative predictive values were also determined [Table/Fig-6].

The Gleason's grading system is based on glandular architecture; nuclear atypia is not evaluated. The Gleason's grading system defines five histological pattern or grades with decreasing differentiation and the sum of two commonest pattern is reported as Gleason's score [6] [Table/Fig-7]. The commonest Gleason's score obtained in our present study was 7, representing 16 cases (51.61%) of all the adenocarcinoma cases reported. Highest PSA level noted was 2358 ng/ml in a case of prostatic adenocarcinoma with a Gleason's score of 7.

| Gleason's score | Number of cases | Percentage (%) |
|---|---|---|
| 6 | 3 | 9.6% |
| 7 | 16 | 51.61% |
| 8 | 5 | 16.1% |
| 9 | 6 | 19.35% |
| 10 | 1 | 3.2% |
| Total | 31 | 100 |

**[Table/Fig-7]:** Comparison of Gleason's score.

## DISCUSSION

Prostate cancer detection has been altered with the use of PSA. But still the detection of prostate cancer in the population continues to be a vexing problem for the clinicians. An ideal screening test should have high specificity, high sensitivity, the disease entity tested for should have an important impact on the social and economic indicators and there should be appropriate curative modalities available to treat the condition once it is detected. Prostatic carcinoma is the most common visceral malignancy in the western world, and there were over 11,000 deaths recorded in India in 2005 [7].

The search for a non-invasive, cost effective, screening strategy for detection of prostatic carcinoma is continuing and the present study attempts to determine whether PSA testing needs to be continued.

### Mean Age of Diagnosis of Prostatic Carcinoma

The mean age of diagnosis of prostatic carcinoma in the present study was 68.8 years. The largest percentage of cancer patients were found to be clustered in the age group of 65 to 75 years. This correlated well with the study conducted by Ghafoori M et al., [8] and Catalona WJ et al., [9]. In study done by Quian et al., mean age for carcinoma was 64.4 years (44 to 77 years) [10]. According to study done by Di Silverio F et al., mean age for prostatic carcinoma was 68.9 years [11]. In a study done by Kyungeun K et al., mean age was 64.4 years (42-78 years) in 148 cases [12]. Our findings are similar to the above studies [Table/Fig-8].

| Present study | Di Silverio F et al., [11] | Kyungeun K et al., [12] | Pinto PA et al., [13] | Lefkowitz GK et al., [14] |
|---|---|---|---|---|
| 68.8 | 68.9 | 63 | 68.5 | 67 |

**[Table/Fig-8]:** Comparision of mean age (in years) of prostatic carcinoma with other studies.

### Mean Age of NPH Cases

In the present study NPH was found to be clustered over much wider age range of 30-90 years. The prevalence of NPH rises markedly with increased age. Maximum number of cases (71) were in the age group of 60-70 years. This is compared with the study conducted by Wei et al., [15] and other studies which do not indicate age clustering due to the large scale prevalence of this condition and the relatively greater proportion of asymptomatic cases in this group. There is no study in literature which has indicated the

age clustering in NPH due to large scale prevalence of this condition and relatively greater proportion of asymptomatic cases in this group. The mean age of NPH obtained in our study is 65.7 years.

### PSA Levels in NPH and Prostatic Carcinoma

In the present study out of 62 cases of NPH for which PSA levels were available, 27 cases had PSA values below 4 ng/ml and 29 cases had PSA value above 4 ng/ml but below 8 ng/ml.There were 6 cases of NPH with PSA value more than 8 ng/ml.

In the present study all the patients with prostatic carcinoma had PSA level more than 4 ng/ml and out of 101 cases for which PSA was available 63 cases had PSA level less than 8 ng/ml and these include 2 cases of prostatic carcinoma also.

According to a study conducted by Ghafoori M et al., serum PSA threshold of 4 ng/ml is usually an indication for prostate biopsy, and PSA levels between 4 ng/ml and 10 ng/ml, which is considered a grey zone, are shown to have a low sensitivity, but values above 10 ng/ml have a high sensitivity for prostate cancer. The sensitivity even reaches 100% if we consider values higher than 15 ng/ml [8].

In our study, a lower cut off point of 4ng/ml had a sensitivity of 96.67 % and specificity of 38.57 %. The present study is compared with following studies [Table/Fig-9].

Results of our studies indicate that prostate adenocarcinoma can be discriminated from prostate nodular hyperplasia by serum PSA with 100% sensitivity and 37.8% specificity.

| | Present study | Ghafoori M et al., [8] | Catalona WJ et al., [9] | Morgan TO et al., [16] | Shiek M et al., [17] |
|---|---|---|---|---|---|
| Sensitivity | 96.67 % | 93.4% | 79% | 94.9% | 93.4% |
| Specificity | 38.57% | 15.3% | 59% | 88.4% | 59% |

**[Table/Fig-9]:** Comparison of sensitivity and specificity of PSA.

### PSA Levels in Low Grade PIN

In the present study low grade PIN was diagnosed in 1.76% of the cases. The mean PSA level in these cases was 7.5 ng/ml, while almost all the cases diagnosed with prostatic carcinoma had PSA value more than 10 ng/ml except 2 cases for which PSA values were between 4-8 ng/ml. The present study was compared with other studies and showed significant positive correlation with the study done by Wang MC et al., [18] [Table/Fig-10].

Prostatic specific antigen is a glycoprotein molecule found exclusively in the cytoplasm of prostatic epithelial cells. These PSA molecules will be released outside to the systemic circulation only when the normal glandular architecture of the prostate is altered. The architectural alternation is more significantly seen in prostatic adenocarcinomas than NPH. This explains why PSA levels are much elevated in prostatic adenocarcinoma than NPH [12].

| Study | PSA Levels |
|---|---|
| Present study | 7.5 ng/ml |
| Wang MC et al., [18] | 4-10 ng/ml |
| Lakhey M et al., [19] | < 5 ng/ml |

**[Table/Fig-10]:** Comparison of PSA levels of low grade PIN lesion of present study with other studies in the table below.

From our study it was clear that there was no correlation between age and serum PSA value. Also, it was observed that there was no correlation between age and Gleason's score [Table/Fig-11].

The findings are in concordance to a study done by Milonas D et al., [20] in which there was no positive correlation between serum PSA value and corresponding Gleason's score [Table/Fig-12].

| Correlations | Pearson's Correlation value | p-value | Inference |
|---|---|---|---|
| Age and Serum PSA level | 0.026 | 0.796 | NS |
| Age and Gleason's score | -0.041 | 0.817 | NS |

**[Table/Fig-11]:** Correlation of Age with serum PSA level and Gleason's score.
*NS- Not Significant

| Correlations | Pearson's correlation value | p-value | Inference |
|---|---|---|---|
| Serum PSA level and Gleason's score | -0.170 | 0.388 | NS |

**[Table/Fig-12]:** Correlation of Gleason's score with PSA value.
*NS- Not Significant

## LIMITATION

One of the major limitation of the study was the inability to incorporate the PSA levels of all the study subjects. Also, the eventual outcome of the patients could not be assessed due to the lack of follow-up study.

## CONCLUSION

There are only few studies in which PSA values are compared with various prostatic lesions. Also, the sample size which was available for the present study further increases the accuracy levels of the study data. PSA is a valid and sensitive marker and may be continued as an early marker for the screening of prostate cancer. Serum PSA is elevated marginally in patients with NPH without inflammation and patients with chronic inflammation. With a cut-off value of 4 ng/ml the diagnostic accuracy was 56%, sensitivity was 96.67% and specificity was 38.5%. Thus, screening of prostatic lesions with serum PSA level is sensitive but not specific. The present study concluded that nodular prostatic hyperplasia was the commonest lesion of the prostate.The commonest age group at presentation for carcinoma and NPH was seventh and sixth decade respectively. Gleason's score 7 was the predominant score observed in prostatic carcinoma. There was no correlation between Gleason's score with age or PSA levels. Strong correlation of PSA levels more than 10 ng/ml with adenocarcinoma was seen in the present study.

Thus, from our study it has been concluded that PSA can still be used as a screening tool for prostatic adenocarcinomas due to its significant positive correlations, especially when the levels are high.The study also highlights the need for a more specific screening test for prostatic adenocarcinoma as the PSA levels are less specific.

## REFERENCES


[1] Semjonow A. Twenty years of prostate-specific antigen-an historical view. European Oncology Review. 2005:54-56.

[2] Labrie F, Dupont A, Suburu R, Cusan L, Tremblay M, Gomez JL, et al. Serum prostate specific antigen as pre-screening test for prostate cancer. J Urol. 1992;147(3):846-51.

[3] Sokoll LJ, Chan DW. Prostate specific antigen. Its discovery and biochemical characteristics. Urol Clin N Amer. 1997;24:253-59.

[4] Oesterling JE. Prostate specific antigen: a critical assessment of the most useful tumor marker for adenocarcinoma of the prostate. J Urol. 1991;145(5):907-23.

[5] Ozcana T, Bizlub M, MuslucN,Gozukara KH, Seyisa S, Akcay B. Elevation of serum and free prostate specific antigen levels after stent implantation in patients with coronary artery disease. Swiss Med Wkly. 2009;139:672-75.

[6] Epstein JI, Allsbrook WC Jr, Amin MB, Egevad LL, ISUP Grading Committee. The 2005 International Society of Urological Pathology (ISUP) consensus conference on Gleason's grading of prostatic carcinoma. The American journal of Surgical Pathology. 2005;29(9):1228-42.

[7] Lalitha k, Suman G. Estimation of time trends of incidence of prostate cancer an indian scenario. Asian Pac J Cancer Prev. 2012;13(12):6245-50.

[8] Ghafoori M, Varedi P, Hosseini SJ, Asgari M, Shakiba M. Value of prostate-specific antigen and prostate-specific antigen density in detection of prostate cancer in an Iranian population of men. Urol J. 2009;6(3):182-88.

[9] Catalona WJ, Smith DA, Ratliff TL, Dodda KM, Coplen DE, Yuan JJ. Measurement of prostate-specifi c antigen in serum as a screening test for prostate cancer. N Engl Med.1991;324:1156-61.

[10] Quian J, Wollan P. The extent and multicentricityof high grade prostatic intraepithelial neoplasia in clinicallylocalized prostatic adenocarcinoma. Hum Pathol. 1997:28(2):143-48.

[11] Di Silverio F, Gentile V, Matteis DA, Mariotti G, Giuseppe V, Luigi PA, et al. Distribution of inflammation, pre-malignant lesions, incidental carcinoma in histologically confirmed benign prostatic hyperplasia: a retrospective analysis. Eur Urol. 2003;43(2):164-75.

[12] Kyungeun K, Pil JP, Jae YR, Shin D, Huh SJ, Yong MC. Limited sampling of radical prostatectomy specimens with excellent preservation of prognostic parameters of prostate cancer. Archives of Pathology & Laboratory Medicine. 2009;133(8):1278-84.

[13] Pinto PA, Chung PH, Rastinehad AR, Baccala AA, Kruecker J, Benjamin CJ, et al. Magnetic resonance imaging/ultrasound fusion guided prostate biopsy improves cancerdetection following transrectal ultrasound biopsy and correlates with multiparametric magnetic resonance imaging. J Urol. 2011;186(4):1281-85.

[14] Lefkowitz GK, Taneja SS, Brown J, Melamed J, Lepor H. Follow-up interval prostate biopsy 3 years after diagnosis of high grade prostatic intraepithelial neoplasia is associated with high likelihood of prostate cancer, independent of change in prostate specific antigen levels. J Urol. 2002;168(4):1415-18.

[15] Wei JT, Calhoun E, Jacobsen SJ. Urologic diseases in America project: benign prostatic hyperplasia. The Journal of urology. 2005 Apr 30;173(4):1256-61.

[16] Morgan TO, Jacobsen SJ, McCarthy WF, Jacobson DJ, McLeod DG, Moul JW. Age-specific reference ranges for serum prostate-specific antigen in black men. New England Journal of Medicine. 1996;335(5):304-10.

[17] Sheikh M, Al-Saeed O, Kehinde EO, Sinan T, Anim JT, Ali Y. Utility of volume adjusted prostate specific antigen density in the diagnosis of prostate cancer in Arab men. Int Urol Nephrol. 2005;37(4):721-26.

[18] Wang MC, Valenzuela LA, Murphy GP, Chu TM. Purification of human prostate specific antigen. Invest Urol.1979;17:159-63.

[19] Lakhey M, Ghimire R, Shrestha R, Bhatta AD. Correlation of serum free prostate-specific antigen level with histological findings in patients with prostatic disease. Kathmandu University Medical Journal. 2010;8(2):158-63.

[20] Milonas D, Smaiyse D, Jievaltas. factors predicting Gleason score 6 upgrading after radical prostatectomy,Cent European J urol 2011:64(4)205-208.



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