SSR Institute of International Journal of Life Sciences
ISSN (O): 2581-8740 | ISSN (P): 2581-8732
Gupta and Sharma *et al.*, 2026
doi: 10.21276/SSR-IIJLS.2026.12.2.18

Original Article

open access

Grading of Prostatic Carcinoma and Its Association with Ki67 and PSA Levels

Nishta Gupta[1]*, Divya Sharma[2]

[1]Assistant Professor, Dept of Pathology, Esic Basaidarapur, Basaidarapur, Delhi-110015, India
[2]Consultant, Dept of Pathology, Vallabhbhai Patel Chest Institute, Basaidarapur, Delhi-110007, India

***Address for Correspondence:** Dr. Nishta Gupta, Assistant Professor, Dept of Pathology, Esic Basaidarapur, Delhi-110015, India
E-mail: nishtagupta@ymail.com

Received: 01 Nov 2025/ Revised: 14 Dec 2025/ Accepted: 25 Feb 2026

ABSTRACT

Background: Prostate Cancer (PC) is a major health issue in the male population. The most useful and instructive predictors of prostate cancer are the Gleason Score (GS) and PSA (Prostate Specific Antigen) levels. This prediction is further refined when Ki67 is used as an immunomarker for tumour volume and proliferation rate. The present study aimed to examine Ki67 expression in prostate carcinoma and to compare Ki67 expression with Gleason grade and PSA levels.

Methods: The study was conducted on 51 patients who underwent prostatic trucut biopsy or transurethral prostate resection. Histopathology was performed on these specimens, followed by Ki67 immunostaining. Gleason's score and PSA levels were also noted. Statistical analysis of the observations was performed using SPSS Software (Statistical Package for Social Sciences) version 23 and Microsoft Excel. Association of categorical variables was analysed using Pearson's chi-square test. A $p<0.05$ was considered significant.

Results: Out of 51 patients, 40 were diagnosed with prostatic carcinoma and 11 with benign prostatic hyperplasia (BPH). Gleason's scoring was performed for carcinoma cases. Most carcinoma cases showed higher Ki-67 immunoreactivity, while BPH cases showed low Ki-67 expression. Higher PSA levels were observed in 60% of prostate cancer cases compared to BPH. A statistically significant association was found between higher PSA levels and higher-grade adenocarcinoma, as well as between Gleason score, Ki-67 immunoreactivity, and PSA levels ($p<0.05$).

Conclusion: This study concluded that Ki-67 immunohistochemical expression shows a strong association with Gleason's score and PSA levels, and helps in the diagnosis of prostate cancer.

Key-words: Prostate, BPH, Gleason's score, Immunohistochemical expression, Ki67, Prostate-specific antigen levels

INTRODUCTION

Prostate cancer (PC) is the second most frequently diagnosed cancer and the fifth leading cause of cancer death in males. Benign Prostatic Hyperplasia (BPH) and Prostate cancer are the two most common diseases that occur in the prostate in older adults. Both of these conditions are disorders of cell differentiation and cell proliferation [1].

How to cite this article
Gupta N, Sharma D. Grading of Prostatic Carcinoma and Its Association with Ki67 and PSA Levels. SSR Inst Int J Life Sci., 2026; 12(2): 9432-9439.

Access this article online
https://iijls.com/

For the growth and survival of normal prostate gland cells, androgens play a very important role. These androgens bind to the androgen receptor (AR), which further enhances the survival and growth gene expression [2].

At the time of diagnosis, clinical staging, serum prostate-specific antigen (PSA), and the Gleason Score (GS) are the primary three parameters on which the prognosis and the choice of therapy of the cancer depend [3]. Gleason Score remains one of the most important and significant diagnostic factors for prostate carcinoma, irrespective of all the histopathological findings as well as clinical presentation of the patients [4]. In cases with limited tissue on needle biopsy, immunohistochemical (IHC) markers are often used to aid in the diagnosis of prostatic adenocarcinoma. It is of great importance in

doi: 10.21276/SSR-IIJLS.2026.12.2.18

the future to know the response to treatment and to guide therapy [5].

At the time of mitotic division, almost all the Ki-67 antigen is relocated to the chromosome surface, whereas during interphase it is exclusively detected within the nucleus. Ki-67 is an excellent marker for determining the growth fraction and index in a given cell population in patients with PC. This is because Ki67 is expressed during all active phases of the cell cycle (G1, S, G2, and mitosis) and is absent from resting cells (G_0). The present study was conducted to evaluate Ki-67 expression in prostate carcinoma and to compare it with Gleason grade and PSA levels.

MATERIALS AND METHODS

Study Design and Setting- This cross-sectional study was conducted in the Department of Pathology at the Himalayan Institute of Medical Sciences (HIMS), Dehradun, over 12 months.

Study Population- A total of 51 samples was included in the study, comprising 40 suspected cases of carcinoma prostate and 11 cases of benign prostatic hyperplasia (BPH) used as controls. The samples were obtained from patients who underwent prostatic Tru-Cut biopsy or transurethral resection of the prostate.

Inclusion and Exclusion Criteria- Cases with marked inflammation of the prostate (prostatitis) and patients who had received chemotherapy or radiotherapy for any illness were excluded from the study. Representative cases of benign prostatic hyperplasia and/or normal prostatic tissue were used as negative controls.

Data Collection and PSA Assessment- Clinical history was recorded in the case reporting form, and all patients were assessed for prostate-specific antigen (PSA) levels.

Histopathological Examination- After fixation in 10% formalin, tissues were processed for grossing according to the standard departmental protocol. Histomorphological examination was performed using Hematoxylin and Eosin (H&E) staining. Morphological grading of carcinoma cases was done using the Gleason scoring system.

Immunohistochemistry- Ki-67 (BIOGENEX Company kit) was used. Immunostaining was graded based on staining intensity and the relative abundance of Ki-67 immunoreactive cells. Staining intensity was graded as 0 (colourless), 1 (yellowish), 2 (brown-yellow), and 3 (dark brown). The staining range was assessed by counting 100 cells and recording nuclear positivity. Scores were assigned as follows: score 0 (no staining), score 1 (≤25% positive cells), score 2 (26–50%), score 3 (51–75%), and score 4 (76–100%).

Statistical Analysis- Ki-67 immunopositivity was compared with the Gleason score and PSA levels. Statistical analysis was performed using SPSS software (version 23) and Microsoft Excel. The association between categorical variables was analysed using Pearson's chi-square test, and $p<0.05$ was considered statistically significant.

RESULTS

Out of 51 patients, 40 were diagnosed with prostate cancer and 11 with benign prostatic hyperplasia (BPH) morphologically (Fig. 1).

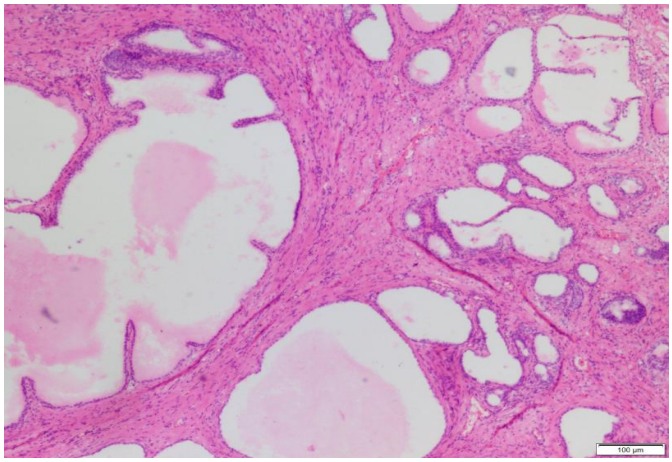

Fig. 1: Shows proliferation of both glandular and stromal components in Benign Prostate Hyperplasia (H&E; 4x10X)

As shown in (Fig. 2), the maximum number of PC patients were in the age group of 61-70 years (n=15; 37.5%), followed by 71-80 years (n=11; 27.5%), while age-wise distribution of BPH (control) was most seen in 51-60 years (n=5; 45.4%). The mean age of the cases was 69.30±8.70 years, and that of controls (BPH) was 63.63±9.62 years. 72.5% (n=29) of cases of adenocarcinoma were active smokers, while 63.6% controls were also smokers. The comparative data did not show statistical significance (p>0.05).

doi: 10.21276/SSR-IIJLS.2026.12.2.18

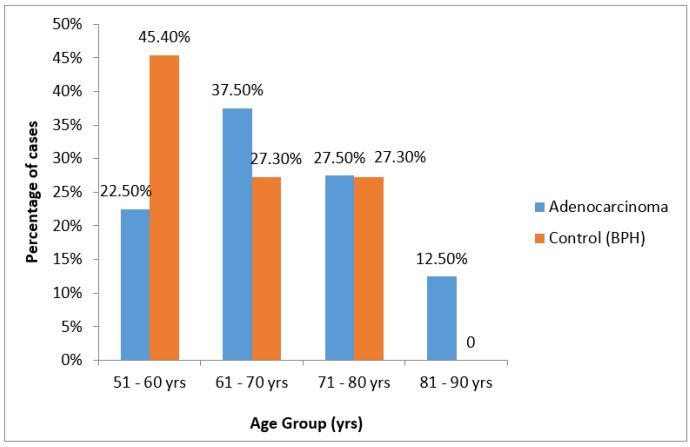

Fig. 2: Age-wise distribution of adenocarcinoma cases (n=40) and BPH (n=11)

Fig. 3 shows that the most common presenting complaint of total cases and controls (n=51) was difficulty in micturition (n=34; 66.6%), followed by incomplete micturition (n=33; 64.7%).

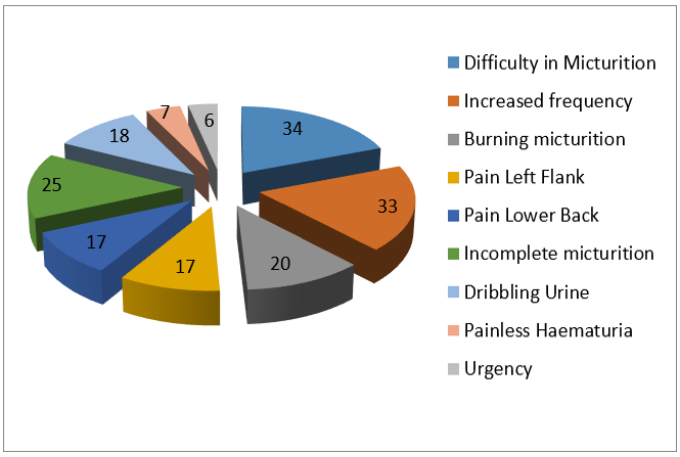

Fig. 3: Distribution according to clinical presentation of total cases and controls (n=51)

Of the 40 adenocarcinoma cases, the largest number (n=24; 60%) had PSA levels of 51-100 ng/ml. Of the total 11 controls (BPH), the largest number of cases (n=10; 90.9%) showed PSA levels in the range of 4-25 ng/ml (Fig. 4).

The mean±sd PSA of malignant cases was 104.82±145.94 ng/ml, and for BPH was 9.53±4.16 ng/ml. On comparing this data, it was found to be statistically significant (p=0.03). It was also observed that among 40 cases of adenocarcinoma, the majority (n=36; 90%) showed Ki-67 immunoreactivity >25%, whereas none of the control group (BPH) showed Ki-67 immunoreactivity >25% (Fig. 5).

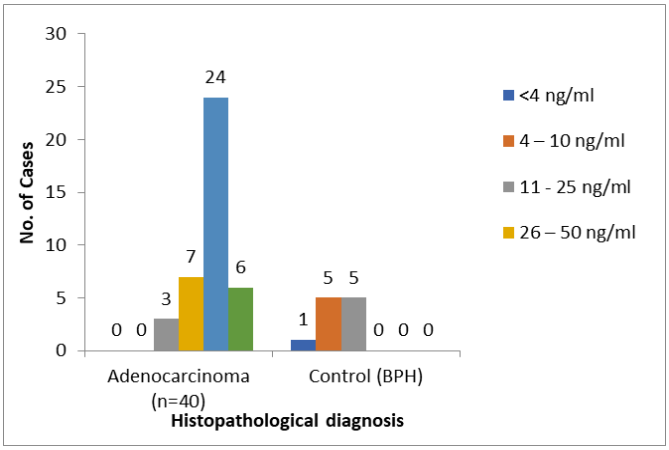

Fig. 4: PSA values in adenocarcinoma cases (n=40) and BPH (Control) (n=11)

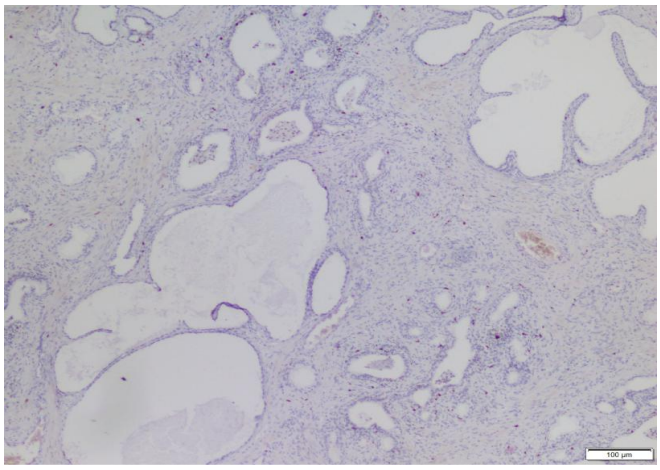

Fig. 5: Shows 12% Ki-67 immunoreactivity in Controls (Benign Prostate Hyperplasia) (H&E; 4x10X)

This was found to be highly significant statistically ($p<0.05$) (Table 1). (Table 2) 76.4% of cases (n=13) of poorly differentiated adenocarcinoma (Fig. 6) showed PSA values in the range of 51-100 ng/ml, followed by 4 cases (23.6%) with PSA >100 ng/ml, while none showed PSA levels <50 ng/ml.

Table 1: Ki-67 immunoreactivity in adenocarcinoma cases (n=40) and BPH (Control) (n=11)

Ki-67 score (%)	Adenocarcinoma (n=40)	BPH (Control) (n=11)
1 (≤25%)	4	11
2 (26-50%)	20	00
3 (51-75%)	14	00
4 (76-100%)	2	00
Total	40	11
Mean±SD	47.50±15.90	9.90±2.84
p-value	0.00	

** Pearson chi-square test; BPH: Benign Prostatic Hyperplasia*

Table 2: Association of PSA levels with Gleason's score in adenocarcinoma cases

PSA (ng/ml)	Gleason's Score (Grade)			Total (n)
	6 (Well differentiated tumors) n (%)	7 (Moderately differentiated tumours) n (%)	8 and 9 (Poorly differentiated tumors) n (%)	
<4	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
4 – 10	0 (0.0%)	0 (0.0%)	0 (0.0%)	0
11 - 25	3 (25%)	0 (0.0%)	0 (0.0%)	3
26 – 50	5 (41.7%)	2 (18.2%)	0 (0.0%)	7
51 – 100	4 (33.3%)	7 (63.6%)	13 (76.4%)	24
>100	0 (0.0%)	2 (18.2%)	4 (23.6%)	6
Total	12	11	17	40

Pearson chi square = 19.63, p= 0.02; PSA: prostate-specific antigen

The well-differentiated adenocarcinoma (Fig. 7) cases (n=12) showed PSA levels in the range of 11-100 ng/ml, and none showed >100ng/ml. There was a statistically significant association between adenocarcinoma grade and PSA levels ($p<0.05$).

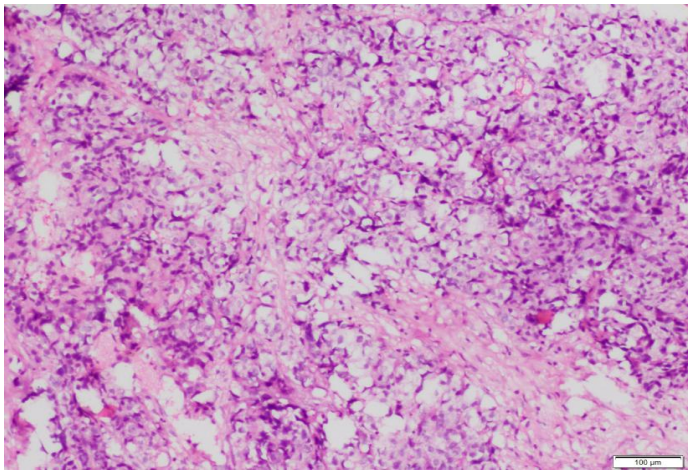

Fig. 6: Poorly differentiated prostate adenocarcinoma, Gleason's score 9 (5+4) (H&E; 4x10X)

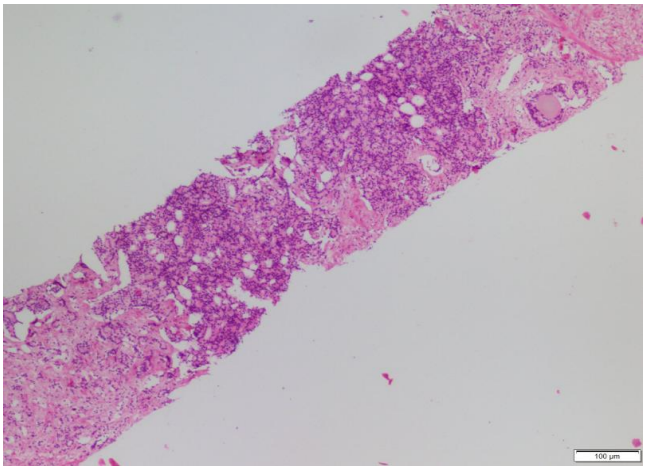

Fig. 7: Well-differentiated prostate adenocarcinoma, Gleason's score 6 (3+3) (H&E; 4x10X)

Table 3 shows that 52.9% (n=9) and 5.8% (n=1) of the cases of poorly differentiated adenocarcinoma had Ki-67 immunoreactivity scores of 3 and 4, respectively (Fig. 8), while none had score 1.

Table 3: Association of Gleason's score with Ki-67 immunoreactivity in adenocarcinoma cases (n=40)

Ki-67 score (%)	Gleason's Score (Grade)			Total
	6 (Well differentiated tumors) n (%)	7 (Moderately differentiated tumors) n (%)	8 and 9 (Poorly differentiated tumors) n (%)	
1 (≤25%)	4 (33.3%)	0 (0.0%)	0 (0.0%)	4
2 (26-50%)	5 (41.7%)	8 (72.7%)	7 (41.3%)	20
3 (51-75%)	3 (25%)	2 (18.3%)	9 (52.9%)	14
4 (76-100%)	0 (0.0%)	1 (9.0%)	1(5.8%)	2
Total	12	11	17	40

Pearson chi square = 22.43, p= 0.008

doi: 10.21276/SSR-IIJLS.2026.12.2.18

It was also observed that 41.7% (n=5) and 25% (n=3) of the well-differentiated adenocarcinoma cases showed Ki-67 immunoreactivity scores of 1 and 2, respectively (Fig. 9), while none showed a score of 4. There was a positive correlation between Gleason's score and Ki-67 score, which was found to be statistically significant ($p<0.05$).

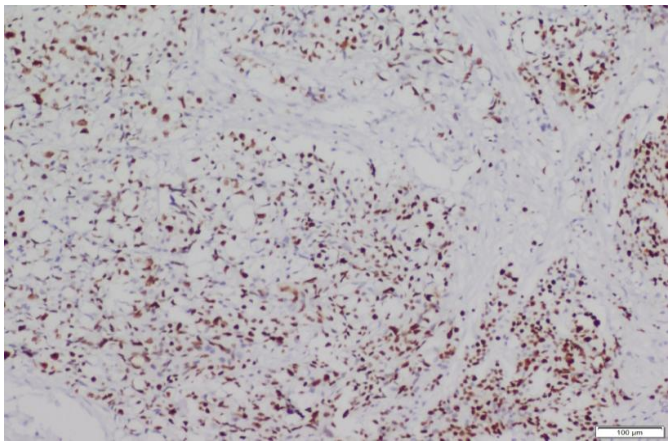

Fig. 8: 76-100% Ki-67 immunoreactivity (Score 4) in poorly differentiated prostate adenocarcinoma, Gleason's score 9 (H&E; 4x10X)

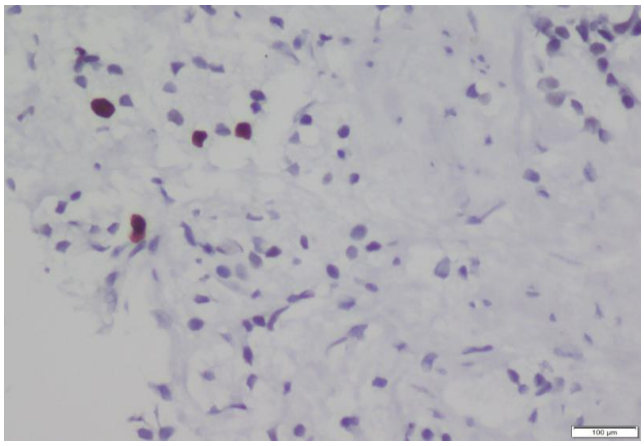

Fig. 9: 25-50% Ki-67 immunoreactivity (Score 2) in the same case of well-differentiated prostate adenocarcinoma, Gleason's score 6 (3+3) (H&E; 4x10X)

Table 4 (a) and (b) show that 90% (n=36) of cases of adenocarcinoma showed Ki-67 immunoreactivity of >25% and PSA levels of >25 ng/ml. In comparison, all cases of BPH (Controls) (n=11) showed Ki-67 immunoreactivity of <25% and PSA levels <25 ng/ml. This was found to be a statistically significant difference between adenocarcinoma and BPH (Controls), given its association with Ki-67 immunoreactivity and PSA levels ($p<0.05$).

Table 4 (a): Association of Ki-67 immunoreactivity with PSA levels in adenocarcinoma cases (n=40)

PSA (ng/ml)	Ki -67 score (%)				Total
	1 (≤25%)	2 (26-50%)	3 (51-75%)	4 (76-100%)	
<4	0	0	0	0	0
4 – 10	0	0	0	0	0
11 - 25	3	0	0	0	3
26 – 50	1	5	1	0	7
51 – 100	0	12	11	1	24
>100	0	3	2	1	6
Total	4	20	14	2	40

Pearson chi square = 34.45, p= 0; PSA: prostate-specific antigen

Table 4 (b): Association of Ki-67 immunoreactivity with PSA levels in BPH (Control) (n=11)

PSA (ng/ml)	Ki -67 score (%)				Total
	1 (≤25%)	2 (26-50%)	3 (51-75%)	4 (76-100%)	
<4	1	0	0	0	1
4 – 10	5	0	0	0	5
11 - 25	5	0	0	0	5
26 – 50	0	0	0	0	0
51 – 100	0	0	0	0	0
>100	0	0	0	0	0
Total	11	0	0	0	11

Pearson chi square = 55, p= 0.29; PSA: prostate-specific antigen

doi: 10.21276/SSR-IIJLS.2026.12.2.18

DISCUSSION

Prostate Cancer (PC) continues to be a major health issue in the male population. However, it is a slowly progressing cancer that usually remains localised, but has the potential to be aggressive and widely invasive [6]. Treatment of PC is largely based on Gleason scoring (grading), PSA levels, and tumour stage (TNM). Of these, the most useful and instructive predictor of prostate cancer is the GS. This prediction is further refined when Ki67 is used as an immunomarker for tumour volume and proliferation rate [7].

In the present study, the mean age of prostate cancer patients was 69.30±8.70 years, while BPH was more common in the 51–60 years age group (mean 63.63±9.62 years). Similar findings were reported by Fisher *et al.* and Sulik *et al.*, who observed that prostate cancer predominantly occurs in older age groups [8,9]. Previous studies by Bostwick *et al.* and Meigs *et al.* also noted that BPH begins to increase in prevalence from the fourth decade, whereas prostate cancer typically occurs 15–20 years later [10,11]. Although earlier studies have suggested that long-term smoking increases the risk of prostate cancer [12–15], the present study did not find a clear association, as a high proportion of smokers was also observed among BPH patients (63.6%).

In comparison, this observation did not show significance ($p>0.05$). But there was no relation between the number of pack years or in patients with a history of active smoking in relation to prostate cancer risk in two studies done by Giles *et al.* [16] and Rohrmann *et al.* [17]. So, it may suggest that a larger study population is required to find any association between smoking and prostate carcinoma.

The most common presenting complaint among cancer patients (n=40) was difficulty with micturition (n=34; 85.0%), followed by increased urinary frequency (n=25; 62.5%), and the least common complaint was urgency (n=6; 15%). A previous study done by Ahmad et al concluded that the classic findings were difficulty in voiding, dysuria, and increased urinary frequency, which were concordant with our study [18]. In the present study, the mean PSA in the malignant cases was 104.82 ng/mL, and that in the control group was 9.53 ng/mL, which was statistically significant ($p=0.03$). This was in accordance with the study by Sophia *et al.* [19]. In the present study, the maximum number of prostate adenocarcinoma cases (n=36; 90%) showed Ki67 immunoreactivity>25%, whereas none of the control group (BPH) cases showed Ki67 immunoreactivity>25%. Ki-67 immunoreactivity in PC was significantly higher than in the control group (BPH). In a previous study by Verma *et al*., Ki-67 expression was significantly up-regulated in prostate cancer (n=32; 64%) compared with BPH (10%; $p=0.003$) [20]. Nikoleishvili *et al.* [21] and Rashed *et al.* [22] also found this marker to be highly expressed in prostate cancer as compared with BPH. Another study done by Park S J et al, in 2010 took a total of 124 patients (105 prostate cancer and 19 BPH) in which he observed that Ki67 immunoreactivity was high in prostate cancer (9.64%) with maximum number of patients with >25% positivity when compared with BPH (2.45%) in which all showed <25% positivity [23]. Our study, hence, agreed with these observations. The hallmark of any malignancy is uncontrolled proliferation. As Ki67 is a proliferative marker, immunohistochemical assessment of Ki67 is the most widely used measure of tumour proliferative potential and should therefore be considered [24]. An important finding of the present study was the association between PSA levels and Gleason's score, as well as the association between Gleason's score and Ki67 immunostaining. It showed that 76.4% of cases of poorly differentiated adenocarcinoma (n=13) had PSA values in the range of 51-100 ng/ml, followed by 4 cases (23.6%) with PSA >100 ng/ml, while none had PSA levels <50 ng/ml. The well-differentiated adenocarcinoma cases (n=12) showed PSA levels of 11-100 ng/mL, and none exceeded 100 ng/mL. It was observed that the higher the stage, the higher the PSA levels. There was a statistically significant difference between the grade of adenocarcinoma and PSA levels. ($p<0.05$). It also showed that 52.9% (n=9) and 5.8% (n=1) of the cases of poorly differentiated adenocarcinoma had Ki67 immunoreactivity scores of 3 and 4, respectively. In comparison, none showed score 1. 41.7% (n=5) and 25% (n=3) of cases with well-differentiated adenocarcinoma had scores of 1 and 2, respectively, for Ki-67 immunoreactivity, while none showed score 4. This concluded that the higher the Gleason grade, the higher the Ki-67 immunostaining and thus the higher the score. There was a statistically significant difference between the GS and Ki-67 scores ($p<0.05$). In a previous study done by Rugwizangoga *et al*., 214 cases of prostate cancer were included. The mean PSA level was 79.57 ng/mL, which correlated with the poorly differentiated

doi: 10.21276/SSR-IIJLS.2026.12.2.18

Gleason grade (p=0.001), indicating that higher Gleason grade was associated with higher PSA levels. The study also showed that 50.94% of cases had >50% Ki67 immunostaining with GS 8 and 9, while 45% showed <50% Ki67 immunostaining with GS 6. The study concluded that higher GS correlated with higher PSA levels and higher Ki-67 immunostaining (p=0.001) [6]. Park *et al.* [23] also observed similar findings. Verma *et al.* [20] reported a statistically significant correlation between Ki-67 positivity and increased Gleason score. Various other studies have concluded that Ki-67 proliferation activity is strongly related to the histopathological tumour pattern. In contrast to other studies, Murti *et al.* found that 7 of 15 patients had low Ki-67 expression and PSA values >50 ng/mL. In comparison, only 2 patients showed high Ki67 expression with PSA levels >50 ng/mL, suggesting no significant association between Ki67 and PSA (p>0.05) [25]. A similar study by Rugwizangoga *et al.* [6] showed an association between PSA levels and Gleason's score, but when the association between Ki67 and PSA was examined, no significant relationship was observed. Two studies were discordant with the present study, and the disagreement persists regarding the clinical implications of malignant tumours detected by screening methods. This showed that a combination of GS and Ki67 index provides better diagnostic and prognostic information than PSA alone. Despite these promising findings of a positive association between Ki67 immunostaining and PSA levels and GS score, there are concerns about Ki67's clinical application. There may be inter-observer variability in the estimation of expression and in categorisation, along with technical variables such as fixation time and storage conditions for monoclonal antibodies. An important limitation of the present study was the limited time (12 months) and the smaller sample size. The present study examined only factors routinely assessed in the clinical management of PC. More focus should also be on novel markers, such as aberrant DNA methylation, miRNA expression, and genes involved in inflammation, which are promising and should be examined in future studies. Therefore, we suggest that multicenter prospective studies with larger sample sizes are required to determine the exact association between Ki67 immunostaining and PSA levels, as well as between Ki67 immunostaining and GS.

CONCLUSIONS

The study concluded that prostate carcinoma is more commonly seen in the sixth decade, with the most common presenting complaint of difficulty in micturition. This study did not find any association between prostate cancer and smoking habits. Serum PSA levels were found to be diagnostic in cases of prostate cancer as compared to the BPH cases. High values of serum PSA levels were associated with a higher Gleason's Score. There was a positive association between the Gleason's Score and the Ki-67 score as well. In addition, a positive association between PSA levels and Ki67 immunostaining was also observed in malignant cases of prostate cancer. This study concluded that Ki-67 immunohistochemical expression shows a strong association with Gleason's score and PSA levels, and helps in the diagnosis of prostate cancer.

CONTRIBUTION OF AUTHORS

Research concept- Divya Sharma
Research design- Divya Sharma
Supervision- Nishta Gupta
Materials- Divya Sharma
Data collection- Divya Sharma
Data analysis and interpretation- Nishta Gupta
Literature search- Divya Sharma
Writing article- Divya Sharma
Critical review- Nishta Gupta
Article editing- Divya Sharma
Final approval- Nishta Gupta

REFERENCES

[1] Adisa JO, Egbujo EC, Ibrahim B, Musa B, Madukwe J. Expression of selected cytokeratins and Ki67 protein in prostatic tumor: Can these be used as tumor markers? Pan Afr Med J., 2015; 20: 21–27.

[2] Lonergan PE, Tindall DJ. Androgen receptor signaling in prostate cancer development and progression. J Carcinog., 2011; 10: 31–37.

[3] Partin AW, Kattan MW, Subong EN, Walsh PC, Wojno KJ, et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer: A multi-institutional update. JAMA., 1997; 277: 1445–51.

[4] Pierorazio PM, Walsh PC, Partin AW, Epstein JI. Prognostic Gleason grade grouping: Data based on

the modified Gleason scoring system. BJU Int., 2013; 111: 753–60.

[5] Berney DM, Gopalan A, Kudahetti S, Fisher G, Ambroisine L, et al. Ki-67 and outcome in clinically localised prostate cancer. Br J Cancer, 2009; 100: 888–93.

[6] Rugwizangoga B, Vuhahula E, Kitinya J. Combination of Ki67 expression and Gleason score for prostatic adenocarcinoma offers better prognostic information. Internet J Urol., 2014; 12: 21–27.

[7] Stattin P, Damber JE, Karlberg L, Bergh A. Cell proliferation assessed by Ki-67 immunoreactivity is a predictive factor for survival in prostate cancer. J Urol., 1997; 157: 219–22.

[8] Fisher G, Yang ZH, Kudahetti S, Møller H, Scardino P, Cuzick J, et al. Prognostic value of Ki-67 for prostate cancer death in a conservatively managed cohort. Br J Cancer, 2013; 108: 271–76.

[9] Sulik M, Maruszak K, Puchalska J, Misiukiewicz-Poć M. Expression of Ki-67 as a proliferation marker in prostate cancer. Pol Ann Med., 2011; 18: 12–19.

[10]Bostwick DG, Cooner WH, Denis L, Jones GW, Scardino PT, et al. Association of benign prostatic hyperplasia and cancer of the prostate. Cancer, 1992; 70: 291–301.

[11]Meigs JB, Mohr B, Barry MJ, Collins MM, McKinlay JB. Risk factors for clinical benign prostatic hyperplasia in a community population. J Clin Epidemiol., 2001; 54: 935–44.

[12]Plaskon LA, Penson DF, Vaughan TL, Stanford JL. Cigarette smoking and risk of prostate cancer in middle-aged men. Cancer Epidemiol Biomarkers Prev., 2003; 12: 604–09.

[13]Dai WS, Gutai JP, Kuller LH, Cauley JA. Cigarette smoking and serum sex hormones in men. Am J Epidemiol., 1988; 128: 796–805.

[14]Kalcher K, Kern W, Pietsch R. Cadmium and lead in the smoke of filter cigarettes. Sci Total Environ., 1993; 128: 21–35.

[15]Saldivar L, Luna M, Reyes E, Soto R, Fortoul TI. Cadmium determination in Mexican-produced tobacco. Environ Res., 1991; 55: 91–96.

[16]Giles GG, Severi G, McCredie MR, English DR, Johnson W, et al. Smoking and prostate cancer: Findings from an Australian case-control study. Ann Oncol., 2001; 12: 761–65.

[17]Rohrmann S, Crespo CJ, Weber JR, Smit E, Giovannucci E, et al. Association of smoking, alcohol consumption and physical activity with lower urinary tract symptoms. BJU Int., 2005; 96: 77–82.

[18]Ahmad A, Tan W. Atypical presentation of prostate cancer and workup of adenocarcinoma of unknown primary. World J Oncol., 2012; 3: 187–90.

[19]Li S, Ding Z, Lin JH, Behl AS, Pericone C, et al. Association of PSA trajectories with risk for metastasis and mortality in nmCRPC. J Clin Oncol., 2018; 12: 29–35.

[20]Verma R, Gupta V, Singh J, Verma M, Gupta G, et al. Significance of p53 and Ki-67 expression in prostate cancer. Urol Ann., 2015; 7: 488–93.

[21]Nikoleishvili D, Pertia A, Trsintsadze O, Gogokhia N, Managadze L, et al. Expression of p27, cyclin D3 and Ki67 in BPH and prostate cancer. Int Urol Nephrol., 2008; 40: 953–59.

[22]Rashed HE, Kateb I. Evaluation of minimal prostate cancer using AMACR, P63 and Ki67. Int J Pathol., 2012; 9: 12–21.

[23]Park SJ, Sung WJ, Kim MJ. p16INK4a-PTEN, E-cadherin, Bcl-2 and Ki-67 expression in prostate cancer. Korean J Pathol., 2010; 44: 682–86.

[24]Desmeules P, Hovington H, Nguilé-Makao M, Léger C, Caron A, et al. Comparison of digital image analysis and visual scoring of Ki-67 in prostate cancer prognosis. Diagn Pathol., 2015; 10: 67–72.

[25]Murti K, Warli SM, Laksmi LI. Relationship between Ki-67 expression, histopathological grading and PSA values in adenocarcinoma prostate. Bali Med J., 2017; 6: 293–97.