DOI: 10.7860/JCDR/2025/77557.21790

Original Article

Pathology Section

Expression of Prostate-specific Membrane Antigen in Prostatic Carcinoma and its Correlation with Gleason Score and Grade Grouping: A Cohort Study

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ABSTRACT

Introduction: Prostate-Specific Membrane Antigen (PSMA), a transmembrane glycoprotein, has emerged as a promising biomarker due to its selective presence in prostate tissue, particularly in prostatic carcinoma. This has been extensively studied in imaging to assess tumour aggressiveness to aid in treatment planning.

Aim: To study the Immunohistochemical (IHC) expression of PSMA in prostatic carcinoma and to correlate PSMA expression with Gleason Score (GS) and grade grouping.

Materials and Methods: The present cohort study was conducted over two years (May 2022 to April 2024) at the Department of Pathology, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India. A total of 63 cases of prostatic adenocarcinoma were included; the PSMA expression was performed and correlated with clinicopathological parameters such as age, nature of specimen, location of tumour and serum Prostate-Specific Antigen (PSA) level. Statistical analysis such as mean, percentage, Standard Deviation (SD), Chi-square test was used as a test of association. The Spearman's Rho Correlation test was used to establish correlation of the parameters with PSMA expression. All tests were performed using Statistical Package for Social Sciences (SPSS), version 26.0.

Results: The PSMA expression was higher in cases with higher GSs (33 cases with GS >7) and Grade group (24 cases with Grade group 5) and the correlation was statistically significant for both (r=0.403, p-value=0.014 and r=0.391, p-value=0.016, respectively). The PSMA expression did not correlate with age (r=0.118, p-value=0.205) serum PSA levels (r=0.088, p-value=0.643), and with Peri-Neural Invasion (PNI) (r=-0.139, p-value=0.486). The study showed a 0.7 fold increase in disease recurrence after curative therapy using the Kaplan-Meier curve analysis.

Conclusion: A significant overexpression of PSMA in prostatic carcinoma suggests its potential as a diagnostic and prognostic marker. High PSMA expression was seen in prostatic carcinoma with higher GS and Grade group in this study. Thus, high PSMA expression is associated with poor prognosis and disease recurrence. Following curative therapy for prostate carcinoma, PSMA can predict disease recurrence and is an independent prognostic marker on biopsies. This study proposes the use of the immunohistochemical marker PSMA for differentiating between indolent and severe disease and further categorising into low risk and high-risk patients.

Keywords: Biopsy, Cancer in men, Prostate-specific membrane antigen, Tumours

INTRODUCTION

Prostate carcinoma is the third most prevalent cancer in men and the eighth leading cause of death [1,2]. The incidence and mortality rates of prostate cancer are significantly influenced by age, with the highest proportion of cases (12.3%) occurring in adults over 65 [3]. Ninety percent of prostate carcinomas are conventional acinar adenocarcinomas, the remaining being adenocarcinoma variants [4]. Although cancer can develop anywhere in the prostate, it mainly occurs in the peripheral zone [4]. The Gleason scoring system is used to grade prostate cancer. In the core biopsy/surgical specimen, it is the sum of the differentiation scores of the two most common architectural patterns in the tumour [5]. GS and grade grouping are important in risk stratifying these patients. Evaluation of the GS has poor inter-observable reproducibility and an inherent difficulty in classifying GS-7 lesions (i.e., GS 3+4 versus GS 4+3) as the grade group changes [5]. Serum PSA is an organ-specific biomarker rather than a tumour-specific one, its accuracy is low and it is raised even in benign prostate hyperplasia [6-8].

PSMA is a carboxypeptidase-active type 2 integral membrane protein. It is expressed on the cytoplasm and membrane of epithelial cells of prostate tissue and the apical surface of endothelial cells [9]. Expression of PSMA is significantly elevated in prostate cancer but expressed sporadically in healthy prostate tissue [10,11]. Apart from prostate, PSMA is also expressed in CNS, small intestine and kidney [12]. Higher grades of prostate cancer and androgen deprivation has been linked to PSMA overexpression [13,14]. Hence, PSMA has a vital role in the progression of prostate cancer however its relationship to the GS and grade grouping is still unclear. PSMA is currently used as a pET imaging biomarker for localisation of prostate cancer, grading, and primary staging [15,16]. The primary determinant of the biological behaviour of prostate cancer is still the tumour grade as determined by the GS and grade grouping [5]. This risk-stratification algorithm is commonly used by clinicians to make treatment decisions, such as active surveillance, curative surgery, and/or radiation therapy [5]. However, these parameters fall short in differentiating high and low risk diseases, whereas PSMA serves as a reliable biomarker to assess the aggressiveness of the disease [5]. Since PSMA binding tracers are increasingly employed for pET, PSMA expression in prostate cancer has attracted significant attention lately [15,16]. The literature search revealed few IHC studies on PSMA till date, likewise little has been researched on the correlation between PSMA and GS and grade grouping [5,17-19].

The present study aimed to evaluate the expression of PSMA in prostatic carcinoma and its correlation with GS and grade grouping. Understanding the relationship between PSMA expression and established grading systems could provide valuable information

for differentiating between mild and severe disease to facilitate categorising into low and high-risk cases.

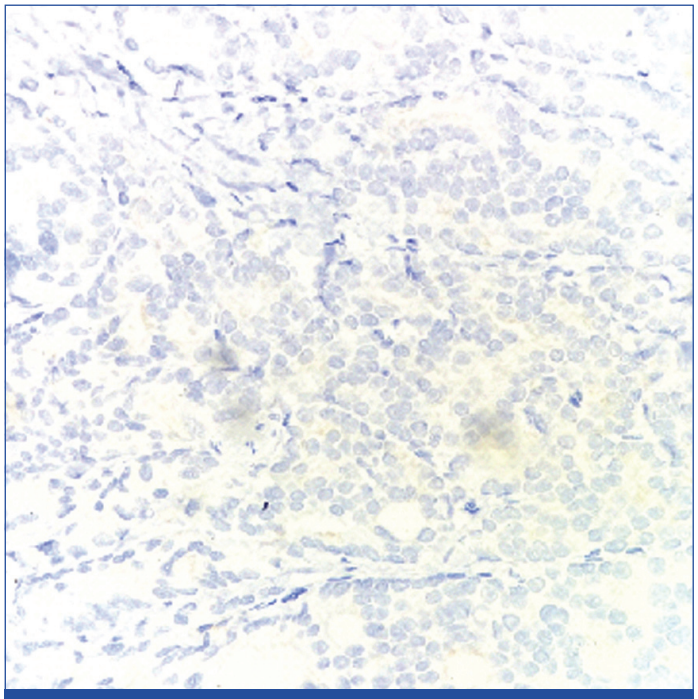
MATERIALS AND METHODS

The present cohort study analysed samples of prostate tissue over two years (May 2022 to April 2024) at the Department of Pathology, Kalinga Institute of Medical Sciences, Bhubaneswar, Odisha, India. The study was approved by the Institutional Research and Ethics Committee (letter no- 944/2022). A total of 63 cases with histopathologically confirmed prostate carcinoma that were consecutively received were included in the study. Prostate tissue samples, both TURP (Transurethral Resection of the Prostate) chips and core biopsies, were collected for analysis. Histopathologically proven cases of primary prostatic adenocarcinoma were included. Inadequate, poorly fixed, autolysed samples, metastatic carcinomas, and urothelial carcinomas were excluded.

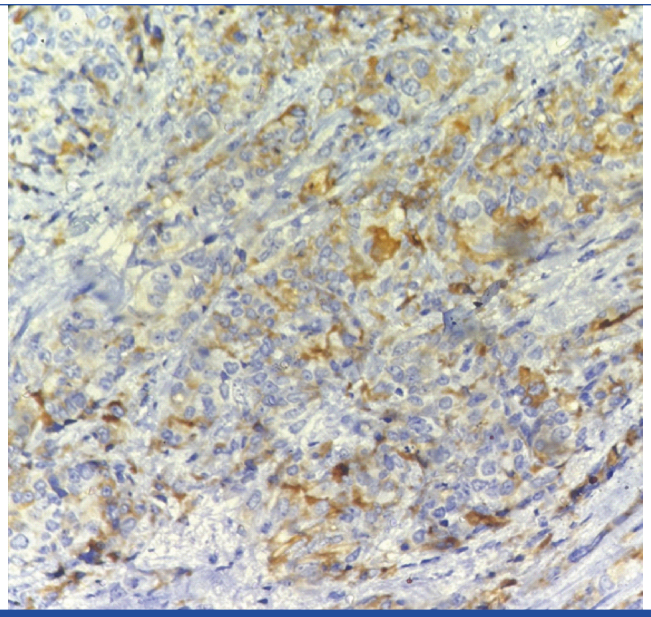
Study Procedure

The clinicopathological parameters correlated were age, nature of the specimen, location of the tumour and serum PSA level. GS and grade group were done on the Haematoxylin and Eosin (H&E) stained slides in accordance with the International Society of Urological Pathology (ISUP) Consensus Conference guidelines [20]. The Gleason scoring system was applied to grade the tumours. The primary and secondary Gleason patterns were assigned to each tissue sample, and the sum of these patterns gave the GS. GS was categorised into four groups (Group A: ≤6, Group B: 3+4=7, Group C: 4+3=7, Group D >7). Based on GSs facilitated clinical classification, grade group was categorised into five groups (Grade Group 1-5) [20].

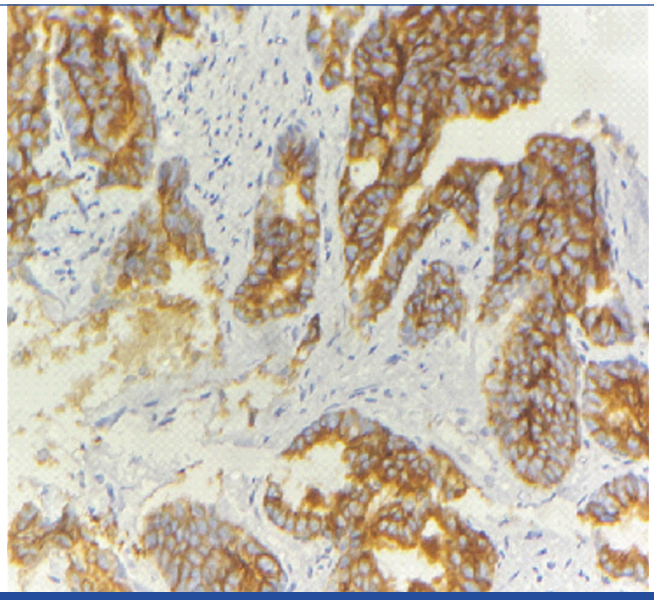
IHC staining for PSMA (pre-diluted, FOLH1/PSMA BIOCYC, Potsdam, Germany) was done on formalin-fixed-paraffin-embedded tissue. Sections of 2-5 microns thickness) on poly-L-lysine coated slides were stained for Immunohistochemistry (IHC) according to institutional standard operating procedure. Positive control for PSMA was prepared from normal duodenal epithelium. Negative controls from the same tumour block were taken by skipping the primary antibody step. Staining intensity of PSMA was assessed by observing the cytoplasmic and/or membranous staining and scored as 1: negative or low; 2: intermediate; 3: high [17]. The subjective assessment of IHC study was done. Negative, Low, Intermediate, and High PSMA intensity along with PNI are depicted in [Table/Fig-1-6], respectively.



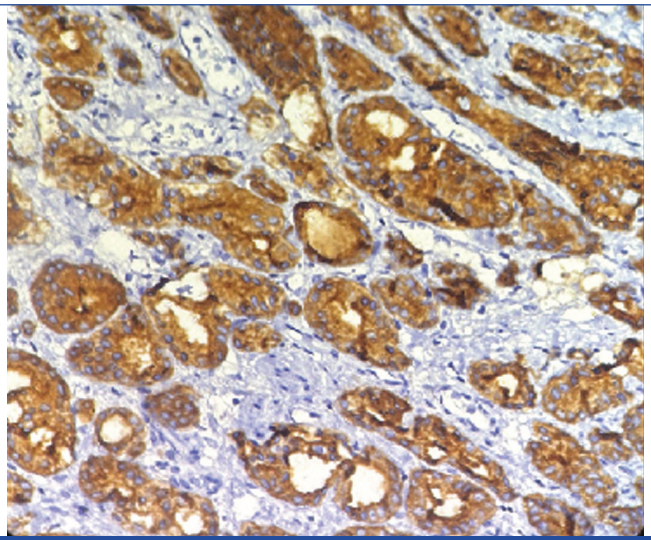
[Table/Fig-1]: Immunohistochemistry 400x negative staining intensity of the PSMA.



[Table/Fig-2]: Immunohistochemistry 400x low staining intensity of the PSMA.



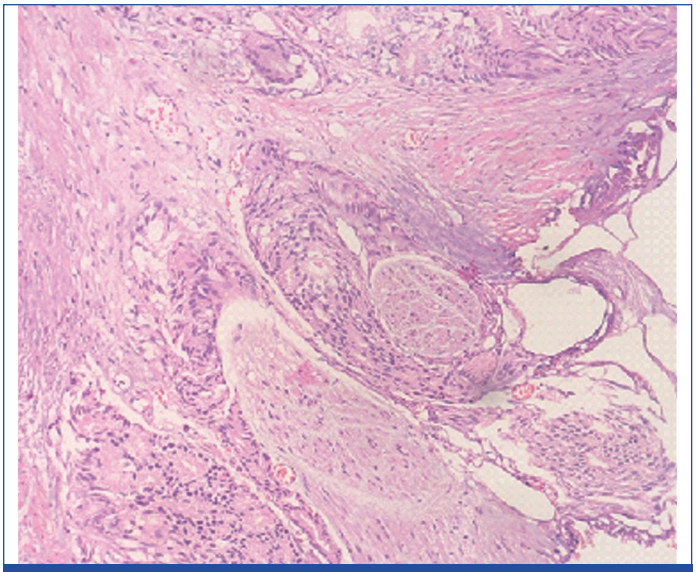
[Table/Fig-3]: Immunohistochemistry 400x intermediate staining intensity of the PSMA.



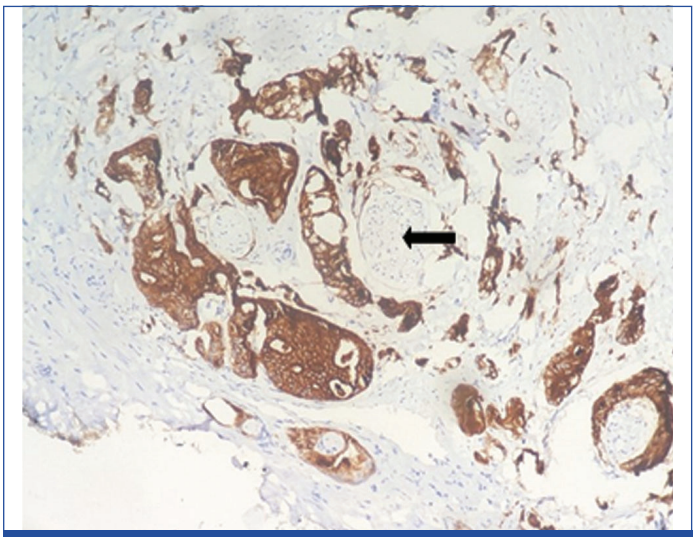
[Table/Fig-4]: Immunohistochemistry 400x high staining intensity of the PSMA.

STATISTICAL ANALYSIS

Statistical analysis was conducted to determine the correlation between PSMA expression levels with GSs and grade grouping. The results were expressed as mean, percentages and SD. Chi-square test was used as test of association and the Spearman's Rho



[Table/Fig-5]: Carcinoma with PNI H&E 400x.



[Table/Fig-6]: PSMA in prostatic adenocarcinoma shows PNI (arrow) 400x.

Correlation test was used to establish correlation between PSMA expression and clinicopathological parameters.The relationship between PSMA expression and PNI was examined using Cox proportional hazards regression model. PSMA expression was adjusted to PNI on biopsy to do multivariate analysis. For multivariate analysis, "PSMA low or negative" was taken as the reference group. Disease-free survival was demonstrated using Kaplan Meier curve, which was statistically validated using the log rank test.

All tests were performed using SPSS, version 26.0. The p-value of <0.05 was considered statistically significant.

RESULTS

The current study included 63 cases of biopsy-proven prostatic adenocarcinoma with an age range from 54 years to 88 years and a mean age of 70.28±7.52 years. A total of 56 (88.88%) cases were Transrectal Ultrasound (TRUS)-guided core biopsies, others were Transurethral Resection of the Prostate (TURP) chips. The serum PSA levels ranged from 1.5 ng/mL to 155 ng/mL with a mean of 67.11±55.58 ng/mL. PNI was identified in 35 (55.55%) cases. The maximum number of cases 43 (68.25%) cases was in group D, i.e., GS of >7, 30 (47.61%) cases were in Grade group 5.

Of 63 cases, 40 (63.50%) cases showed high expression of PSMA. The majority of the patients were in the age group of 71-80 years and showed high PSMA expression. There was no statistically significant relationship between PSMA expression and age group. (r=0.118, p-value=0.205). Majority of the cases were TRUS-guided core biopsies i.e., 34 cases out of 40 (85%) showed high PSMA expression. There was no significant association between PSMA expression and the nature of specimen (p-value=0.130). Only core biopsies (56 cases) were taken into account for location of the tumour as location cannot be ascertained in cases of TURP chips specimens. The right lobe of the prostate was involved in 35 (62.5%) cases. The highest number of cases, i.e., 18 of 40 (45%) cases showed high expression of PSMA with serum PSA level less than 50 ng/mL. The correlation of PSMA expression with serum PSA level (r=0.088, p-value=0.643) and PNI (r=-0.139, p-value=0.486) was not statistically significant.

Group D cases exhibited high PSMA expression in 82.5% of cases. The correlation between PSMA expression and GS was statistically significant (r=0.403, p=0.014). High PSMA expression was noted in 60% of cases of Grade group 5. A statistically significant correlation existed between PSMA expression and grade grouping (r=0.391, p=0.016). The correlation of PSMA intensity with the clinicopathological parameters is shown in [Table/Fig-7]. The Spearman's Rho Correlation of the parameters is shown in [Table/Fig-8].

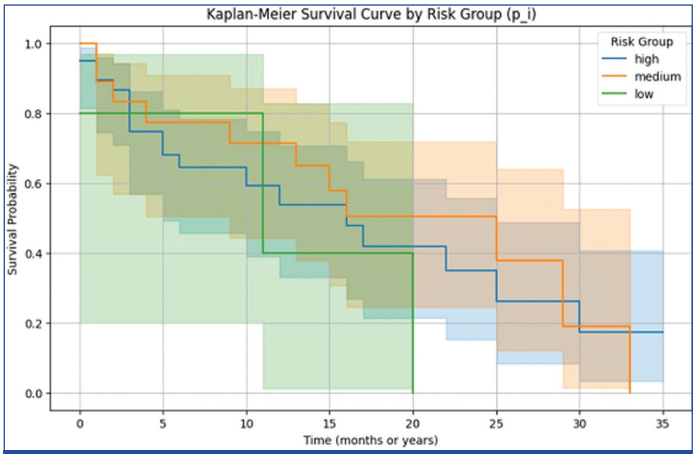
Parameters	PSMA intensity				p-value
	No. of cases (n=63) (%)	Negative or low (n=5) (%)	Intermediate (n=18) (%)	High (n=40) (%)	
Age group (Years)					
50-60	4 (6.34)	0	2 (11.11)	2 (5)	0.205
61-70	29 (46.03)	2 (40)	12 (66.67)	15 (37.5)	
71-80	25 (39.68)	3 (60)	4 (22.22)	18 (45)	
>80	5 (7.93)	0	0	5 (12.5)	
Nature of specimen					
Core biopsy	56 (88.88)	5 (100)	17 (94.44)	34 (85)	0.130
TURP chips	7 (11.11)	0	1 (5.55)	6 (15)	
Serum PSA (ng/mL)					
<50	31 (49.20)	3 (60)	10 (55.56)	18 (45)	0.643
50-100	8 (12.69)	0	1 (5.56)	7 (17.5)	
>100	24 (38.09)	2 (40)	7 (38.89)	15 (37.5)	
PNI					
Identified	35 (55.55)	3 (60)	12 (66.67)	20 (50)	0.486
Not identified	28 (44.44)	2 (40)	6 (33.33)	20 (50)	
GS					
Group A (≤6)	6 (9.52)	1 (20)	5 (27.78)	0	0.014
Group B (3+4=7)	9 (14.28)	1 (20)	3 (16.67)	5 (12.5)	
Group C (4+3=7)	5 (7.93)	1 (20)	2 (11.11)	2 (5)	
Group D (>7)	43 (68.25)	2 (40)	8 (44.44)	33 (82.5)	
GG					
Group 1	6 (9.52)	1 (20)	5 (27.78)	0	0.016
Group 2	9 (14.28)	1 (20)	3 (16.67)	5 (12.5)	
Group 3	5 (7.93)	1 (20)	2 (11.11)	2 (5)	
Group 4	13 (20.63)	2 (40)	2 (11.11)	9 (22.5)	
Group 5	30 (47.61)	0	6 (33.33)	24 (60)	
Location of the tumour (Core biopsy cases only)	(n=56)	(n=5)	(n=17)	(n=34)	0.511
Left lobe	21 (37.5)	2 (40)	8 (47.05)	11 (32.35)	
Right lobe	35 (62.5)	3 (60)	9 (52.94)	23 (67.64)	

[Table/Fig-7]: Association of PSMA intensity with clinicopathological parameters.

Kaplan Meier curve confirmed with increasing PSMA expression, the recurrence free survival was correspondingly reduced [Table/Fig-9]. The cases with low PSMA intensity resulted in fewer follow-ups in patients; as a result, the curve terminated at a particular time.

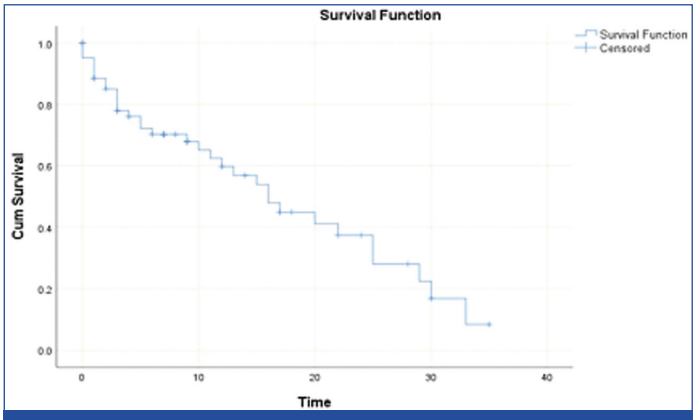
Parameters		Age	Serum PSA level (ng/mL)	Gleason score (GS)	Grade group	PNI	PSMA intensity
Age	Correlation coefficient	1.000	-0.012	0.185	0.200	-0.105	0.118
	p-value		0.924	0.146	0.117	0.414	0.357
Serum PSA level (ng/mL)	Correlation coefficient	-0.012	1.000	0.067	0.157	0.205	0.088
	p-value	0.924		0.601	0.221	0.107	0.495
Gleason score (GS)	Correlation coefficient	0.185	0.067	1.000	0.961**	0.031	0.403**
	p-value	0.146	0.601		0.000	0.808	0.001
Grade group	Correlation coefficient	0.200	0.157	0.961**	1.000	0.011	0.391**
	p-value	0.117	0.221	0.0001		0.930	0.002
PNI	Correlation coefficient	-0.105	0.205	0.031	0.011	1.000	-0.139
	p-value	0.414	0.107	0.808	0.930		0.278
PSMA intensity	Correlation coefficient	0.118	0.088	0.403**	0.391**	-0.139	1.000
	p-value	0.357	0.495	0.001	0.002	0.278	

[Table/Fig-8]: Correlation coefficient matrix of the parameters.
**Correlation is significant at the 0.01 level(2-tailed)



[Table/Fig-9]: Kaplan-Meier curves showing recurrence free survival of patients following surgery.

Survival probabilities decreased as the Grade group increased, suggesting that higher Grade groups might be associated with worse outcomes. The overall survival analysis of all the prostatic carcinoma cases is depicted in [Table/Fig-10]. The median for survival time are illustrated in [Table/Fig-11]. Intermediate and high PSMA expression are linked to 0.60 and 0.70 fold increased risk of disease recurrence after treatment, respectively, as compared to PSMA-low or negative tumours (Univariate Cox Regression, p=0.44, p=0.58, respectively) illustrated in [Table/Fig-12]. The study employed multivariate Cox regression to predict disease recurrence by adjusting PSMA expression to the PNI [Table/Fig-13]. PNI identified cases showed high-risk of disease recurrence.



[Table/Fig-10]: Overall survival analysis of prostatic carcinoma cases.

Variables		Median survival/ time estimate (months)	Standard error	95% Confidence interval	p-value
Overall		16	2.60	10.90-21.09	
PSMA intensity	1	11	8.16	0.00-26.98	0.726
	2	25	7.32	10.64-39.35	
	3	16	4.20	7.76-24.23	
PNI	Not Identified	25	4.07	17.01-32.98	0.065
	Identified	15	4.47	6.24-23.75	
Grade group	1	20	12.22	0.00-43.95	0.858
	2	11	4.27	2.63-19.36	
	3	15	1.63	11.79-18.20	
	4	22	6.04	10.16-33.83	
	5	12	5.04	2.11-21.88	

[Table/Fig-11]: Median for survival time.

Variables	HR	95% CI	p-value
PSMA negative or low	1 (Ref.)		
PSMA intermediate	0.601	0.16-2.20	0.44
PSMA high	0.709	0.20-2.43	0.58

[Table/Fig-12]: Cox regression analysis on biopsy cohort, for disease recurrence-univariate analysis.
HR: Hazard's ratio, CI: Confidence Interval

Variables	HR	95% CI	p-value
PSMA negative or low	1 (Ref.)		
PSMA intermediate	0.53	0.14-1.99	0.35
PSMA high	0.81	0.23-2.81	0.74
PNI (Identified)	2.19	1.01-4.74	0.04

[Table/Fig-13]: Cox regression analysis on biopsy cohort, for disease recurrence-multivariate analysis.
HR: Hazard's ratio, CI: Confidence Interval

DISCUSSION

Carcinogenesis in prostatic adenocarcinoma is a complex process requiring multiple elements to interact simultaneously for the cancer to start, grow, and spread. The conventional risk stratification using GS and grade has been instrumental in planning management protocols.

Prognostic challenges in prostate cancer: It is challenging to assign prostate cancer cases to specific risk groups- a prerequisite for individualised treatment decisions [5]. Tumour distinction is difficult due to the inter-observer variability of the GS and complex grading systems such as GS 7 (3+4 versus 4+3) [5]. Serum PSA level is also non-specific. In contrast, high PSMA expression is associated with high tumour grade and metastatic disease [5]. Hence, PSMA may be a reliable biomarker to distinguish individuals who require active management from those who require close monitoring only.

Role of PSMA in risk categorisation: The biological behaviour of prostatic carcinoma is always determined by the tumour grade, which helps clinicians risk stratify patients [5,19]. GS and grade grouping have an impact on tumour grade. Clinical stage, GS, grade grouping, and serum PSA level are the factors which influence the treatment of prostatic cancer [5]. However, these criteria are insufficient to categorise patients into low and high-risk groups. This study showed high PSMA expression in cases with higher GS and higher Grade group. Thus, PSMA is a potential marker in differentiating between indolent disease and aggressive disease. High PSMA expression is indicative of aggressive disease and a poor prognosis and vice versa.

Findings related to age, nature of specimen, PSA, GS, and PNI: The age range in our study was 54 to 88 years (mean 70.58±7.52 years), comparable to the findings by Sihag D and Laddha P [21]. This wide age range may be due to availability of screening tests by serum PSA, longer life expectancy and diagnosis of cases in elderly males. We note a proportional increase in expression of PSMA with increase in age, though it did not attain statistical significance (r=0.118, p=0.205). Bravaccini S et al., and Varma AV et al., have noted this too [5,18]. The mean age reported by Kasperzyk JL et al., was 65.8±6.3 years with a statistically significant correlation between PSMA expression and age group [19]. We found high PSMA expression in 34 of the 56 core biopsies without any correlation between the nature of specimen and PSMA expression (p-value=0.13). Bravaccini S et al., reported a positive correlation between PSMA expression and core biopsy (p-value <0.0001) [5]. Serum PSA levels and the GS have numerous drawbacks. Serum PSA level is an organ-specific biomarker rather than a tumour-specific one, it has low accuracy and may exhibit an aberrant rise even with benign prostatic hyperplasia [5]. The serum PSA levels in this study were similar to those stated by Varma AV et al., (4.4 to 115 ng/mL) and Marchal C et al., (1 to 137 ng/mL) [20,22]. Likewise, the relationship between PSMA expression and serum PSA level was not statistically significant (r=0.088, p-value=0.643). Marchal C et al., concluded that PSA does not regulate the expression of PSMA protein [22]. In this study, 5-10% of the cases with higher GSs (8-10) had very low serum PSA levels. Varma AV et al., explain this as loss of expression of the PSA-encoding gene in poorly differentiated prostatic carcinomas [18]. In contrast, Bravaccini S et al., found a positive correlation between PSMA expression and serum PSA level at diagnosis (p-value=0.002) [5]. Serum PSA may be high in benign conditions like prostatitis and benign hyperplasia of the prostate [18]. Patients with low serum PSA levels are less likely to undergo prostate biopsy in clinical practice hence, cancers with low serum PSA tend to be discovered at a later stage than those with higher PSA. Consequently, the prognosis for high-grade cancers with low serum PSA levels is worse than that of tumours with high serum PSA levels [23].

PNI refers to the tendency of prostate carcinomas to develop and invade along nerves and reflects tumour aggressiveness [17,18]. The study found majority of tumours with PNI had high PSMA expression and were high-grade tumours. However, the PSMA expression and PNI did not correlate significantly (r=-0.139, p=0.486). In contrast, Varma AV et al., found a significant correlation between PNI in high-grade cancers and increased PSMA expression [18].

Clinical implications of PSMA expression: Majority of the cases in group D (GS>7) had high PSMA expression compared to other groups i.e., GS <7. (r=0.403, p=0.014). Hence, there was a proportional increase in PSMA expression with increased GS. Our results were similar to several others who also found a statistically significant correlation between PSMA expression and GS [5,17-19]. Prostatic cancers with higher GSs and higher PSMA tend to be more aggressive. Grade group 5 accounted for the maximum number of cases which showed high PSMA expression. There was a positive correlation between Grade group and PSMA expression (r=0.391, p=0.016), as documented elsewhere [5,17-19]. This correlation suggests that high PSMA expression characterised aggressive tumours and may be a useful biomarker for risk assessment and treatment planning. The ability to assess PSMA expression in prostate carcinoma patients could have other clinical implications including PSMA-targeted therapies that could improve treatment outcomes. We found a high PSMA expression with greater intensity was associated with greater probability of disease recurrence after curative therapy. A high PSMA expression on biopsy predict disease recurrence in multivariate studies irrespective of the status of known prognostic variables like serum PSA level or Gleason grading. These findings were similar to that of others [5,17-19]. The clinical implications are staging prostate cancer, detecting biochemical recurrence, monitoring treatment response and selecting patients for targeted therapies [15,16]. As PSMA is highly expressed on prostate cancer cells, PSMA-based imaging is superior to traditional imaging techniques like CT or bone scans, which can lead to significant changes in treatment decisions and patient management [15]. High PSMA expression in high-grade tumours and metastatic disease is of clinical importance in categorising patients into low-risk and high-risk groups [5]. PSMA plays a promising role in the management of prostate cancer, primarily as a highly sensitive imaging biomarker used in PET scans. Thus, PSMA detects even small metastatic lesions, allowing accurate staging, treatment planning, and monitoring of disease progression, especially in cases of biochemical recurrence or advanced metastatic prostate cancer [15,16].

Limitation(s)

This study is limited by a small sample size that precluded significant association with other clinicopathological factors. Since there were fewer cases of Grade group 3 than Grade group 2, we could not find any correlation between GS (3+4) i.e., Grade group 2 and GS (4+3) i.e., Grade group 3. Further research with a larger study population will shed more light on the involvement of PSMA in the carcinogenesis of prostate cancers, as a prognostic indicator or a therapeutic target.

CONCLUSION(S)

Most of the prostatic adenocarcinomas with higher GSs and Grade groups showed high PSMA expression that correlates with an unfavourable prognosis and risk of recurrence. PSMA can discriminate aggressive disease from indolent disease, thereby differentiating a subset of patients who require active therapy from those who require observation and follow-up. It can aid in risk stratification and prognostication of prostate cancer at the time of diagnosis. Thus, PSMA has proven to be an important biomarker for improved clinical workup and management of patients with prostate cancer.

Acknowledgement

Subhadra Priyadarshini, Biostatistician, Department of Research and Development, Kalinga Institute of Medical Sciences, KIIT University, Bhubaneswar, Odisha, India for statistical help.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Jan 01, 2025
- Manual Googling: Mar 29, 2025
- iThenticate Software: Apr 12, 2025 (13%)

ETYMOLOGY: Author Origin

EMENDATIONS: 6

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? Yes
- For any images presented appropriate consent has been obtained from the subjects. Yes

Date of Submission: **Dec 26, 2024**
Date of Peer Review: **Feb 27, 2025**
Date of Acceptance: **Apr 14, 2025**
Date of Publishing: **Oct 01, 2025**