Section: Pathology

Original Research Article

# IMMUNOHISTOCHEMICAL EXPRESSION OF ESTROGEN RECEPTOR, PROGESTERONE RECEPTOR AND KI-67 AS PREDICTORS OF TUMOUR AGGRESSIVENESS IN PROSTATE ADENOCARCINOMA: CORRELATION WITH GLEASON GRADE, SERUM PSA AND CLINICOPATHOLOGICAL PARAMETERS

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*Received* : 18/05/2026
*Received in revised form* : 12/07/2026
*Accepted* : 27/07/2026

*Keywords:*
*Prostate adenocarcinoma; Estrogen receptor (ER); Progesterone receptor (PR); Ki-67; Immunohistochemistry; Gleason Grade Group; Gleason score; Prostate-specific antigen (PSA); Prognostic biomarkers.*

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DOI: 10.47009/jamp.2026.8.4.137

Source of Support: Nil,
Conflict of Interest: None declared

*Int J Acad Med Pharm*
2026; 8 (4); 813-818

## ABSTRACT

**Background:** Prostate adenocarcinoma is one of the most common malignancies among men and demonstrates marked biological heterogeneity despite similar Gleason grades and serum PSA levels. While histopathological grading remains the cornerstone of prognostication, additional biomarkers are required to improve risk stratification and therapeutic decision-making. Estrogen Receptor (ER), Progesterone Receptor (PR), and Ki-67 have emerged as potential prognostic biomarkers, reflecting hormonal signaling and tumour proliferative activity. Altered expression of these markers has been associated with tumour aggressiveness, adverse pathological features, and disease progression; however, their clinical significance in routine pathological practice remains incompletely established. Aim: To evaluate the immunohistochemical expression of Estrogen Receptor (ER), Progesterone Receptor (PR), and Ki-67 in prostate adenocarcinoma and correlate their expression with Gleason Grade Group, Gleason score, serum PSA, histological growth patterns, lymphovascular invasion (LVI), perineural invasion (PNI), and other clinicopathological parameters.

**Materials and Methods:** A prospective observational cross-sectional study was conducted on 104 consecutive histopathologically confirmed cases of prostate adenocarcinoma at the Department of Pathology, Uttar Pradesh University of Medical Sciences (UPUMS), Saifai. Formalin-fixed paraffin-embedded tissue sections were stained with hematoxylin and eosin for histopathological evaluation and subjected to immunohistochemistry for ER, PR, and Ki-67. Tumours were graded according to the WHO Classification of Urinary and Male Genital Tumours (5th Edition, 2022) and ISUP Grade Groups. Statistical analysis was performed using the Pearson Chi-square test, with $p < 0.05$ considered statistically significant.

**Results:** The majority of patients belonged to the 61–70-year age group (34.6%). ER and PR positivity were significantly more frequent in well-differentiated tumours and lower Gleason Grade Groups, whereas high Ki-67 expression predominated in high-grade tumours, elevated serum PSA levels, aggressive histological patterns, lymphovascular invasion, and perineural invasion ($p < 0.001$). ER and PR expression demonstrated a significant inverse correlation with tumour grade, while Ki-67 showed a strong positive association with tumour aggressiveness and adverse clinicopathological parameters.


ISSN (O): 2687-5365; ISSN (P): 2753-6556

**Conclusion:** This study demonstrates that ER, PR, and Ki-67 are valuable adjunct immunohistochemical biomarkers in prostate adenocarcinoma. Reduced ER and PR expression together with increased Ki-67 labeling index are significantly associated with higher Gleason grades and adverse pathological features. Incorporating these biomarkers into routine histopathological evaluation may improve prognostic stratification and facilitate individualized therapeutic management.

## INTRODUCTION

Prostate cancer is the second most commonly diagnosed malignancy and the fifth leading cause of cancer-related mortality among men worldwide, accounting for approximately 1.47 million new cases and 397,000 deaths in 2022.[1] The global burden of prostate cancer continues to rise due to increasing life expectancy, improved awareness, widespread prostate-specific antigen (PSA) screening, and advances in diagnostic modalities.[2] In India, the incidence of prostate cancer has steadily increased over the last two decades, particularly in urban populations, making it an important public health concern.[3]

Prostatic adenocarcinoma demonstrates remarkable biological heterogeneity, ranging from indolent localized tumors to highly aggressive metastatic disease.[4] Histopathological grading using the Gleason grading system and the International Society of Urological Pathology (ISUP) Grade Group classification remains the gold standard for prognostic assessment and therapeutic decision-making.[5] However, patients with similar Gleason scores often exhibit considerable variation in tumour progression, biochemical recurrence, treatment response, and overall survival, highlighting the need for additional prognostic biomarkers.[6]

Tumour progression in prostate adenocarcinoma is regulated by complex interactions between hormonal signalling pathways, cellular proliferation, genetic alterations, and the tumour microenvironment.[7] While androgen receptor signalling plays a central role in prostate carcinogenesis, increasing evidence suggests that Estrogen Receptor (ER) and Progesterone Receptor (PR) also contribute significantly to tumour initiation, progression, and metastatic potential.[8]

Estrogen exerts its biological effects through ER-α and ER-β, which have distinct functions in the prostate. ER-α is predominantly associated with epithelial proliferation, chronic inflammation, and tumour progression, whereas ER-β demonstrates anti-proliferative, anti-inflammatory, and tumour-suppressive effects.[9] Loss of ER-β expression has been associated with higher Gleason grade, increased tumour aggressiveness, biochemical recurrence, and poor clinical outcome.[10]

Progesterone receptor expression has also been implicated in prostate carcinogenesis through its interaction with androgen receptor signalling and regulation of epithelial differentiation.[11] Several studies have reported reduced PR expression in poorly differentiated and high-grade prostate carcinomas, suggesting its potential role as a favourable prognostic biomarker.[12] Nevertheless, the biological significance of ER and PR expression in prostate adenocarcinoma remains controversial because published studies have demonstrated inconsistent results regarding their prognostic utility.[13]

Ki-67 is a well-established nuclear proliferation marker expressed during all active phases of the cell cycle except G0 and is considered one of the most reliable indicators of tumour proliferative activity.[14] Increased Ki-67 labelling index has consistently been associated with higher Gleason score,advanced pathological stage, lymph vascular invasion, biochemical recurrence, distant metastasis, and reduced disease-specific survival.[15] Consequently, Ki-67 has emerged as an important adjunctive prognostic biomarker in prostate cancer and has been incorporated into several contemporary risk stratification models.[16]

Recent molecular and immunohistochemical studies have emphasized that the combined assessment of hormonal receptors and proliferation markers may provide superior prognostic information compared with conventional histopathological grading alone.[17] Correlating ER, PR, and Ki-67 expression with clinicopathological variables such as serum PSA level, Gleason Grade Group, histological growth pattern, lymphovascular invasion (LVI), and perineural invasion (PNI) may improve risk stratification and facilitate individualized treatment planning.[18]

Although several international studies have investigated these biomarkers, data from the Indian population remain limited, and few studies have simultaneously evaluated ER, PR, and Ki-67 in relation to multiple adverse prognostic parameters.[19] Furthermore, the integration of these biomarkers into routine histopathological reporting has not yet been standardized despite growing evidence supporting their prognostic significance.[20]

In this context, the present study was undertaken to evaluate the immunohistochemical expression of Estrogen Receptor (ER), Progesterone Receptor (PR), and Ki-67 in 104 histopathologically confirmed cases of prostate adenocarcinoma. The study further aimed to determine their association with Gleason Grade Group, Gleason score, serum PSA level, histological growth patterns, lymphovascular invasion, perineural invasion, and other clinicopathological parameters in order to assess their potential role as reliable prognostic biomarkers in routine pathological practice.


ISSN (O): 2687-5365; ISSN (P): 2753-6556

## MATERIALS AND METHODS

This prospective observational cross-sectional study was conducted in the Department of Pathology, Uttar Pradesh University of Medical Sciences (UPUMS), Saifai, in collaboration with the Department of Urology, over a period of 18 months. A total of 104 consecutive, histopathologically confirmed cases of prostatic adenocarcinoma were included. Only newly diagnosed, treatment-naïve patients were enrolled to ensure unbiased evaluation of clinicopathological features and immunohistochemical biomarker expression. Clinical details, serum prostate-specific antigen (PSA) levels, and pathological findings were obtained from hospital records and histopathology requisition forms.

Tissue Processing and Routine Histopathology:

All TRUS-guided core biopsies, transurethral resection of prostate (TURP), simple prostatectomy, and radical prostatectomy specimens were received in 10% neutral-buffered formalin and processed according to standard histopathological protocols. Following gross examination, representative sections were routinely dehydrated, cleared, paraffin embedded, and sectioned at 4–5 µm thickness. The sections were stained with hematoxylin and eosin (H&E) for microscopic evaluation.

Cases with inadequate tissue, poor fixation, extensive necrosis, previously treated carcinoma (chemotherapy, radiotherapy, or hormonal therapy), benign prostatic lesions, and metastatic tumors involving the prostate were excluded to ensure accurate histopathological assessment and immunohistochemical interpretation.

Histopathological Evaluation:

Microscopic examination was performed independently by two experienced pathologists. Tumors were classified according to the World Health Organization (WHO) Classification of Urinary and Male Genital Tumours, 5th Edition (2022). Histomorphological parameters evaluated included:

- Histological growth pattern
- Gleason primary and secondary patterns
- Gleason score
- ISUP Grade Group
- Perineural invasion (PNI)
- Lymphovascular invasion (LVI)
- Tumor architecture

Discordant cases were reviewed jointly to achieve a consensus diagnosis.

Immunohistochemistry:

Immunohistochemistry (IHC) was performed on 4–5 µm thick formalin-fixed paraffin-embedded tissue sections using standardized laboratory protocols. The following antibodies were evaluated:

- Estrogen Receptor (ER)
- Progesterone Receptor (PR)
- Ki-67 proliferation marker

Appropriate positive and negative controls were included in each staining run.

Evaluation of Immunohistochemical Markers:

Estrogen Receptor (ER): Only nuclear staining in tumor cells was considered positive. Cases were categorized as ER-positive or ER-negative.

Progesterone Receptor (PR): PR expression was assessed based on nuclear immunoreactivity, and tumors were classified as PR-positive or PR-negative.

Ki-67 Labeling Index: Ki-67 expression was evaluated in hotspot areas by counting at least 500 to 1000 tumor cells under high-power magnification. The Ki-67 labeling index was expressed as the percentage of positively stained tumor nuclei and categorized into low and high proliferative index according to the predefined study criteria.

Clinicopathological Parameters

The following variables were systematically recorded for each case:

- Patient age
- Clinical presentation
- Serum PSA level
- Histological growth pattern
- Gleason score
- ISUP Grade Group
- ER expression
- PR expression
- Ki-67 labeling index
- Lymphovascular invasion (LVI)
- Perineural invasion (PNI)

**Statistical Analysis**

Data were entered into **Microsoft Excel** and analyzed using **IBM SPSS Statistics version 26.0**.

- Continuous variables were expressed as **mean ± standard deviation (SD)**.
- Categorical variables were presented as **frequencies and percentages**.
- Associations between **ER, PR, Ki-67 expression** and clinicopathological parameters were analyzed using the **Pearson Chi-square test** or **Fisher's exact test**, wherever appropriate.
- A **p-value <0.05** was considered statistically significant, while **p <0.001** was considered highly significant.

This methodology enabled comprehensive evaluation of the prognostic significance of ER, PR, and Ki-67 in relation to Gleason Grade Group, Gleason score, serum PSA, histological growth pattern, lymphovascular invasion, and perineural invasion in patients with prostate adenocarcinoma.

## RESULTS

**Clinicopathological Characteristics of the Study Cohort**

A total of 104 histopathologically confirmed cases of prostatic adenocarcinoma were included in the present study. The clinicopathological characteristics were analyzed with respect to Estrogen Receptor (ER), Progesterone Receptor (PR), and Ki-67 expression.


ISSN (O): 2687-5365; ISSN (P): 2753-6556

The mean age of the study population was 69.2 ± 9.4 years (range: 45–89 years). The majority of patients belonged to the 61–70 years age group (34.6%), followed by the 71–80 years group (31.7%). Most patients presented with lower urinary tract symptoms, including urgency, increased frequency, burning micturition, dysuria, and hematuria.

Serum PSA levels demonstrated a wide distribution, with higher PSA values predominantly observed in patients with high Gleason Grade Groups and aggressive histological patterns. Histopathological examination showed that well-formed glands (25.0%) and poorly formed glands (22.1%) were the most common architectural patterns, followed by solid sheets (18.3%), cribriform glands (15.4%), single cells/cords (9.6%), glomeruloid pattern (6.7%), and mixed morphology (2.9%). Increasing Gleason Grade Groups were associated with a progressive shift from gland-forming architecture toward solid and single-cell growth patterns.

**Immunohistochemical Expression of ER, PR and Ki-67**

Immunohistochemical evaluation demonstrated distinct expression patterns among the three biomarkers. Overall, ER positivity was observed in 39 (37.5%) cases, PR positivity in 34 (32.7%) cases, while high Ki-67 labeling index was identified in 55 (52.9%) tumors.ER and PR expression were predominantly observed in well-differentiated adenocarcinomas, whereas Ki-67 expression increased progressively with loss of glandular differentiation and increasing tumour grade.

The highest frequency of ER and PR positivity was observed in patients aged 61–70 years, whereas high Ki-67 expression increased progressively in older patients, particularly those above 70 years, indicating increased tumour proliferative activity with advancing age.

Association of ER, PR and Ki-67 Expression with Clinicopathological Parameters in Prostate Adenocarcinoma (n = 104)

**Table 1**

| Clinicopathological Parameter | Category | ER Positive | PR Positive | High Ki-67 | Total | p-value |
|---|---|---|---|---|---|---|
| **Age Group** | 41–50 years | 4 | 4 | 1 | 5 | 0.112 |
| | 51–60 years | 9 | 8 | 5 | 16 | 0.084 |
| | 61–70 years | 15 | 13 | 18 | 36 | 0.041 |
| | 71–80 years | 9 | 7 | 21 | 33 | 0.006 |
| | 81–90 years | 2 | 2 | 10 | 14 | <0.001 |
| **Histological Growth Pattern** | Well-formed glands | 16 | 15 | 6 | 26 | <0.001 |
| | Poorly formed glands | 11 | 10 | 11 | 23 | 0.028 |
| | Cribriform glands | 5 | 4 | 11 | 16 | 0.019 |
| | Solid sheets | 3 | 2 | 15 | 19 | <0.001 |
| | Glomeruloid | 3 | 2 | 4 | 7 | 0.041 |
| | Single cells/Cords | 1 | 1 | 9 | 10 | <0.001 |
| | Mixed pattern | 0 | 0 | 2 | 3 | 0.372 |
| **Serum PSA** | <10 ng/mL | 17 | 15 | 4 | 24 | <0.001 |
| | 10–20 ng/mL | 14 | 12 | 15 | 38 | 0.018 |
| | >20 ng/mL | 8 | 7 | 36 | 42 | <0.001 |
| **ISUP Grade Group** | Grade Group 1 | 14 | 13 | 3 | 21 | <0.001 |
| | Grade Group 2 | 10 | 9 | 8 | 23 | 0.021 |
| | Grade Group 3 | 7 | 6 | 12 | 20 | 0.014 |
| | Grade Group 4 | 5 | 4 | 15 | 19 | <0.001 |
| | Grade Group 5 | 3 | 2 | 17 | 21 | <0.001 |
| **Lymphovascular Invasion (LVI)** | Present | 9 | 8 | 32 | 44 | <0.001 |
| | Absent | 30 | 26 | 23 | 60 | |
| **Perineural Invasion (PNI)** | Present | 11 | 10 | 35 | 49 | <0.001 |
| | Absent | 28 | 24 | 20 | 55 | |
| **Overall Biomarker Expression** | Positive/High | **39 (37.5%)** | **34 (32.7%)** | **55 (52.9%)** | **104** | |

A statistically significant association was observed between histological growth pattern and biomarker expression (p <0.001). Well-formed glandular tumors demonstrated the highest ER and PR positivity, whereas solid sheets and single-cell growth patterns exhibited the highest Ki-67 labeling index, indicating increased proliferative activity in poorly differentiated carcinomas.

**Correlation with Gleason Grade Group:**

Increasing Gleason Grade Groups showed a progressive decline in ER and PR expression, while Ki-67 expression increased significantly.

- Grade Group 1 tumors showed the highest ER and PR positivity.
- Grade Groups 4 and 5 demonstrated markedly reduced hormonal receptor expression.
- High Ki-67 labeling index was predominantly observed in Grade Groups 4 and 5.

A highly significant association was observed between Gleason Grade Group and all three biomarkers (p <0.001).

**Correlation with Serum PSA:**

Patients with serum PSA >20 ng/mL demonstrated significantly lower ER and PR positivity and higher Ki-67 expression compared with patients having PSA <10 ng/mL.


ISSN (O): 2687-5365; ISSN (P): 2753-6556

High PSA levels were significantly associated with aggressive histological architecture and increased tumour proliferative activity (p <0.001).

**Correlation with Lymphovascular Invasion (LVI):**

Among the 44 patients with lymphovascular invasion, the majority demonstrated negative ER and PR expression together with high Ki-67 labeling index.

In contrast, tumors without lymphovascular invasion predominantly showed retained ER/PR expression and lower Ki-67 proliferation.

A highly significant association was observed between LVI and biomarker expression (p <0.001), indicating that increased proliferative activity is associated with vascular invasion.

**Correlation with Perineural Invasion (PNI):**

Perineural invasion was more frequently identified in tumors showing loss of ER and PR expression and high Ki-67 labeling index.

Tumors lacking perineural invasion demonstrated comparatively lower proliferative activity.

The association between PNI and biomarker expression was statistically significant (p <0.001).

## DISCUSSION

The immunohistochemical expression of Estrogen Receptor (ER), Progesterone Receptor (PR), and Ki-67 demonstrated considerable variation in the present study, reflecting the inherent biological heterogeneity of prostatic adenocarcinoma. Comparison with published literature supports the validity and external generalizability of our findings. ER positivity was observed in 37.5% of cases, while PR positivity was seen in 32.7%. In contrast, high Ki-67 expression was identified in 52.9% of tumors, indicating increased proliferative activity in a substantial proportion of patients. These findings closely resemble those reported by Bonkhoff et al. and Fixemer et al., who demonstrated that hormonal receptor expression decreases progressively with tumour dedifferentiation, whereas proliferative activity increases with advancing tumour grade and aggressive biological behaviour.[9,10]

The histological growth pattern observed in our study also closely paralleled internationally recognized pathological observations. Well-formed glandular adenocarcinomas demonstrated the highest ER and PR positivity with relatively low Ki-67 labeling index, whereas cribriform glands, solid sheets, and single-cell/cord patterns exhibited markedly reduced hormonal receptor expression together with significantly increased Ki-67 expression. This distribution is concordant with the WHO Classification of Urinary and Male Genital Tumours (2022) and the observations of Humphrey et al., who identified cribriform and solid architectural patterns as important adverse prognostic features associated with aggressive tumour biology.[4,18] Collectively, these findings demonstrate that biomarker expression closely reflects tumour differentiation and architectural pattern.

The relationship between biomarker expression and Gleason Grade Group in our study also aligned with globally accepted trends. ER and PR expression progressively declined with increasing Gleason Grade Group, whereas Ki-67 labeling index increased significantly (p <0.001). This pattern is comparable with the findings of Berlin et al. and Cimadamore et al., who reported that elevated Ki-67 expression is strongly associated with higher Gleason score, biochemical recurrence, metastatic disease, and poor disease-specific survival.[15,17] Our findings therefore support the utility of Ki-67 as a robust marker of tumour proliferation and adverse prognosis.

Similarly, serum PSA demonstrated a significant association with immunohistochemical marker expression. Patients with PSA >20 ng/mL showed significantly lower ER and PR positivity together with increased Ki-67 labeling index, suggesting aggressive tumour biology. Comparable observations have been reported in the European Association of Urology (EAU) Guidelines and by Humphrey et al., who demonstrated that elevated PSA levels correlate with higher tumour burden, advanced pathological stage, and poorer clinical outcomes.[16,18]

The present study further demonstrated that lymphovascular invasion (LVI) and perineural invasion (PNI) were significantly associated with reduced ER and PR expression and increased Ki-67 proliferation. Tumours exhibiting LVI and PNI showed a markedly higher proliferative index, indicating greater invasive potential. Similar findings have been reported by Grindstad et al. and Fujimura et al., who concluded that vascular and neural invasion are frequently associated with loss of hormonal receptor expression and increased tumour aggressiveness.[11,12]

In the present study, high Ki-67 expression was observed in 52.9% of patients, a distribution comparable with the 45–60% prevalence reported in contemporary international studies involving high-grade prostate adenocarcinoma. Berlin et al. demonstrated that elevated Ki-67 is an independent predictor of biochemical recurrence and cancer-specific mortality.[15] Likewise, Cimadamore et al. (2023) reported that Ki-67 significantly improves prognostic stratification when combined with Gleason Grade Group and serum PSA.[17] These observations validate our findings that increased proliferative activity is closely linked with aggressive tumour behaviour.

Similarly, Bonkhoff et al. demonstrated that preservation of ER expression is predominantly observed in low-grade prostate carcinomas, whereas receptor loss accompanies tumour progression and higher Gleason grades.[9] Fixemer et al. further reported that reduced ER-β expression correlates with advanced pathological stage and poor prognosis,[10] observations that closely parallel our results.


ISSN (O): 2687-5365; ISSN (P): 2753-6556

Overall, comparison across published studies demonstrates a consistent global trend:

- ER and PR expression is highest in well-differentiated, low Gleason Grade Group tumours.
- High Ki-67 labeling index is predominantly observed in poorly differentiated tumours with cribriform, solid, and single-cell growth patterns.
- Elevated serum PSA, lymphovascular invasion, and perineural invasion are significantly associated with increased Ki-67 expression and reduced hormonal receptor positivity.
- Combined evaluation of ER, PR, and Ki-67 provides superior prognostic information compared with conventional histopathological grading alone.

The close concordance between the findings of the present study and contemporary international literature reinforces the reliability, reproducibility, and clinical applicability of ER, PR, and Ki-67 immunohistochemistry in prostatic adenocarcinoma. Incorporating these biomarkers into routine pathological reporting, together with WHO 2022 classification, ISUP Grade Group, Gleason score, serum PSA, LVI, and PNI, may improve prognostic stratification, facilitate individualized therapeutic planning, and support precision oncology in patients with prostate cancer.

## CONCLUSION

The present study demonstrated a clear association between immunohistochemical biomarker expression and tumour aggressiveness. ER and PR expression decreased progressively with increasing Gleason Grade Group, serum PSA level, lymphovascular invasion, perineural invasion, and poorly differentiated histological patterns. Conversely, Ki-67 labeling index increased significantly with higher tumour grade, elevated PSA, aggressive architectural patterns, LVI, and PNI ($p < 0.001$). These findings suggest that loss of hormonal receptor expression together with increased proliferative activity identifies biologically aggressive prostate adenocarcinoma and may provide valuable adjunctive prognostic information beyond conventional histopathological grading.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556