Journal of Pioneering Medical Sciences
Received: August 22, 2026 | Accepted: September 09, 2026 | Published: November 15, 2026
Volume 15, Issue S02, Pages 211-217
DOI https://doi.org/10.47310/jpms202615S0224



Diagnostic and Prognostic Utility of Immunohistochemical Markers in Prostatic Adenocarcinoma: A Core Needle Biopsy-Based Study

Mohammed Alsaweed[1*] and Hafiza Sobia Ramzan[2]
[1]Department of Medical Laboratory Sciences, College of Applied Medical Sciences, Majmaah University, Al Majmaah 11952, Saudi Arabia
[2]Department of Biochemistry, Institute of Molecular Biology and Biotechnology, University of Lahore, Lahore, Pakistan

*Corresponding author: Mohammed Alsaweed (e-mail: m.alsaweed@mu.edu.sa).

©2026 the Author(s). This is an open access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0

Abstract **Objectives:** Prostate Cancer (PC) is of great diagnosis and prognosis challenge because of the large biological heterogeneity. Core needle biopsies are the gold standard of diagnosis, but limited sampling and overlap of morphological features with benign mimickers can lead to diagnostic uncertainty, especially in Atypical Small Acinar Proliferation (ASAP). Also, at the stage of the first biopsy, it is still hard to predict how aggressive the tumors are. Immunohistochemical (IHC) markers may increase diagnostic accuracy and early risk stratification. **Objectives:** To assess the diagnostic utility of a combined AMACR and p63 immunohistochemistry in resolving cases of atypical prostate biopsy. To assess the prognostic significance of PTEN, Androgen Receptor (AR) and NF-κB expression in prostatic adenocarcinoma by correlating these markers with clinicopathological parameters. **Methods:** This is a prospective descriptive observational study conducted over a period of 8 months in a tertiary care centre Lahore, Pakistan. The present study included 235 cases of Transrectal Ultrasound (TRUS)-guided 12-core prostate biopsy. Histopathological evaluation was performed, with cases classified as benign, ASAP, HGPIN or adenocarcinoma. IHC staining for AMACR and p63 was performed in atypical and equivocal cases, while PTEN, AR and NF-κB were assessed in confirmed carcinoma cases. Statistical analysis was done using GraphPad Prism Version 10.0 and a p value of <0.05 was considered significant. **Results:** In cases of ASAP, dual staining using AMACR and p63 increased diagnostic resolution by confirming malignant transformation or ruling out carcinoma in equivocal biopsies. Loss of PTEN and high expression of AR and NF-κB were significantly associated with higher Gleason scores, higher tumor burden, perineural invasion and presentation with metastases at diagnosis. **Conclusion:** Immunohistochemical profiling of atypical prostate biopsies in combination with standard histopathological assessment improves diagnostic accuracy and provides early prognostic information. Assessing biomarkers at the level of the biopsy may enable management approaches in prostate cancer that are more accurate and biologically relevant.

Key Words Prostatic Adenocarcinoma, Immunohistochemistry, Atypical Small Acinar Proliferation, AMACR, p63, PTEN, Androgen Receptor, NF-κB, Clinicopathological Associations, Core Needle Biopsy

INTRODUCTION

Prostate cancer is one of the main challenges in diagnosis and therapy in modern oncology. Even with the advances in imaging, molecular biology and systemic therapies, the disease still exhibits marked biological heterogeneity, resulting in a wide variation in clinical behavior ranging from indolent tumors that can be actively surveiled to rapidly progressive metastatic disease. Diagnosis is based on histopathological examination of core needle biopsies, but under- and over-diagnosis occur due to limited sampling, architectural mimickers and subjective interpretation. Moreover, the ability to identify tumors that will behave aggressively at the time of initial biopsy continues to be a recurrent clinical dilemma [1,2].

Prostate cancer is the second most common diagnosed and the fifth leading cause of cancer death in men around the world [3,4]. GLOBOCAN 2020 estimates more than 1.4 million new cases and 375,000 deaths worldwide, with the incidence projected to double by 2040 due to population aging [5]. Incidence rates are steadily increasing in India and other South East Asian countries, especially in metropolitan cities due to better detection, increased PSA testing and demographic transitions [6]. Screening for PSA has improved early detection but is controversial in terms of risks of overdiagnosis and overtreatment [6,7].

Over the last two decades a number of immunohistochemical and molecular markers have been introduced to improve diagnostic accuracy and to investigate

associations with clinicopathological features and potential risk markers. Basal cell markers such as p63 and high molecular weight cytokeratin and AMACR as positive marker of malignancy are now routinely used in Atypical Small Acinar Proliferation (ASAP) and limited carcinoma [9,10]. However, aberrant staining patterns, overlap with benign mimickers and inter-laboratory variability remain limitations to universal reliability. Similarly, markers under investigation, including PTEN loss, Androgen Receptor (AR) immunoreactivity and NF-κB p65 nuclear staining have been associated with tumor grade, metastasis and castration resistance, but their independent predictive utility and routine clinical application remain uncertain [11-13].

There is still an important gap in the interpretation of the first core needle biopsy. Gleason grading is robust but samples a small fraction of the tumor volume and therefore may underestimate disease grade or extent in some patients [14]. Moreover, molecular heterogeneity results in differential response to therapy with the progression to Castration Resistant Prostate Cancer (CRPC) being characterized by re-activation of the AR pathway and inflammatory signaling through NF-κB that promote disease progression [15,16].

In this biopsy-based study, the primary objective was to examine whether AMACR and p63 immunohistochemistry assisted morphological classification of Atypical Small Acinar Proliferation (ASAP). The secondary objective was to explore associations between PTEN loss, Androgen Receptor (AR) staining and NF-κB p65 nuclear staining and WHO Grade Group, tumour burden, perineural invasion and metastasis present at diagnosis among selected untreated adenocarcinoma cases. These objectives address diagnostic categorization and contemporaneous clinicopathological associations; longitudinal prognostic performance was not evaluated.

METHODS

This prospective descriptive observational study was conducted at Tertiary Care Hospital, Lahore, Pakistan after approval from the Institutional Ethics Committee (approval reference and date to be supplied by the authors). All procedures were performed according to institutional guidelines and informed consent was obtained from eligible participants.

Study Population and Sampling Design

The study was conducted for a period of 8 months from January 2025 to August 2025. We included in the study population patients who presented to the Urology Department with lower urinary tract symptoms and evidence of prostatomegaly (Grade I to III on digital rectal examination) and who subsequently underwent Transrectal Ultrasound (TRUS) guided 12-core prostate biopsy. Consecutive sampling was used. A minimum sample size of 58 was reported on the basis of regional prevalence assumptions; the calculation parameters and source estimate require confirmation. A total of 235 biopsy cases was evaluated in the descriptive series, although this total does not establish adequate precision for every marker-specific subgroup. The overall biopsy series included benign diagnoses and non-prostatic malignancies. Marker-specific analyses used their respective eligible subsets, including 20 evaluable ASAP cases and 83 selected untreated primary adenocarcinoma cases; the detailed eligibility and exclusion pathway requires verification.

Clinical Evaluation and Data Collection

All the patients were subjected to detailed clinical evaluation including history, digital rectal examination (DRE grading), serum PSA estimation and radiological imaging wherever indicated. Relevant demographic, clinical, biochemical and imaging data were recorded in a structured proforma. Histopathological parameters evaluated included diagnostic category (benign, ASAP, HGPIN, carcinoma), Gleason score and WHO Grade Group (for carcinoma), tumor volume, number of cores involved, perineural invasion and presence of associated lesions. Metastasis status at the time of diagnosis was recorded as a clinicopathological feature. No longitudinal progression, recurrence, or survival outcomes were reported in the present analysis.

Histopathological Processing and Microscopy

TRUS-guided biopsy cores were fixed in 10% neutral buffered formalin for 24 hours and processed by standard paraffin embedding techniques. Sections of 3-5 µm thickness were obtained by rotary microtomy, mounted on albumin-coated slides and routinely stained with Hematoxylin and Eosin (H&E). Lesions were classified as benign prostatic tissue, Atypical Small Acinar Proliferation (ASAP), High-Grade Prostatic Intraepithelial Neoplasia (HGPIN), or adenocarcinoma by microscopic evaluation. For malignant cases, additional parameters such as tumor burden and perineural invasion were recorded.

Immunohistochemistry and Interpretation

Selected cases were analyzed by Immunohistochemistry (IHC). Of the 21 cases initially classified as ASAP, 20 had evaluable tissue and underwent AMACR and p63 staining; one had insufficient tissue for this analysis. Immunohistochemistry for PTEN, Androgen Receptor (AR) and NF-κB (p65) was reported for a selected cohort of 83 untreated primary adenocarcinomas. Antigen retrieval was performed using a standard protocol (citrate buffer, microwave method). Blocking, primary antibody incubation, polymer-HRP detection and DAB chromogen visualization were performed. AMACR and p63 were classified as either positive or negative. The study classified PTEN loss using a threshold of less than 10% cytoplasmic tumour-cell staining; this criterion and the use of internal staining controls require author verification. Semi-quantitative assessment of AR and NF-κB expression was performed based on intensity of nuclear staining (0-3 scale). For each antibody, appropriate positive and negative controls were used.

Statistical Analysis

All data were entered, tabulated and analyzed systematically using Microsoft Excel 2007 and GraphPad software (GraphPad Prism Version 10.0, GraphPad Software Inc., San Diego, CA, USA). Descriptive statistics were used to provide an overview of demographic, clinical and histopathological variables.

Categorical variables were analyzed using Chi-square test or Fisher's exact test as appropriate. Continuous variables were compared using appropriate parametric or non-parametric tests according to data distribution. Correlations were calculated to evaluate the association between the immunohistochemical markers and clinicopathological parameters. Graphical representations such as bar charts, box plots and correlation plots were created using GraphPad Prism. The reported significance threshold was a two-tailed p-value of less than 0.05. Multiple markers and subgroup comparisons were examined; the manuscript does not specify a correction for multiple testing and borderline p-values should be interpreted cautiously. The analyses are presented as descriptive or exploratory rather than as independently adjusted prognostic models.

RESULTS

During the study period, 235 TRUS-guided core needle biopsies were analyzed, with a mean patient age of 66 years (range: 26-84 years). The first general objective was to describe the diagnostic distribution and clinicopathological features of prostatic adenocarcinoma. As a response to this objective, the histomorphological evaluation at the beginning showed benign prostatic tissue in 111/235 cases (47.2%), Atypical Small Acinar Proliferation (ASAP) in 21/235 (8.9%), prostatic adenocarcinoma in 101/235 (43.0%) and non-prostatic malignancies in 2/235 (0.9%) (Figure 1A and 1B). Benign biopsies often showed changes consistent with inflammation. Of 101 cases diagnosed as carcinoma, 98 were classifiable into WHO Grade Groups.

The distribution was dominated by intermediate to high grade tumors. Perineural Invasion (PNI) was present in 59% (58/98) of evaluable carcinomas and was significantly associated with increasing Grade Group ($p = 0.0149$; Figure 2). High-grade PIN was present in 56.6% of carcinoma cases. The PSA levels were significantly higher in the carcinoma and ASAP groups compared to benign non-inflammatory tissue (Figure 3). However, PSA did not correlate significantly with the tumor volume ($p = 0.2393$). Dichotomizing the carcinomas into low-grade (Grade Groups 1-3) and high-grade (Grade Groups 4-5), PSA was weakly but significantly associated with higher-grade disease ($p = 0.0352$).

According to the first specific aim, diagnostic utility of AMACR and p63 in atypical cases, 21 cases (8.9% of 235) were initially diagnosed as ASAP based on morphology alone. One case was excluded due to the lack of sufficient tissue, so 20 cases were immunohistochemically evaluated. In the control cohort ($n = 40$), p63 had a sensitivity and specificity of 95 and 100%, respectively, whereas AMACR had a sensitivity and specificity of 90% each (Figure 4). Sequential p63 and AMACR staining supported IHC-assisted reclassification in 18 of the 20 evaluable ASAP cases (90%); this result does not by itself establish diagnostic accuracy against an independent reference standard. Specifically, 55% (11/20) were downgraded to benign, 35% (7/20) were reclassified as carcinoma on IHC-assisted review and only 10% (2/20) remained indeterminate.

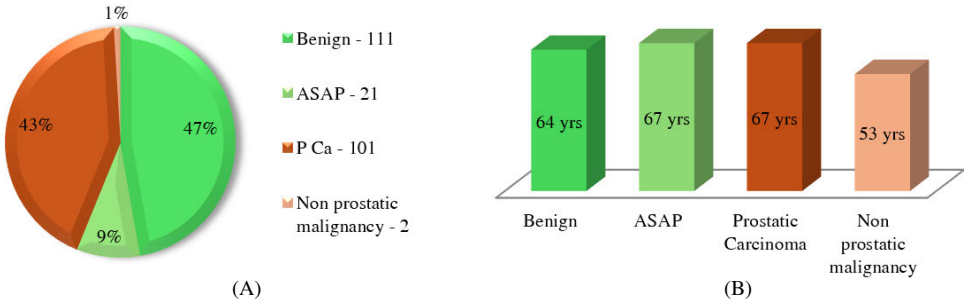


Figure 1: (A) All Cases with Diagnoses (B) Mean Age Distribution

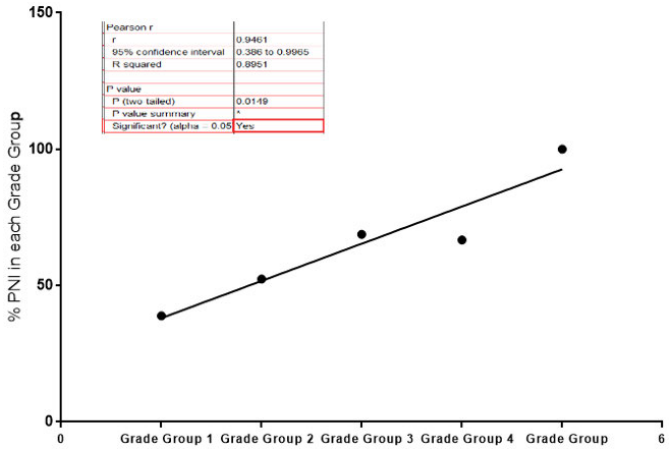


Figure 2: Association between WHO Grade Group and the Percentage of Cases with Perineural Invasion (PNI)

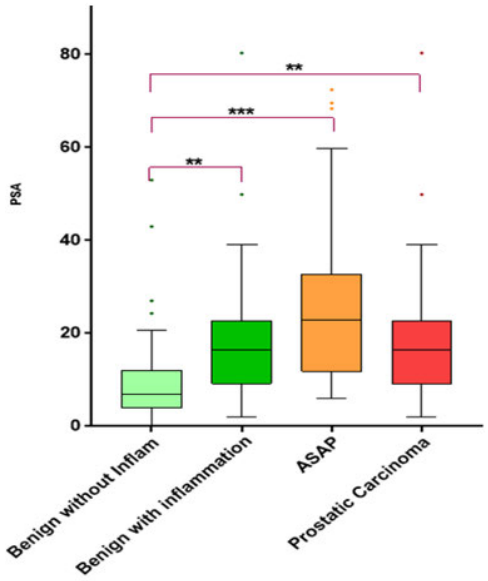


Figure 3: Serum Prostate-Specific Antigen (PSA) Distribution by Morphological Biopsy Category (Box Plot; Significance Annotations are Reproduced from the Original Analysis; the Exact Test and Post-Hoc Comparisons Require Confirmation)

IHC		Controls – 40		Result			
		Malignant (20)	Benign (20)	Sensitivity	Specificity	*p value*	
p63 (40 cases)	**Malignant** (Negative stain)	19 (TP)	0 (FP)	95%	100%	<0.0001	
	Benign (Positive stain)	1 (FN)	20 (TN)				
AMACR (40 cases)	**Malignant** (Positive staining)	18 (TP)	2 (FP)	90%	90%	<0.001	
	Benign (Negative staining)	2 (FN)	18 (TN)				

Figure 4: Diagnostic Sensitivity and Specificity of p63 and AMACR

The findings suggest that combined staining can aid morphological interpretation in selected equivocal biopsies; two cases remained indeterminate.

For the clinicopathological marker analysis, 83 selected untreated primary prostatic adenocarcinoma cases were evaluated from the 101 initially classified carcinoma cases. Loss of PTEN protein was identified in 37.3% (31/83) of cases. The rate of PTEN loss increased with higher Grade Groups and was 50% in Grade Group 5 tumors; this association was statistically significant ($p = 0.0137$). PTEN loss was also significantly associated with increasing tumor volume ($p = 0.019$) and the presence of metastasis at diagnosis ($p = 0.0053$). Loss of PTEN was more common in cases with perineural invasion and higher PSA levels, although these associations were not statistically significant. HGPIN areas invariably retained PTEN expression and intratumoral heterogeneity was seen in ~2% of cases.

Nuclear positivity for Androgen Receptor (AR) was seen in 79.5% (66/83) of the carcinoma cases. The percentage of AR positive cases increased with increasing Grade Group. Strong to moderate immunoreactivity was seen in 65% of cases. AR positivity was significantly associated with perineural invasion ($p = 0.0122$) and was significantly associated with metastasis present at diagnosis ($p<0.001$).

However, there was no significant correlation between AR expression with PSA or tumor volume. When staining intensity was split into low versus high expression, staining-intensity category did not show a statistically significant association with Grade Group in the reported comparison.

Nuclear positivity for NF-κB (p65) was observed in 69.9% (58/83) of cases. Expression increased significantly with Grade Group progression ($p = 0.0037$) and staining intensity was significantly associated with higher grades ($p = 0.0017$). NF-κB positivity was also significantly associated with tumor volume ($p = 0.0407$), perineural invasion ($p = 0.0032$) and metastasis at diagnosis ($p<0.0001$). There was no significant association between NF-κB expression and PSA levels.

To examine an immunohistochemical co-expression pattern, AR and NF-κB were analysed together. Moderate to high concordant expression was found in 37% of cases and associated significantly ($p = 0.0073$). Stratified into high versus low expression groups, rates of metastasis increased progressively from concordant low expression to discordant expression to concordant high expression (Figure 4), suggesting an exploratory relationship with metastasis present at diagnosis rather than demonstrated molecular synergy.

Overall, the results provide descriptive observations relevant to the diagnostic and clinicopathological aims. The proportion of Atypical Small Acinar Proliferation (ASAP) among biopsy specimens was 8.9% (21/235), underlining the diagnostic difficulties in routine practice. The combination of AMACR and p63 immunohistochemistry supported IHC-assisted reclassification of 18/20 (90%) evaluable ASAP cases, without establishing independent diagnostic accuracy. In the selected carcinoma IHC cohort, PTEN loss was significantly associated with higher tumor grade, greater tumor burden and presence of metastasis at diagnosis, reflecting a clinicopathological association in this sample. Both Androgen Receptor (AR) and NF-κB p65 staining were reported to be associated with adverse pathological features including perineural invasion and metastatic presentation. Moreover, AR-NF-κB co-expression was described in relation to metastasis status, but immunohistochemical co-expression cannot demonstrate molecular pathway synergy.

DISCUSSION

This study offers an insight into the diagnostic spectrum of routine TRUS-guided prostate cores based on biopsy and highlights clinically significant "risk signals" beyond morphology alone. The mean age of 66 years is consistent with the normal age distribution of prostate cancer cohorts. It is not unexpected that we found a predominance of intermediate- to high-grade tumors in a tertiary referral center. Perineural Invasion (PNI) was common (59%) and increased with Grade Group, as previously reported where PNI on biopsy was associated with adverse pathology and poorer outcomes. Initial studies have shown that biopsy PNI is associated with increased pathologic stage [17] and more recent analyzes support its link with recurrence risk, especially in higher-grade disease [18,19]. The observed elevation of PSA in carcinoma/ASAP compared to benign non-inflammatory biopsies is biologically plausible but the weak relationship between PSA and tumor burden in our cohort is consistent with the well-known limitation of PSA as an imprecise surrogate of volume and aggressiveness in the setting of benign inflammatory changes.

Atypical Small Acinar Proliferation (ASAP) accounted for 8.9% (21/235) of biopsies in our series, within reported ranges but higher than some population-based reports-likely reflecting referral and case-mix effects at a tertiary center. The literature review and large clinical series report a wide range of ASAP rates and emphasize that ASAP is not a single entity but a diagnosis of limited tissue and uncertainty [15,20,21]. Contemporary follow-up studies also demonstrate that an appreciable minority of men with ASAP have cancer on subsequent evaluation (often ~30-40%), supporting the clinical importance of resolving ASAP whenever possible [22]. Sequential p63 and AMACR staining supported reclassification of 18/20 (90%) evaluable ASAP cases, with two cases remaining indeterminate. This is highly consistent with the established utility of pairing a basal cell marker (p63) with a positive carcinoma marker (AMACR/P504S). The diagnostic utility of p63/AMACR-based approaches in small foci and atypical proliferations was demonstrated by Molinié *et al.* [23]. Later studies have also supported the combination of basal cell markers with AMACR to reduce diagnostic ambiguity [24]. The performance we measured (95% sensitivity and 100% specificity for p63; 90% sensitivity/specificity for AMACR) is consistent with previous reports, where p63 usually has very high specificity and AMACR has strong sensitivity but may occasionally stain benign mimics, accounting for the small proportion of cases that remain indeterminate even after IHC [23,24].

PTEN loss was observed in 37.3% (31/83) of selected carcinoma cases in the clinicopathological analysis and was higher with Grade Group, tumor volume and metastasis at diagnosis. This pattern is consistent with the general literature defining PTEN loss as a hallmark of aggressive prostate cancer biology, mediated by PI3K/AKT pathway activation and associated with unfavorable outcomes. Extensive validation work has shown clinical-grade PTEN immunohistochemistry to be analytically robust and clinically informative [11]. Other clinical studies have shown a link between PTEN loss and worse prognosis and risk of recurrence [25]. An additional meta-analysis confirms that PTEN loss is enriched in higher Grade Groups and associated with worse clinical outcomes [26]. A significant concordant finding in our study was preserved PTEN expression in HGPIN, consistent with the idea that PTEN loss is more characteristic of invasive, biologically aggressive disease than pre-invasive lesions.

In our cohort, AR nuclear positivity was found in 79.5% of carcinomas and showed reported associations with metastasis present at diagnosis and PNI. This further supports growing evidence that elevated AR signaling can promote invasive and metastatic phenotypes in certain biological contexts, including epithelial-mesenchymal transition and metastatic progression [27]. But AR biology

in prostate cancer is complex and published results are not uniform: some studies have reported inverse or variable correlations between AR immunostaining and histologic grade [28], whereas other work highlights consistent AR expression across benign, PIN and carcinoma with prognostic significance dependent on context, treatment status and methodology [29]. Our results report associations with metastatic presentation and PNI, but do not demonstrate that AR immunoreactivity independently predicts future progression, recurrence or survival.

In this series, NF-κB (p65) nuclear immunoreactivity showed reported associations with Grade Group, tumour volume, PNI and metastasis present at diagnosis ($p<0.0001$ for metastasis). These data are consistent with pivotal mechanistic and tissue-based studies demonstrating constitutive NF-κB activation in prostate cancer and its role in survival signaling, invasion and metastatic behaviour [30,31]. Increased nuclear localization of NF-κB has been shown in metastatic disease settings such as lymph-node metastasis supporting the clinical relevance of nuclear p65 scoring [32]. More recent analyzes further elaborate that both canonical and alternative NF-κB pathways contribute to clinical aggressiveness, treatment resistance and progression [33,34]. The absence of correlation between NF-κB and PSA in our cohort is not surprising, as inflammatory and oncogenic transcriptional programs can drive invasion/metastasis without proportional changes in PSA secretion.

Lastly, the reported concordant moderate-to-high AR-NF-κB co-expression pattern in our cohort, occurring more often among cases with metastasis at diagnosis, is consistent with the recognized crosstalk between inflammatory signaling and androgen-axis regulation in prostate cancer progression. Transcriptomic and mechanistic studies demonstrate that co-activation of AR and NF-κB can reprogram gene expression toward aggressive phenotypes [35]. Integrative reviews have highlighted feedback loops where NF-κB can enhance AR signaling and contribute to castration-resistant evolution, while AR signaling can differentially modulate NF-κB pathways [36,37]. While our co-expression-metastasis gradient was not always statistically significant in all sub-group comparisons, the observed pattern is hypothesis-generating and does not establish a molecular interaction, independent prognostic performance or readiness for routine risk-stratification use.

CONCLUSION

In this biopsy-based series, AMACR and p63 assisted the morphological reassessment of selected ASAP cases, although two remained equivocal and an independent diagnostic reference standard was not documented for all cases. In the selected untreated adenocarcinoma cohort, PTEN loss and AR and NF-κB p65 immunoreactivity showed reported associations with adverse clinicopathological features, including metastasis present at diagnosis. These descriptive findings do not establish independent prediction of progression, recurrence or survival, nor do AR-NF-κB staining patterns demonstrate molecular synergy. Larger multicentre studies with standardised IHC scoring, clearly defined reference standards and longitudinal follow-up are required before broader prognostic or therapeutic use can be recommended.

Limitations

The study was conducted at a single tertiary-care centre and the reported IHC analyses involved only 20 evaluable ASAP cases, a 40-case diagnostic control set and a selected 83-case carcinoma cohort. These sample sizes limit precision and generalizability of subgroup findings. The manuscript does not report longitudinal follow-up, recurrence, survival analysis or external marker validation; metastasis assessed at diagnosis cannot be used to infer future metastatic progression. IHC-assisted reclassification of ASAP is not equivalent to validated diagnostic accuracy without an independent reference standard. Semi-quantitative IHC interpretation may be affected by technical and observer variability and the reported associations may be confounded by Grade Group, PSA or tumour burden. Multiple exploratory statistical comparisons increase the possibility of chance findings, particularly for borderline p-values. Further details regarding cohort selection, antibody protocols, scoring thresholds and ethical approval require confirmation by the authors.

REFERENCES

[1] Epstein, J.I. *et al.* "The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma." *Am. J. Surg. Pathol.* vol. 40, no. 2, 2016, pp. 244-252.

[2] Humphrey, P.A. *et al.* "The 2016 WHO classification of tumours of the urinary system and male genital organs-Part B: Prostate and bladder tumours." *Eur. Urol.* vol. 70, no. 1, 2016, pp. 106-119.

[3] Sung, H. *et al.* "Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide." *CA Cancer J. Clin.* vol. 71, no. 3, 2021, pp. 209-249.

[4] Siegel, R.L. *et al.* "Cancer statistics, 2024." *CA Cancer J. Clin.* vol. 74, no. 1, 2024, pp. 17-48.

[5] Bray, F. *et al.* "The ever-increasing importance of cancer as a leading cause of premature death worldwide." *Cancer*, vol. 127, no. 16, 2021, pp. 3029-3030.

[6] Mathur, P. *et al.* "Cancer statistics, 2020: Report from national cancer registry programme, India." *JCO Glob Oncol.* vol. 6, 2020, pp. 1063-1075.

[7] Ilic, D. *et al.* "Prostate cancer screening with Prostate-Specific Antigen (PSA) test: Updated systematic review and meta-analysis." *Cochrane Database Syst. Rev.* vol. 3, 2018, CD004720.

[8] US Preventive Services Task Force. "Screening for prostate cancer: US Preventive Services Task Force recommendation statement." *JAMA.* vol. 319, no. 18, 2018, pp. 1901-1913.

[9] Jiang, Z. *et al.* "P504S/AMACR, a useful marker for prostate cancer diagnosis: A review of recent literature." *Adv. Anat. Pathol.* vol. 26, no. 2, 2019, pp. 91-98.

[10] Varma, M. and B. Jasani. "Diagnostic utility of immunohistochemistry in prostate pathology." *Histopathology.* vol. 76, no. 1, 2020, pp. 38-52.

[11] Lotan, T.L. *et al.* "Clinical-grade PTEN immunohistochemistry assay validation in prostate cancer." *Clin. Cancer Res.* vol. 25, no. 21, 2019, pp. 6596-6603.

[12] Jamaspishvili, T. *et al.* "Clinical implications of PTEN loss in prostate cancer." *Nat. Rev. Urol.* vol. 15, no. 4, 2018, pp. 222-234.
[13] Jin, R. *et al.* "NF-κB pathway activation in prostate cancer progression." *Cancer Lett.* vol. 508, 2021, pp. 1-10.
[14] Stark, J.R. *et al.* "Gleason score underestimation in prostate biopsy and its clinical impact." *Eur Urol.* vol. 77, no. 6, 2020, pp. 705-712.
[15] Watson, P.A. *et al.* "Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer." *Nat. Rev. Cancer.* vol. 15, no. 12, 2015, pp. 701-711.
[16] Labrecque, M.P. and E.S. Antonarakis. "The androgen receptor in prostate cancer: Biology and therapeutic implications." *Nat. Rev. Urol.* vol. 16, no. 6, 2019, pp. 331-344.
[17] de la Taille, A. *et al.* "Perineural invasion on prostate needle biopsy: An independent predictor of final pathologic stage." *Urology.* vol. 54, no. 6, 1999, pp. 1039-1043.
[18] Ström, P. *et al.* "Perineural invasion and risk of prostate cancer recurrence." *Eur. Urol. Focus.* vol. 6, no. 5, 2020, pp. 1026-1032.
[19] Ramineni, M. *et al.* "Perineural invasion as prognostic indicator in prostate cancer: Contemporary analysis." *BJU Int.* vol. 135, no. 2, 2025, pp. 210-218.
[20] Adamczyk, L.A. *et al.* "Clinical significance of atypical small acinar proliferation in prostate biopsies." *Pathol. Res. Pract.* vol. 210, no. 7, 2014, pp. 415-419.
[21] Tsampoukas, G. *et al.* "Atypical small acinar proliferation: Contemporary review and outcomes." *Cancers (Basel).* vol. 14, no. 3, 2022, 612.
[22] Kim, J.H. *et al.* "Risk of prostate cancer detection following diagnosis of ASAP." *Urol. Oncol.* vol. 39, no. 3, 2021, pp. 191.e9-191.e15.
[23] Molinié, V. *et al.* "Diagnostic utility of p63 and AMACR in atypical prostate biopsies." *Am. J. Surg. Pathol.* vol. 28, no. 3, 2004, pp. 357-363.
[24] Boran, C. *et al.* "Combined p63 and AMACR immunostaining in prostate needle biopsies." *Diagn Pathol.* vol. 6, 2011, pp. 69.
[25] Shah, R.B. *et al.* "PTEN loss as a prognostic biomarker in prostate cancer." *Hum. Pathol.* vol. 84, 2019, pp. 102-110.
[26] Kisiel, J.B. *et al.* "PTEN loss and clinical outcomes in prostate cancer: Systematic review and meta-analysis." *Eur. Urol.* vol. 87, no. 1, 2025, pp. 55-66.
[27] Lin, T.H. *et al.* "Androgen receptor signaling promotes invasion and metastasis in prostate cancer." *Oncogene.* vol. 37, no. 23, 2018, pp. 3089-3102.
[28] Osman, I. *et al.* "Androgen receptor expression in prostate cancer progression." *Hum Pathol.* vol. 44, no. 9, 2013, pp. 1639-1645.
[29] Sweat, S.D. *et al.* "Androgen receptor expression in prostate cancer." *Cancer*, vol. 86, no. 4, 1999, pp. 620-626.
[30] Shukla, S. *et al.* "Activation of NF-κB in prostate cancer progression." *Oncogene.* vol. 23, no. 38, 2004, pp. 6653-6661.
[31] Domingo-Domenech, J. *et al.* "NF-κB activation in prostate cancer metastasis." *Cancer Res.* vol. 65, no. 21, 2005, pp. 10002-10009.
[32] Ismail, H.A. *et al.* "Expression of NF-κB in prostate cancer metastasis." *Cancer Res.* vol. 64, no. 22, 2004, pp. 8192-8197.
[33] Labouba, I. *et al.* "NF-κB pathway activation in aggressive prostate cancer." *Oncotarget*, vol. 6, no. 28, 2015, pp. 25585-25597.
[34] Al-Rashidi, S. *et al.* "NF-κB signaling in advanced prostate cancer: Mechanisms and therapeutic implications." Fr*ont Oncol.* vol. 13, 2023, 1145782.
[35] Malinen, M. *et al.* "Crosstalk between androgen receptor and NF-κB signaling in prostate cancer." *Oncogene*, vol. 36, no. 15, 2017, pp. 2036-2045.
[36] Staal, J. *et al.* "Androgen receptor and NF-κB pathway interaction in prostate cancer progression." *Nat. Rev. Urol.* vol. 15, no. 6, 2018, pp. 331-342.
[37] Khurana, N. *et al.* "Inflammatory signaling and androgen receptor interaction in prostate cancer." *Trends Cancer*, vol. 4, no. 4, 2018, pp. 262-276.