

Utilization of p53 and Ki-67 Biomarkers in Evaluation of Prostate Cancer at Benue State University Teaching Hospital, Makurdi, Nigeria

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Abstract: Prostate cancer (PCa) is the most common malignancy and leading cause of cancer mortality among Nigerian men, with majority presenting late with high-grade disease. Affordable prognostic biomarkers are needed to complement Gleason grading in resource-constrained settings. The objectives of the study is to evaluate the immunohistochemically expression frequencies of p53 and Ki-67 in Nigerian men with PCa and determine their correlation with Gleason score (ISUP Grade Group) and serum prostate-specific antigen (PSA). A prospective cross-sectional study was conducted at Benue State University Teaching Hospital, Makurdi, from 1 May 2025 to 30 April 2026. Forty-seven patients with histologically confirmed prostate adenocarcinoma were recruited via purposive sampling. Formalin-fixed paraffin-embedded blocks were subjected to immunohistochemistry for p53 and Ki-67 using streptavidin-biotin immunoperoxidase technique. Positivity was defined as $\geq 10\%$ nuclear staining. Correlation with Gleason score and PSA was assessed using Spearman's rho. Significance set at $p < 0.05$. The result showed that Mean age was 67.3 ± 10.2 years (range 37-84). Using ISUP 2019, Grade Group 1: 4.2%, Group 2: 12.8%, Group 3: 14.9%, Group 4: 42.6%, Group 5: 25.5%; 68.1% were poorly differentiated (Gleason 8-10). p53 positivity was 23.4% (11/47) and Ki-67 positivity was 74.5% (35/47). Ki-67 showed statistically significant association with higher Gleason score ($p = 0.001$) and strong positive correlation with PSA ($r = +0.876$, $p = 0.001$). p53 showed moderate positive correlation with PSA ($r = +0.496$, $p = 0.005$) but no significant correlation with Gleason score ($p = 0.103$) In conclusion, Ki-67 is highly expressed and strongly associated with aggressive clinicopathological features, supporting its utility as a pragmatic prognostic biomarker in Nigerian men with PCa. The prognostic role of p53 remains inconclusive in this population.

Keywords: prostate cancer, Ki-67, p53, Gleason score, PSA, immunohistochemistry, Nigeria, biomarker

INTRODUCTION

Prostate cancer (PCa) is the second most frequent malignancy in men worldwide and the sixth leading cause of cancer mortality, with 1,276,106 new cases and 358,989 deaths reported in 2018 (Bray et al., 2018). The burden is disproportionately high among men of African descent, who present with more aggressive disease and mortality rates approximately 2.5 times higher than White men (O'Keefe et al., 2015; Schaeffer et al., 2024). In Nigeria, PCa is the most diagnosed cancer among men, with hospital prevalence reported as high as 127-182.5 per 100,000 male admissions (Osegbe, 1997; Badmus et al., 2010).

Despite the global reliance on prostate-specific antigen (PSA) for detection and monitoring, PSA is organ-specific but not disease-specific, rising in benign prostatic hyperplasia, prostatitis, and prostatic infarction (Chen et al., 2023; David et al., 2024). At a cutoff of 4.0 ng/mL, its positive predictive value is only ~25-30%, leading to unnecessary biopsies (Tricoli et al., 2004; Catalona et al., 2017). This limitation has driven development of refined biomarkers including Prostate Health Index (PHI), 4Kscore, PCA3, Mi-Prostate Score, and genomic classifiers such as Decipher, Prolaris, and Oncotype DX (Bryant et al., 2015; Knezevic et al., 2013; Jairath et al., 2020). However, these advanced tests are expensive, technically demanding, and largely inaccessible in resource-constrained settings like Nigeria.

The Gleason grading system remains the mainstay of prognostication but is subjective, prone to inter-observer variability, and does not quantify proliferative activity (Epstein et al., 2016). There is therefore a need for affordable, immunohistochemistry (IHC)-based markers that can be implemented within existing histopathology infrastructure to improve risk stratification.

Two such candidates are p53 and Ki-67. p53, encoded on chromosome 17p13.1, is the guardian of the genome, regulating cell cycle arrest, DNA repair, and apoptosis via MDM2 feedback (Teroerde et al., 2021). Mutations lead to stabilization and nuclear accumulation detectable by IHC. Ki-67, encoded by MKI67 on 10q26.2, is expressed in active cell cycle phases (late G1, S, G2, M) but absent in G0, making it a robust marker of growth fraction (Sun & Kaufman, 2018).

Data on p53 and Ki-67 in African populations remain limited and inconsistent. Much of the evidence derives from Caucasian and Asian cohorts, and extrapolation to Nigerian men, who exhibit distinct tumour biology and higher aggressiveness, may be inappropriate. This study was therefore designed to determine the utility of p53 and Ki-67 in evaluating PCa at Benue State University Teaching Hospital, Makurdi, Nigeria.

LITERATURE REVIEW AND THEORETICAL UNDERPINNING

Theoretical Framework

This study is anchored on the cell-cycle dysregulation model of tumour progression within the multistep model of carcinogenesis and Hallmarks of Cancer framework (Hanahan & Weinberg, 2011). The model

posits that malignancy arises from loss of growth-suppressive control and gain of unchecked proliferative capacity, which manifest histologically as dedifferentiation and clinically as tumour burden.

Four propositions underpin this study

1. Loss of growth suppression (p53): Wild-type p53 is maintained at low levels by MDM2-mediated ubiquitination. Cellular stress disrupts p53-MDM2 interaction, leading to p53 stabilization and transcription of target genes (BAX, PUMA, CDKN1A) for cell cycle arrest or apoptosis (Teroerde et al., 2021). Missense mutations, particularly at CpG hotspots (R175H, R248Q, R273H), impair degradation, causing nuclear accumulation detectable by IHC.
2. Unchecked proliferation (Ki-67): Ki-67 is a nuclear non-histone protein absent in quiescent cells, thus reflecting tumour growth fraction. Because Gleason grading assesses architecture, not proliferation, Ki-67 is expected to add objective prognostic information (Uxa et al., 2021; Song et al., 2024).
3. Histological dedifferentiation: Higher Gleason patterns (4 and 5) characterized by fused, cribriform glands and sheets of cells reflect increased proliferative drive and genomic instability, predicted to correlate with Ki-67 and p53 alteration (Epstein et al., 2016).
4. Tumour burden (PSA): Highly proliferative, architecturally disrupted tumours release more PSA, predicting positive correlation between PSA and Ki-67, and less consistently with p53.

Biomarkers in Prostate Cancer

PSA revolutionized PCa management since 1986 but lacks specificity (Schröder et al., 2009). PHI, calculated as $(p2PSA/fPSA) \times \sqrt[3]{tPSA}$, improves detection of clinically significant PCa with pooled sensitivity 90% (White et al., 2018; Liu et al., 2022). The 4Kscore (total PSA, free PSA, intact PSA, hK2) achieved AUC 0.719-0.820 for high-grade PCa in the ProtecT trial of 4,765 patients (Bryant et al., 2015). PCA3, a prostate-specific mRNA 10-100-fold overexpressed in PCa tissue, shows sensitivity 0.65 and specificity 0.73 (AUC 0.75) in meta-analysis of 12,295 men (Boehm et al., 2023). However, these tests require specialized platforms.

p53 Expression in PCa: Frequency of p53 positivity varies widely from 5% to 65% due to antibody clones and cutoffs (5-20%) (Verma et al., 2015). Verma et al. (2015) in 50 Indian cases found 64% positivity in poorly differentiated versus 20% in well-differentiated tumours. Liu et al. (2020) confirmed upregulation in high-grade disease. Conversely, Anunobi et al. (2015) in Lagos reported only 14.8% positivity in 54 cases with no Gleason association, and Madani et al. (2011) found 42.9% positivity in 49 TURP specimens without significant Gleason correlation, highlighting population heterogeneity.

Ki-67 Expression in PCa: Evidence is more consistent. Verma et al. (2015) showed mean Ki-67 index rising from 12.4% in Gleason 6 to 42.6% in Gleason 8-10. Murti et al. (2017) in 45 Indonesian cases

found Ki-67 >10% significantly associated with Gleason ≥ 8 and T-stage. Rashed et al. (2016) and Song et al. (2024) validated Ki-67 >20% as independent predictor of biochemical recurrence and PCa-specific mortality. In Nigeria, Dallang et al. (2025) reported high Ki-67 expression correlating with grade and aggressiveness, recommending routine assessment.

Conceptual Framework

Independent variables: Age, PSA, Gleason/ISUP grade → Dependent variables: p53 immunoexpression and Ki-67 labeling index. Covariates include comorbidities and medications affecting biomarkers, controlled via exclusion criteria.

METHODOLOGY

Study Design and Setting

This was a prospective, cross-sectional study conducted at Benue State University Teaching Hospital (BSUTH), Makurdi, a 400-bed tertiary facility serving Benue State (population ~5.7 million, 2016 estimate) and neighbouring Taraba, Nasarawa, Cross River, and Kogi states. Study period: 1 May 2025 to 30 April 2026.

Study Population and Sampling

Patients presenting to the urology clinic with histologically confirmed prostate adenocarcinoma during the study period were recruited by purposive sampling. Sample size was calculated using Cochran formula (Cochran, 1963): $n = Z^2pq/d^2$, where $Z=1.96$ (95% confidence), $p=0.14$ (14% PCa prevalence among urology patients in 2023: 42/299), $q=0.86$, $d=0.10$, yielding $n=46.3 \approx 47$.

Inclusion Criteria: (a) histologically confirmed PCa within study period, (b) informed consent.

Exclusion Criteria: (a) on androgen deprivation therapy, (b) bilateral orchidectomy, (c) radiotherapy or chemotherapy for PCa, (d) medications/diseases influencing p53/Ki-67, (e) refusal to consent.

Data Collection and Laboratory Procedures

Clinical data (age, DRE findings, PSA) were collected via structured proforma. Serum PSA was measured via chemiluminescence immunoassay. Gleason scoring was performed using light microscopy according to 2019 ISUP modified system by two pathologists. Grade Groups: 1 (Gleason ≤ 6), 2 (3+4=7), 3 (4+3=7), 4 (4+4=8), 5 (9-10).

Immunohistochemistry: 4- μ m sections from 10% formalin-fixed paraffin-embedded blocks were stained

using streptavidin-biotin immunoperoxidase technique (Dako) as described by Verma et al. (2015). Primary antibodies: monoclonal mouse anti-p53 (DO-7 clone) and anti-Ki-67 (MIB-1 clone). Positive controls: colonic carcinoma for p53, tonsil for Ki-67. Negative controls omitted primary antibody. Assessment by a single histopathologist blinded to clinical data. p53 and Ki-67 labeling index = percentage of positively stained nuclei in 500 tumour cells in hot spots at $\times 400$ magnification. For analysis, categorized as positive ($\geq 10\%$) and negative ($< 10\%$), with continuous index retained for correlation.

Data Analysis

Data analyzed with SPSS version 26. Descriptive statistics: mean $\pm$ SD, frequencies. Spearman's rank correlation coefficient assessed relationship between biomarker expression, Gleason grade, and PSA. $p < 0.05$ considered significant.

Ethical Considerations

Approval obtained from BSUTH Health Research Ethics Committee (BSUTH/CMAC/HREC/93/V.III/XX). Written informed consent obtained. No patient bore financial cost. Confidentiality maintained per Declaration of Helsinki.

RESULTS / FINDINGS

Sociodemographic and Clinicopathological Characteristics

Forty-seven patients were recruited. Age range 37-84 years, mean 67.3 ± 10.2 years, peak in seventh decade (42.6%). Histology: 100% acinar adenocarcinoma. Using ISUP 2019 grading: Grade Group 1, 2 cases (4.2%); Group 2, 6 (12.8%); Group 3, 7 (14.9%); Group 4, 20 (42.6%); Group 5, 12 (25.5%). Categorized by differentiation: well-differentiated (Gleason 6) 4.2%, moderately differentiated (Gleason 7) 27.7%, poorly differentiated (Gleason 8-10) 68.1%. Serum PSA: < 10 ng/mL 2.1%, 10-20 ng/mL 6.4%, 21-30 ng/mL 31.9%, > 30 ng/mL 59.6%.

Expression Frequencies of p53 and Ki-67

p53: Positive in 11 cases (23.4%), negative in 36 (76.6%). Distribution by grade: well-differentiated 1/2 (2.1% of total), moderately differentiated 3/13 (6.4%), poorly differentiated 7/32 (14.9%).

Ki-67: Positive in 35 cases (74.5%), negative in 12 (25.5%). Positivity increased with grade, with highest prevalence in Grade Groups 4-5.

Correlation with Gleason Score

p53 expression showed very weak, non-significant correlation with Gleason score (Spearman rho = +0.158, p = 0.649 for categorical; p = 0.103 for continuous index, 2-tailed, N=47).

Ki-67 expression showed statistically significant positive association with Gleason score (p = 0.042 categorical, p = 0.001 for continuous index, Spearman correlation).

Correlation with PSA

p53: Moderate positive correlation with PSA (Spearman r = +0.496, p = 0.005).

Ki-67: Strong positive correlation with PSA (Spearman r = +0.876, p = 0.001).

[Tables should be inserted: Table 1 Sociodemographic, Table 2 p53 vs Gleason, Table 3 Ki-67 vs Gleason, Table 4 p53 vs PSA, Table 5 Ki-67 vs PSA; Figures: Pie charts of p53 and Ki-67 positivity]

DISCUSSION

This study evaluated p53 and Ki-67 as adjunct biomarkers for prostate cancer prognostication in a Nigerian cohort characterized by late presentation and high-grade disease, consistent with national reports (Anyimba et al., 2025; Tolani et al., 2025).

Sociodemographic Pattern

Mean age 67.3 years aligns with Nigerian median age 66-67 years reported by Abdus-Salam et al. (2024) and Tolani et al. (2025). The exclusive adenocarcinoma histology corroborates literature reporting 73.7-99.1% adenocarcinoma in Nigeria (Bello et al., 2025). The predominance of ISUP Grade Groups 4-5 (68.1%) and PSA >30 ng/mL (59.6%) mirrors findings by Dallang et al. (2025) who reported 71.8% poorly differentiated tumours, attributed to low awareness, absence of organized screening, and late referral.

p53 and Gleason Grade

The 23.4% p53 positivity rate is higher than 14.8% reported by Anunobi et al. (2015) in Lagos but lower than 42.9% by Madani et al. (2011) and 64% in poorly differentiated cases by Verma et al. (2015). The non-significant correlation with Gleason ($p=0.103$) aligns with Anunobi et al. (2015), Madani et al. (2011), and Sasor et al. (2000), who concluded p53 is an inconsistent grade discriminator. This may reflect biological reality: p53 IHC is imperfect surrogate for TP53 status; missense mutations cause accumulation (positive), whereas nonsense mutations/deletions cause null expression (scored negative) despite aggressive biology (Teroerde et al., 2021). Variations in antibody clones, cutoffs (5-20%), and small sample size also contribute.

Ki-67 and Gleason Grade

In contrast, Ki-67 positivity of 74.5% and its significant association with Gleason ($p=0.001$) supports a robust literature. Verma et al. (2015) showed progressive increase from 12.4% in Gleason 6 to 42.6% in Gleason 8-10. Murti et al. (2017), Sulik et al. (2011), Stoiculescu et al. (2025), Ruhela et al. (2025), and Song et al. (2024) validated Ki-67 as independent predictor of biochemical recurrence. Nigerian data from Dallang et al. (2025) similarly recommended routine Ki-67 for risk stratification. Biological plausibility is clear: Gleason patterns 4-5 represent loss of glandular differentiation with increased proliferation, directly quantified by Ki-67, which is absent in G0 (Sun & Kaufman, 2018).

Correlation with PSA

Both markers correlated with PSA, but with differing strength. Ki-67 showed strong correlation ($r=0.876$), consistent with Murti et al. (2017) and Verma et al. (2015), supporting concept that proliferative tumours have higher burden and disrupt architecture, increasing PSA leakage. However, clustering of 59.6% cases at PSA >30 ng/mL may inflate rho, requiring cautious interpretation.

p53 showed moderate correlation ($r=0.496$, $p=0.005$), suggesting association with tumour burden despite lack of grade correlation. Previous studies are divided: Iemelyanova et al. (2009) found higher p53 in high PSA/high-grade disease, whereas Madani et al. (2011) found no correlation. Discrepancies likely reflect cut-off heterogeneity and TP53 biology.

Overall, results support cell-cycle dysregulation model: unchecked proliferation (Ki-67) tracks with dedifferentiation and burden, while p53 loss is less linearly related to grade in this population.

Implications to Research and Practice

Clinical Practice Implications

1. Pragmatic risk stratification: In resource-limited settings where Decipher (GC >0.6 threshold), Prolaris (CCP score), and Oncotype DX (GPS 0-100) are inaccessible, Ki-67 IHC (cost ~\$15-25 per test) can serve as adjunct to Gleason. Specifically, Ki-67 $\geq 10\%$ could flag intermediate Gleason 7 patients who may behave aggressively and warrant earlier definitive therapy or closer surveillance, as suggested by Dallang et al. (2025).
2. Pathology workflow: Ki-67 labeling index should be reported routinely alongside Gleason Grade Group. Standardization of scoring (hot-spot counting of 500 cells, MIB-1 clone, $\geq 10\%$ cutoff) would improve reproducibility, addressing inter-observer variability in Gleason.
3. Patient counselling: High Ki-67 plus PSA >30 ng/mL identifies high-volume, high-proliferation phenotype needing multidisciplinary discussion (NCCN high-risk protocol: EBRT + ADT). Low Ki-67 despite elevated PSA may suggest large-volume but indolent disease.
4. p53: Given low positivity (23.4%) and non-significant grade correlation, p53 IHC alone should not guide clinical decisions in Nigerian practice until validated with molecular TP53 sequencing.

Research Implications

This study contributes African data to address underrepresentation noted by Schaeffer et al. (2024). It highlights need for standardized IHC protocols and integration with genomic classifiers. Future implementation research should evaluate cost-effectiveness of Ki-67 vs PHI (which reduces unnecessary biopsies 15-45% at threshold 25; White et al., 2018) in Nigerian screening pathways.

For International Journal of Cancer, Clinical Inventions and Experimental Oncology (IJCCEO) audience, this work demonstrates translational utility of cell-cycle biomarkers in low-middle income countries and aligns with precision oncology goal of affordable prognostication.

CONCLUSION

In a cohort of 47 Nigerian men with prostate cancer presenting predominantly with high-grade, high-PSA disease, Ki-67 was highly expressed (74.5%) and significantly correlated with ISUP Grade Group and PSA, supporting its utility as a reliable, affordable prognostic biomarker for aggressive disease. p53 was expressed in only 23.4% of cases and correlated moderately with PSA but not with Gleason score,

rendering its prognostic role inconclusive in this population. Incorporating Ki-67 into routine histopathological evaluation may improve risk stratification beyond Gleason alone in resource-constrained settings like Nigeria.

Future Research

1. Larger, multi-centre prospective cohorts with ≥ 200 patients across geopolitical zones of Nigeria to validate Ki-67 cutoff and overcome leverage bias from high-PSA clustering.
2. Molecular correlation: Pair IHC with TP53 sequencing, MKI67 mRNA quantification, and assessment of TMPRSS2:ERG fusion prevalence (50% Caucasian, 31.3% African American, 15.9% Japanese; Olleik et al., 2018) to clarify race-specific biology.
3. Longitudinal outcomes: Evaluate Ki-67 and p53 as predictors of biochemical recurrence, metastasis-free survival, and prostate cancer-specific mortality, adjusting for NCCN risk groups, similar to validation of Decipher (Jairath et al., 2020) and Prolaris (Cuzick et al., 2015).
4. Standardization study: Inter-observer reproducibility of Ki-67 scoring (manual vs digital image analysis) and determination of optimal positivity threshold (5%, 10%, 20%) for Nigerian population.
5. Cost-effectiveness analysis: Compare Ki-67 IHC versus PHI and 4Kscore in reducing unnecessary biopsies and guiding treatment decisions in low-resource settings.
6. Combination biomarker panels: Investigate combined Ki-67 + p53 + AMACR + PTEN loss panel to improve prognostic accuracy beyond single markers.

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