Section: Miscellaneous

Original Research Article

ANGIOGENIC INDEX AS AN ADJUNCT TO GLEASON GRADING IN PROSTATE CANCER A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Angiogenesis plays a crucial role in tumor growth, progression, and metastasis in solid malignancies, including prostate cancer. Although Gleason grading remains the cornerstone for assessing tumor aggressiveness, it does not fully reflect the underlying biological processes driving disease progression. The angiogenic index has emerged as a quantitative measure of tumor angiogenesis, integrating microvessel density and endothelial activity. This study aimed to evaluate the angiogenic index in prostate cancer and to analyze its correlation with Gleason grade and Gleason score.

Materials and Methods: This hospital-based cross-sectional analytical study included 47 histopathologically confirmed cases of prostate adenocarcinoma. Gleason grading and scoring were performed according to the ISUP-modified Gleason system. Angiogenesis was assessed on formalin-fixed, paraffin-embedded tissue sections using immunohistochemistry for endothelial markers. Microvessel density was determined in vascular "hot spots," and the angiogenic index was calculated as a composite measure of angiogenic activity. Correlations between angiogenic index and Gleason grade and score were analyzed using appropriate statistical tests.

Results: The mean age of patients was 66.4 ± 7.8 years, and the mean serum PSA level was 38.6 ± 21.4 ng/mL. High-grade tumors (Gleason score ≥8) constituted the majority of cases. Both microvessel density and angiogenic index showed a progressive increase with rising Gleason grade groups ($p < 0.001$). A strong positive correlation was observed between angiogenic index and Gleason score (Spearman's $r = 0.78$, $p < 0.001$). High angiogenic activity was significantly more common in high-grade tumors ($p < 0.001$), and the angiogenic index was markedly higher in high-grade compared to low-grade prostate cancers (84.3 ± 11.6 vs 52.4 ± 9.1; $p < 0.001$).

Conclusion: The angiogenic index demonstrates a strong association with Gleason grade and Gleason score, reflecting increasing angiogenic activity with tumor aggressiveness in prostate cancer. Incorporation of angiogenic index into routine histopathological assessment may enhance prognostic stratification and provide additional biological insight beyond conventional grading.

Keywords: Prostate cancer; Angiogenesis; Angiogenic index; Microvessel density; Gleason score; Tumor aggressiveness.

INTRODUCTION

Prostate cancer is one of the most commonly diagnosed malignancies among men worldwide and represents a major contributor to cancer-related morbidity and mortality.[1] Its clinical behavior ranges from indolent, slow-growing tumors to highly aggressive disease with early metastasis. Accurate assessment of tumor aggressiveness is therefore essential for prognostication, treatment planning, and

risk stratification.[2] Currently, histopathological evaluation using the Gleason grading system and Gleason score remains the cornerstone for assessing tumor differentiation and biological behavior.[3] However, tumors with similar Gleason scores may still demonstrate heterogeneous clinical outcomes, highlighting the need for additional objective biological markers that reflect tumor activity and progression potential.[4]

Angiogenesis, defined as the formation of new blood vessels from pre-existing vasculature, is a fundamental process in tumor growth and metastasis. Solid tumors, including prostate cancer, depend on angiogenesis for sustained growth beyond a critical size (approximately 1–2 mm^3) and for dissemination to distant organs.[5] Tumor-induced angiogenesis is regulated by a complex balance between pro-angiogenic factors such as vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and angiopoietins, and anti-angiogenic factors including thrombospondin-1 and endostatin. A shift in this balance toward pro-angiogenic signaling—often referred to as the "angiogenic switch"—is considered a key event in malignant progression.[6]

In prostate cancer, increased angiogenic activity has been associated with tumor progression, local invasion, and metastatic potential. Microvessel density (MVD), assessed by immunohistochemical staining for endothelial markers such as CD31, CD34, or CD105, has traditionally been used as a surrogate marker of angiogenesis. Several studies have demonstrated higher MVD in malignant prostate tissue compared to benign prostatic hyperplasia and normal prostate, with a trend toward increased MVD in higher Gleason grades.[7-9] However, MVD assessment alone has limitations, including interobserver variability, lack of functional information, and inability to reflect the dynamic balance between angiogenic stimulators and inhibitors.

The concept of an angiogenic index has emerged to provide a more comprehensive and quantitative measure of tumor angiogenesis. The angiogenic index integrates parameters related to endothelial proliferation, microvessel density, and/or expression of angiogenic markers, thereby offering a composite indicator of angiogenic activity within tumor tissue.[10] Unlike isolated markers, the angiogenic index is thought to better represent the biological aggressiveness of the tumor microenvironment and its capacity for sustained growth and dissemination. Increasing evidence suggests that higher angiogenic indices are associated with poor differentiation, advanced stage, and adverse clinical outcomes in various solid tumors, including prostate cancer.[11]

Gleason grade and Gleason score reflect architectural patterns and degree of glandular differentiation but do not directly capture underlying molecular and microenvironmental changes such as angiogenesis.[12] Correlating the angiogenic index with Gleason grade and score may therefore provide valuable insights into the biological basis of tumor aggressiveness. Demonstrating a positive correlation would support the role of angiogenesis as a key determinant of histological severity and could help identify high-risk tumors within the same Gleason category. Moreover, such correlations may have therapeutic implications, particularly in the era of targeted therapies and anti-angiogenic agents, where patient selection based on tumor angiogenic activity could optimize treatment outcomes.[13]

In this context, evaluating the angiogenic index as a measure of angiogenesis in prostate cancer and examining its relationship with Gleason grade and Gleason score is clinically relevant. A better understanding of this association may enhance prognostic assessment, contribute to refined risk stratification, and provide a biological rationale for incorporating angiogenesis-based markers into routine histopathological evaluation of prostate cancer. The study was aimed to evaluate angiogenesis in prostate carcinoma using an angiogenic index and to analyze its correlation with Gleason grade and Gleason score.

MATERIALS AND METHODS

Study Design and Setting: This was a hospital-based, cross-sectional analytical study conducted in the Department of Pathology in collaboration with the Department of Urology at a tertiary care teaching hospital in India. The study was carried out over a defined study period of 24 months between January 2023 to January 2025, after obtaining approval from the Institutional Ethics Committee.

Study Population and Sample Selection: The study included histopathologically confirmed cases of prostate adenocarcinoma diagnosed on transrectal ultrasound-guided core needle biopsy specimens or radical prostatectomy specimens received during the study period. Only newly diagnosed, treatment-naïve cases were included to avoid the confounding effects of prior hormonal therapy, chemotherapy, or radiotherapy on tumor angiogenesis. Cases with inadequate tissue for immunohistochemical evaluation, extensive necrosis, poorly preserved samples, or prior history of prostate cancer treatment were excluded from the study. A total of 47 cases fulfilling the inclusion criteria were enrolled using a consecutive sampling method.

Histopathological Evaluation and Gleason Grading: All hematoxylin and eosin (H&E) stained sections were reviewed independently by two experienced pathologists who were blinded to the angiogenic findings. Prostate adenocarcinoma was confirmed based on standard histomorphological criteria. Gleason grading was performed according to the International Society of Urological Pathology (ISUP) 2014/2016 modified Gleason grading system. The primary and secondary architectural patterns were identified, and the Gleason score was calculated by summation of the two most predominant patterns.

Based on the Gleason score, tumors were further categorized into Gleason grade groups for correlation analysis.

Immunohistochemical Assessment of Angiogenesis: Formalin-fixed, paraffin-embedded tissue blocks were selected for immunohistochemical (IHC) evaluation of angiogenesis. Sections of 3–4 µm thickness were cut and mounted on poly-L-lysine–coated slides. Immunohistochemical staining was performed using a monoclonal antibody against an endothelial cell marker (CD34/CD31/CD105, specify marker), following standard streptavidin–biotin or polymer-based detection protocols. Appropriate positive controls (known vascular tissue) and negative controls (omission of primary antibody) were included in each staining batch to ensure staining reliability.

Evaluation of Microvessel Density: Immunostained sections were examined under light microscopy. Areas of highest vascular density (so-called "hot spots") were identified at low power (×40 or ×100). Within these hot spots, individual microvessels were counted at high power magnification (×400) in three non-overlapping fields, and the mean value was calculated for each case. Any brown-stained endothelial cell or endothelial cell cluster clearly separated from adjacent vessels, tumor cells, or connective tissue was considered a single microvessel, irrespective of the presence of a visible lumen. The mean microvessel density (MVD) was calculated for each case and expressed as the average number of microvessels per high-power field.

Calculation of Angiogenic Index: The angiogenic index was calculated as a composite quantitative measure of angiogenesis, derived from microvessel density and endothelial proliferation/activity parameters. For each case, the angiogenic index was calculated using the formula:

Angiogenic Index = (Mean microvessel density × endothelial cell staining intensity score).

Based on the angiogenic index values, cases were categorized into low, intermediate, and high angiogenic activity groups using cut-off values derived from tertile distribution of angiogenic index scores, as adopted in previously published study.[14]

Correlation with Gleason Grade and Score: The angiogenic index values were correlated with Gleason grade, Gleason score, and Gleason grade groups to assess the relationship between angiogenesis and tumor histological aggressiveness. Comparisons were made between low-grade and high-grade tumors, as well as across increasing Gleason score categories, to determine trends in angiogenic activity with tumor differentiation.

Statistical Analysis: Data were entered into a predesigned proforma and analyzed using Statistical Package for the Social Sciences (SPSS) software, version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables such as microvessel density and angiogenic index were expressed as mean ± standard deviation. Categorical variables were expressed as frequencies and percentages. The correlation between angiogenic index and Gleason score was assessed using Spearman's correlation coefficient. Comparisons between angiogenic index across different Gleason grade groups were performed using one-way ANOVA for normally distributed data, and Mann–Whitney U or Kruskal–Wallis tests for non-parametric data. A p-value of <0.05 was considered statistically significant.

RESULTS

The study included 47 histopathologically confirmed cases of prostate adenocarcinoma. The mean age of patients was 66.4 ± 7.8 years, with the majority belonging to the 60–69 years age group (51.1%). Serum PSA levels were markedly elevated, with a mean value of 38.6 ± 21.4 ng/mL, and more than two-thirds of patients (70.2%) presenting with PSA levels >20 ng/mL. Most specimens were obtained from TRUS-guided core needle biopsies (72.3%), while radical prostatectomy specimens constituted 27.7% of cases [Table 1].

Table 1: Baseline Clinicopathological Characteristics of Prostate Cancer Patients (n = 47).

Variable	Frequency (%) / Mean ± SD
Age (years)	66.4 ± 7.8
Age group (years)	
50–59	6 (12.8%)
60–69	24 (51.1%)
≥70	17 (36.1%)
Serum PSA (ng/mL)	38.6 ± 21.4
PSA <10	5 (10.6%)
PSA 10–20	9 (19.1%)
PSA >20	33 (70.2%)
Specimen type	
TRUS biopsy	34 (72.3%)
Radical prostatectomy	13 (27.7%)

PSA – Prostate-specific antigen; TRUS – Transrectal ultrasound.

Gleason grade group distribution revealed a predominance of higher-grade tumors. Grade Group 5 (Gleason score 9–10) was the most frequent category, accounting for 27.7% of cases, followed by Grade Group 4 (Gleason score 8) in 23.4%. Intermediate-grade tumors (Grade Groups 2 and 3) together constituted 38.3% of cases, while low-grade tumors (Grade Group 1) were relatively uncommon, seen in only 10.6% of patients [Table 2].

Table 2: Distribution of Gleason Grade Groups (ISUP) Among Study Participants (n = 47).

Gleason Grade Group	Gleason Score	Frequency (%)
Grade Group 1	≤6	5 (10.6%)
Grade Group 2	3+4=7	8 (17.0%)
Grade Group 3	4+3=7	10 (21.3%)
Grade Group 4	8	11 (23.4%)
Grade Group 5	9–10	13 (27.7%)

ISUP – International Society of Urological Pathology.

A progressive and statistically significant increase in both microvessel density and angiogenic index was observed with increasing Gleason grade group. Mean MVD increased from 28.4 ± 4.9 vessels/HPF in Grade Group 1 to 57.8 ± 8.4 vessels/HPF in Grade Group 5. Similarly, the angiogenic index showed a marked rise from 41.2 ± 6.3 in low-grade tumors to 91.2 ± 10.5 in the highest grade group. One-way ANOVA demonstrated a highly significant difference across grade groups ($p < 0.001$), indicating increasing angiogenic activity with tumor dedifferentiation [Table 3].

Table 3: Comparison of Microvessel Density and Angiogenic Index Across Gleason Grade Groups.

Gleason Grade Group	MVD (vessels/HPF)	Angiogenic Index
	Mean ± SD	
Grade Group 1	28.4 ± 4.9	41.2 ± 6.3
Grade Group 2	34.6 ± 6.1	52.8 ± 7.4
Grade Group 3	41.9 ± 5.8	64.5 ± 8.2
Grade Group 4	49.3 ± 7.2	77.6 ± 9.1
Grade Group 5	57.8 ± 8.4	91.2 ± 10.5
p-value	<0.001	<0.001

MVD – Microvessel density; HPF – High-power field; SD – Standard deviation.

Correlation analysis revealed a strong positive association between angiogenic index and Gleason score. The angiogenic index showed a significant correlation with Gleason score ($r = 0.78$, $p < 0.001$), suggesting that higher angiogenic activity is closely linked to increasing histological aggressiveness of prostate cancer [Table 4].

Table 4: Correlation Between Angiogenic Index and Gleason Score.

Variable	Correlation coefficient (r)	p-value
Angiogenic Index vs Gleason Score	0.78	<0.001

r – Spearman's correlation coefficient.

High angiogenic activity was predominantly observed in high-grade prostate cancers. Among patients with high angiogenic index values, 87.0% had high-grade tumors, whereas low angiogenic activity was mainly seen in low-grade cancers. The association between angiogenic activity category and tumor grade was statistically significant (χ^2 test, $p < 0.001$), indicating that increased angiogenesis is strongly linked with higher tumor grade [Table 5].

Table 5: Association Between Angiogenic Activity Categories and Tumor Grade (n = 47).

Angiogenic Activity	Overall	Low-grade (≤7) (n=16)	High-grade (≥8) (n=31)	p-value
	Frequency (%)			
Low	9 (19.1%)	7 (43.8%)	2 (6.5%)	<0.001
Intermediate	15 (31.9%)	6 (37.5%)	9 (29.0%)	
High	23 (48.9%)	3 (18.8%)	20 (64.5%)	

Low-grade – Gleason score ≤7; High-grade – Gleason score ≥8.

The mean angiogenic index was significantly higher in high-grade prostate cancers (84.3 ± 11.6) compared to low-grade tumors (52.4 ± 9.1). This difference was statistically significant on independent samples t-test ($p < 0.001$), further reinforcing the role of angiogenesis as a marker of tumor aggressiveness [Table 6].

Table 6: Comparison of Angiogenic Index Between Low-Grade and High-Grade Prostate Cancer.

Tumor Grade	Angiogenic Index (Mean ± SD)	p-value
Low grade (≤ Gleason 7)	52.4 ± 9.1	<0.001
High grade (≥ Gleason 8)	84.3 ± 11.6	

DISCUSSION

The present study evaluated angiogenesis in prostate cancer using an angiogenic index and examined its relationship with Gleason grade and Gleason score. The findings demonstrate a clear and progressive increase in angiogenic activity with increasing histological aggressiveness, underscoring the pivotal

role of angiogenesis in prostate cancer progression. The study population predominantly comprised elderly men with advanced disease, reflected by high mean PSA levels and a higher proportion of high-grade tumors, a pattern commonly reported in Indian studies by Mittal et al., and Sankarapillai et al., where late presentation is frequent.[15,16]

A key observation of this study was the stepwise rise in microvessel density (MVD) and angiogenic index across Gleason grade groups, with the highest values seen in Grade Group 5 tumors. The statistically significant difference across grade groups (ANOVA, $p < 0.001$) indicates that angiogenesis intensifies as tumor differentiation decreases. This finding aligns with earlier studies Upadhyaya et al., Shrestha et al., and Azad et al., that have shown increased vascularity in poorly differentiated prostate carcinomas compared to well-differentiated tumors.[17-19] Biologically, high-grade tumors exhibit increased metabolic demands and hypoxia-driven upregulation of pro-angiogenic factors such as VEGF and hypoxia-inducible factor-1α, leading to enhanced endothelial proliferation and neovascularization.[20]

The strong positive correlation observed between angiogenic index and Gleason score (Spearman's $r = 0.78$, $p < 0.001$) reinforces the close link between angiogenesis and histological severity. Similar correlations have been reported by Gao et al., and Grizzi et al., and subsequent investigators, who demonstrated that increased MVD is associated with higher Gleason scores and adverse prognostic features.[21,22] The angiogenic index, by integrating microvessel density with endothelial activity, appears to provide a more comprehensive measure of tumor angiogenesis than MVD alone, potentially reducing observer variability and better reflecting the biological aggressiveness of the tumor microenvironment.[23]

Another important finding was the significant predominance of high angiogenic activity in high-grade tumors (Gleason score ≥8), as demonstrated by the chi-square analysis ($p < 0.001$). Nearly nine out of ten tumors with high angiogenic index values belonged to the high-grade category, whereas low angiogenic activity was largely confined to low-grade cancers. This observation is consistent with prior reports by Feng et al. and Gautam et al., suggesting that angiogenesis is not merely a consequence of tumor growth but an active driver of invasion and progression in aggressive prostate cancer phenotypes.[24,25] Increased vascular density facilitates tumor cell intravasation, enhances nutrient delivery, and promotes metastatic potential.[26]

The comparison between low-grade and high-grade tumors further highlighted the discriminatory value of the angiogenic index. High-grade prostate cancers exhibited a significantly higher mean angiogenic index than low-grade tumors (84.3 ± 11.6 vs 52.4 ± 9.1; $p < 0.001$). This marked difference suggests that angiogenic index may serve as an adjunctive prognostic marker, particularly in cases where Gleason score alone may not fully capture biological behavior.[27] Similar differences in angiogenic markers between low- and high-grade prostate cancers have been documented in both biopsy-based and prostatectomy-based studies by Gourdin et al., and Crocetto et al.[28,29]

From a clinical perspective, these findings have important implications. Gleason grading remains the gold standard for risk stratification; however, tumors with similar Gleason scores can show variable outcomes. Incorporation of angiogenesis-related parameters such as angiogenic index may help refine prognostication, identify biologically aggressive tumors within the same Gleason category, and potentially guide therapeutic decision-making.[30] In the era of targeted therapy, tumors with high angiogenic activity may also represent candidates for anti-angiogenic or combination treatment strategies, although this requires further validation.[31]

CONCLUSION

Overall, the present study supports the concept that angiogenic index is a robust marker of tumor angiogenesis and is strongly correlated with Gleason grade and score in prostate cancer. The consistent increase in angiogenic activity with worsening histological grade provides biological plausibility and aligns well with existing literature. Further large-scale and prospective studies incorporating clinical outcomes such as biochemical recurrence and survival would be valuable to establish the angiogenic index as a routine prognostic adjunct in prostate cancer pathology.

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