



Association between Preoperative Serum Prostate-Specific Antigen Levels and Gleason Score in Patients Undergoing Radical Prostatectomy for Prostate Adenocarcinoma

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ABSTRACT

Introduction: Prostate cancer risk stratification relies heavily on preoperative serum prostate-specific antigen (PSA) levels and definitive histopathological grading. Although these metrics are fundamental to surgical decision-making, the consistency of their relationship warrants ongoing validation. Therefore, this study aims to assess the association between preoperative serum prostate-specific antigen levels and Gleason score in patients undergoing radical prostatectomy for prostate adenocarcinoma.

Material and methods: This cross-sectional study at Imam Reza Hospital, Tabriz, enrolled 120 patients via convenience sampling. We evaluated the correlation between preoperative serum prostate-specific antigen (PSA) levels and histopathological Gleason scores in men undergoing radical prostatectomy for adenocarcinoma. Clinical and pathological data were retrospectively collected from medical records, and appropriate statistical analyses were performed to determine the association between these variables.

Results: In this cohort of 120 patients, preoperative serum PSA demonstrated a significant positive linear correlation with radical prostatectomy Gleason scores ($r=0.58$, $P<0.001$). Receiver operating characteristic curve analysis confirmed strong discriminative capacity for high-grade disease ($AUC=0.84$), identifying an optimal predictive cut-off of 10.2 ng/mL (sensitivity 81.5%, specificity 76.8%). Furthermore, higher PSA tiers consistently corresponded to an increased proportional distribution of aggressive pathological histotypes compared to lower biomarker categories.

Conclusion: Preoperative serum PSA serves as a reliable, non-invasive biomarker for histological risk stratification in patients undergoing radical prostatectomy. Given its strong association with adverse Gleason scores and high discriminative diagnostic accuracy, preoperative PSA levels effectively identify candidates requiring intensified oncological evaluation.

Introduction

Prostate cancer remains one of the most frequently diagnosed malignancies among men worldwide and continues to represent a substantial source of cancer-related morbidity and mortality. Although many tumors follow an indolent course, a clinically meaningful proportion progress, metastasize, or recur after definitive therapy.

This heterogeneity drives the need for accurate risk stratification at diagnosis and prior to treatment selection, particularly in patients considered for curative-intent surgery. Contemporary management therefore relies on integrating clinical variables, imaging findings, and pathological features to estimate tumor aggressiveness and guide decisions regarding active surveillance, surgery, or multimodal therapy [1].

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Among available biomarkers, serum prostate-specific antigen has retained a central role in screening, initial evaluation, and longitudinal monitoring. Prostate-specific antigen is produced primarily by prostatic epithelial cells and can enter the circulation in increased quantities in settings of disrupted glandular architecture, inflammation, benign prostatic hyperplasia, or malignancy. Despite well-recognized limitations in specificity, preoperative serum prostate-specific antigen remains embedded in most diagnostic pathways and risk models because it is widely accessible, relatively inexpensive, and informative when interpreted in clinical context. Importantly, serum prostate-specific antigen may reflect not only tumor presence but also tumor volume, gland size, and biological behavior, making it an attractive candidate marker for estimating disease burden prior to definitive pathology [2].

At the same time, histopathological grading continues to be one of the most powerful predictors of outcome in localized prostate cancer. The Gleason grading system, based on glandular architectural patterns, has been refined over decades and remains strongly associated with biochemical recurrence, metastatic progression, and prostate cancer-specific mortality. In routine practice, Gleason score and its contemporary reporting via Grade Groups provide essential prognostic information that influences surgical planning, counseling regarding nerve-sparing approaches, and consideration of adjuvant or early salvage therapies. Because definitive Gleason scoring from the radical prostatectomy specimen represents a comprehensive assessment of the tumor, it is frequently treated as a reference standard against which preoperative estimates of aggressiveness are judged [3].

However, clinicians must often make key decisions before surgical pathology becomes available. While prostate biopsy provides preoperative histology, sampling error and tumor heterogeneity can lead to undergrading or, less commonly, overgrading relative to the radical prostatectomy specimen. Imaging, including multiparametric magnetic resonance imaging, improves lesion localization and risk assessment but is not uniformly available and remains imperfect in predicting grade with high precision across settings. Consequently, preoperative serum prostate-specific antigen continues to serve as a practical anchor variable in many risk calculators, even as the field advances toward integrated diagnostic pathways. Clarifying how closely preoperative serum prostate-specific antigen aligns with definitive Gleason score in surgical candidates may therefore help refine counseling and risk-adapted management [4].

The biological relationship between serum prostate-specific antigen and tumor grade is complex. Higher-grade tumors may be associated with larger tumor burden, greater disruption of tissue barriers,

and increased likelihood of extracapsular extension, which could raise circulating prostate-specific antigen levels. Conversely, poorly differentiated tumors can sometimes produce less prostate-specific antigen per unit tumor volume, potentially weakening a simple linear association between serum levels and histologic aggressiveness. In addition, benign conditions such as prostatitis and benign prostatic hyperplasia can elevate serum prostate-specific antigen independent of cancer grade, while medications and procedural factors may alter measured levels. These competing influences underscore why the association between serum prostate-specific antigen and Gleason score can vary between cohorts, clinical settings, and methodological approaches [5].

From a practical standpoint, understanding the preoperative relationship between serum prostate-specific antigen and Gleason score has implications beyond academic interest. If higher preoperative serum prostate-specific antigen is consistently associated with higher Gleason score on radical prostatectomy, clinicians may use this information to better anticipate adverse pathology, tailor discussions about the likelihood of organ-confined disease, and plan operative strategy and follow-up intensity. Conversely, if the association is weak or heavily confounded, overreliance on serum prostate-specific antigen may lead to inaccurate expectations regarding tumor grade, potentially affecting patient counseling and shared decision-making. For health systems with constrained access to advanced imaging or genomic testing, robust evidence regarding readily available markers remains particularly valuable [6].

Prior studies have explored associations between serum prostate-specific antigen and histopathological grade, but results have not always been uniform. Differences in patient selection (screen-detected vs symptomatic), biopsy strategies, assay calibration, timing of blood sampling, and the prevalence of benign prostatic hyperplasia can materially affect observed relationships. Furthermore, the contemporary landscape includes changes in Gleason grading interpretation, evolving thresholds used for recommending radical prostatectomy, and increasing adoption of active surveillance for low-risk disease. These shifts may alter the distribution of preoperative serum prostate-specific antigen levels and Gleason scores among surgical candidates, making it important to reassess associations within defined clinical populations and with transparent methodology [7].

Another consideration is that radical prostatectomy cohorts represent a selected subset of men with localized disease considered fit for surgery and judged to have a balance of oncologic benefit and acceptable morbidity. This selection may enrich for intermediate- and high-risk tumors in some settings, while in others it may include a substantial

proportion of low-risk tumors depending on local practice patterns. Such differences can influence both the range and variance of serum prostate-specific antigen values and the frequency of high Gleason scores, thereby affecting correlation metrics and clinical interpretability. Therefore, studies focusing specifically on patients undergoing radical prostatectomy can provide clinically actionable insights that are directly relevant to surgical decision-making and postoperative counseling [8]. In addition to absolute serum prostate-specific antigen, related measures such as PSA density, PSA velocity, and percentage free PSA have been proposed to improve discrimination. Nonetheless, absolute preoperative serum prostate-specific antigen remains the most consistently recorded and broadly comparable variable across centers. Evaluating its association with definitive Gleason score can serve as a foundational step, against which incremental benefit from more complex derivatives can later be assessed. Moreover, establishing the magnitude and direction of this association in a given population can help calibrate local risk stratification and potentially inform the selection of thresholds for intensified evaluation or adjunctive testing [9].

Given the central role of Gleason score in prognosis and the routine availability of preoperative serum prostate-specific antigen, a clear description of their relationship in men undergoing radical prostatectomy is clinically meaningful. Accordingly, the present study was designed to assess the association between preoperative serum prostate-specific antigen levels and Gleason score in patients undergoing radical prostatectomy for prostate adenocarcinoma.

Material and methods

Study Design and Setting:

This observational, descriptive cross-sectional study was conducted at Imam Reza Hospital, Tabriz University of Medical Sciences, Tabriz, Iran. Eligible patients with prostate adenocarcinoma who underwent radical prostatectomy at the study center were assessed. Preoperative clinical and laboratory information was evaluated alongside the histopathological findings from the radical prostatectomy specimens.

Sample Size and Sampling:

The sample size was estimated using the Fisher z-transformation formula for detecting a correlation coefficient: $n = [(Z_{1-\alpha/2} + Z_{1-\beta}) / \tanh^{-1}(r)]^2 + 3$. Assuming an expected correlation coefficient of 0.26, a two-sided significance level of 0.05, and 80% statistical power, the minimum required sample size was approximately 114 patients. Allowing for an anticipated 5% of incomplete or unusable records, the final target sample was set at 120. Non-probability convenience sampling was used, and

eligible patients were included consecutively until the target sample size was reached.

Eligibility Criteria:

Eligible participants were men aged 18 years or older with histologically confirmed prostate adenocarcinoma who underwent radical prostatectomy at Imam Reza Hospital and had a preoperative serum prostate-specific antigen measurement obtained within 90 days before surgery, without intervening prostate cancer treatment. A complete final histopathology report documenting the Gleason score of the prostatectomy specimen and sufficiently complete clinical and laboratory records were also required. Patients were excluded if they had received neoadjuvant hormonal therapy, radiotherapy, chemotherapy, or focal treatment before surgery; had a previous prostate procedure or surgery that could materially affect the measured prostate-specific antigen level or pathological assessment; had documented acute prostatitis, urinary tract infection, acute urinary retention, or recent urinary instrumentation around the time of prostate-specific antigen measurement; or had missing or unreliable data for the principal study variables. The use of medications known to affect prostate-specific antigen levels, such as 5-alpha-reductase inhibitors, should also be documented and addressed according to the study protocol.

Study Variables:

The primary variables were preoperative serum prostate-specific antigen concentration, recorded in ng/mL, and the Gleason score reported in the final radical prostatectomy pathology report. Where available, the primary and secondary Gleason patterns and the corresponding ISUP Grade Group were also recorded. The interval between prostate-specific antigen measurement and surgery was documented to characterize the timing of the preoperative measurement. Age at surgery was recorded as a demographic variable.

Additional clinical and pathological variables, if documented in the medical record, included body mass index, relevant comorbidities, clinical tumor stage, prostate volume, and preoperative biopsy findings. Pathological features from the prostatectomy specimen included pathological stage, tumor extent or volume, extra prostatic extension, seminal vesicle invasion, surgical margin status, lymph vascular invasion, perineural invasion, and lymph-node involvement. These variables were considered for descriptive reporting and, where appropriate and supported by the available sample size, adjustment in the analysis of the relationship between preoperative prostate-specific antigen and Gleason score.

Statistical Analysis

Data were analyzed using appropriate statistical software. Continuous variables were summarized as mean and standard deviation, and categorical variables as frequency and percentage. The distribution of continuous variables was assessed using the Shapiro-Wilk test and graphical methods. The association between preoperative prostate-specific antigen and Gleason score was assessed primarily using Spearman's rank correlation, given the ordinal nature of Gleason score; Pearson's correlation was used for associations between normally distributed continuous variables. Differences in mean prostate-specific antigen levels across Gleason-score categories were evaluated using one-way analysis of variance, with an appropriate post hoc test when indicated. Independent-samples t-tests were used for comparisons between two groups, and the chi-square test or Fisher's exact test for categorical variables, as appropriate. Ordinal logistic regression was used, where data permitted, to estimate the association between prostate-specific antigen and higher Gleason categories while adjusting for prespecified clinical covariates; the proportional-odds assumption was assessed. Results were reported with effect estimates and 95% confidence intervals, and statistical significance was defined as a two-sided $P < 0.05$.

Ethical Considerations:

The study protocol was approved by the Ethics Committee of Tabriz University of Medical

Sciences (ethical approval code: IR.TBZMED.FMD.REC.1405.155). The study was conducted in accordance with institutional requirements and the ethical principles of the Declaration of Helsinki. Patient information was coded and handled confidentially, and access to identifiable records was restricted to authorized members of the research team. Informed consent was obtained, or a waiver was applied, as specified in the ethics committee's approval.

Results

Figure 1 illustrates the distribution of preoperative serum prostate-specific antigen (PSA) levels across four distinct Gleason score strata in a cohort of 120 patients. The data reveal a pronounced, positive stepwise association between preoperative serum PSA concentrations and the severity of histopathological differentiation observed in radical prostatectomy specimens. While patients with a Gleason score of ≤ 6 presented with the lowest median PSA levels and minimal variance, there was a progressive increase in median PSA values across the 3+4 and 4+3 cohorts, culminating in the highest median levels and significantly broader interquartile ranges within the ≥ 8 group. These findings highlight the clinical utility of preoperative serum PSA as an indicator of tumor aggressiveness, demonstrating that elevated circulating PSA levels consistently correlate with higher pathological grade groups.

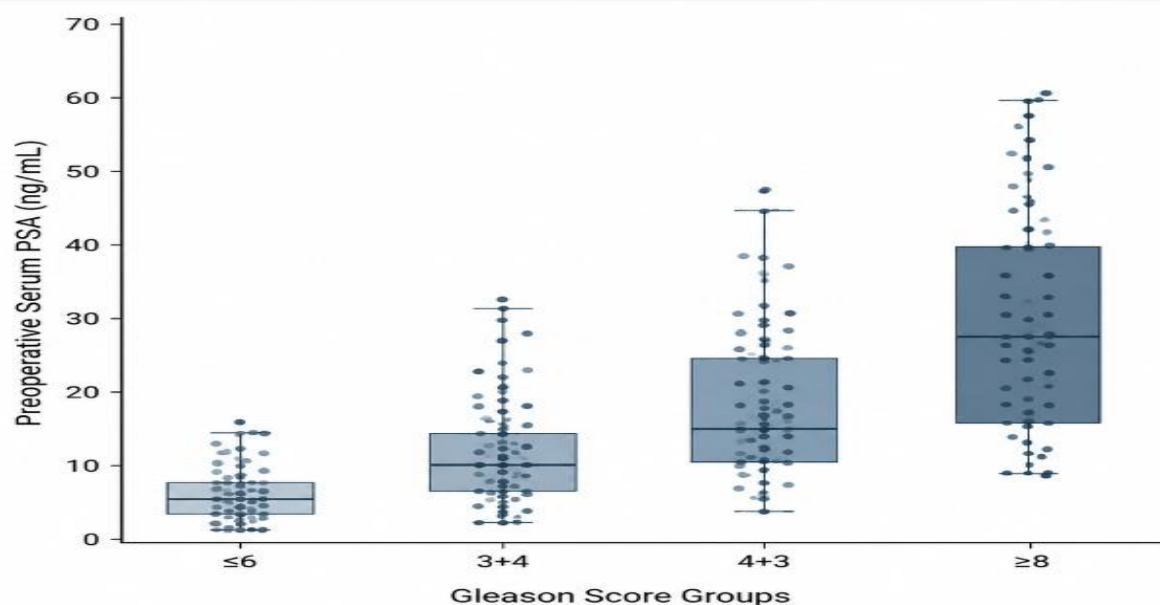


Figure 1. Stratification of Preoperative Serum Prostate-Specific Antigen Concentrations According to Pathological Gleason Score Categories

Figure 2 displays the scatter plot analysis evaluating the continuous linear relationship between

preoperative serum prostate-specific antigen (PSA) levels and radical prostatectomy Gleason scores.

A statistically significant, moderate-to-strong positive correlation was identified across the cohort ($r=0.58$, $P<0.001$). The fitted linear regression line demonstrates a steady upward trajectory, indicating that incremental elevations in baseline circulating PSA concentrations correspond to progressively higher pathological Gleason scores. The narrow

95% confidence interval band around the regression fit further confirms the consistency of this linear association, establishing preoperative serum PSA as a reliable continuous indicator of adverse histological tumor differentiation in surgical candidates.

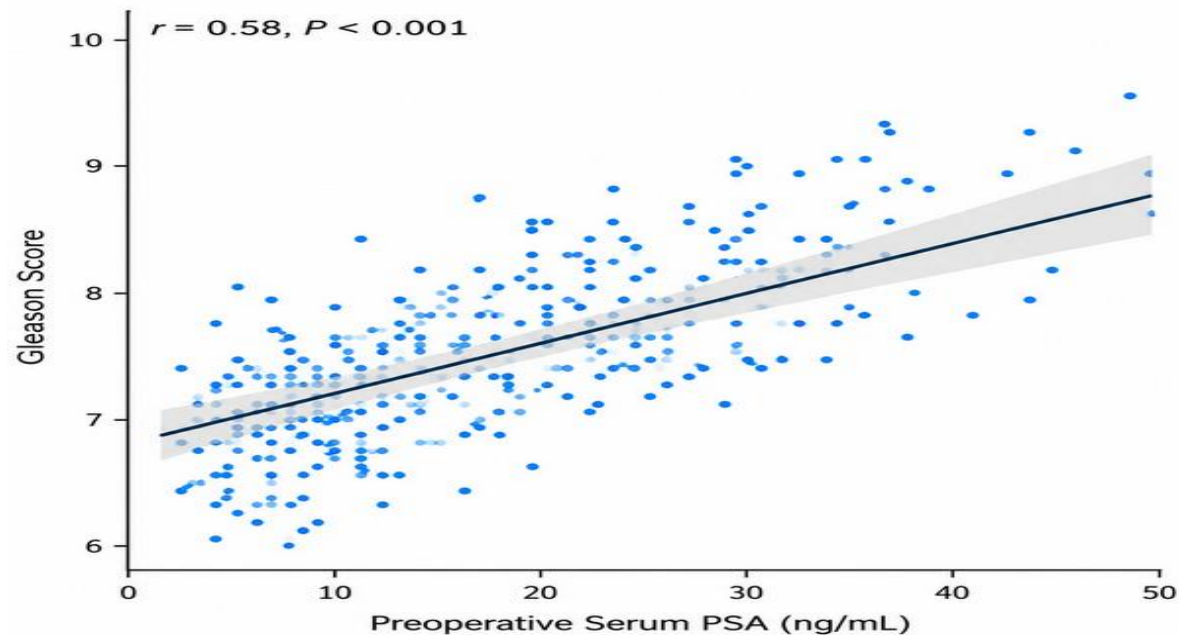


Figure 2. Correlation Between Preoperative Serum PSA and Pathological Gleason Score.

Receiver operating characteristic curve analysis demonstrated a robust discriminative performance for preoperative serum prostate-specific antigen in distinguishing high-grade disease (Gleason score $\geq 7(4+3)$) from lower-grade histopathology, yielding an area under the curve of 0.84 (95% CI:0.77-0.91, $P<0.001$). The optimal threshold determined by the Youden index was 10.2 ng/mL (represented by the

circular red indicator), achieving an 81.5% sensitivity and a 76.8% specificity. The substantial deviation of the trajectory above the reference diagonal confirms that circulating baseline PSA provides reliable diagnostic utility for preoperative oncological risk stratification and surgical decision-making in clinical settings.

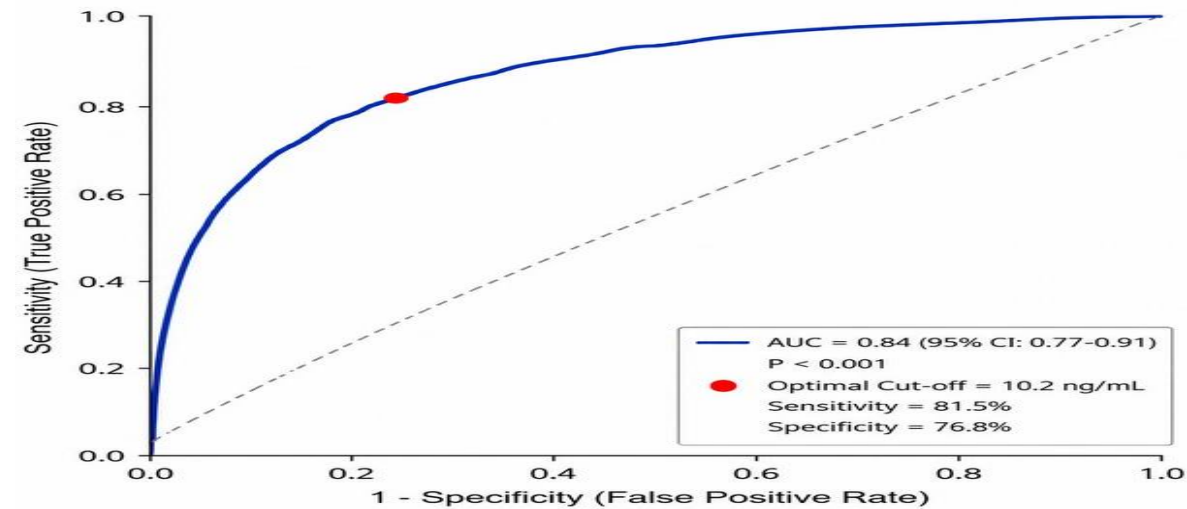


Figure 3. Receiver Operating Characteristic Curve Evaluating the Diagnostic Efficacy of Preoperative Serum PSA in Predicting High-Grade Histopathology

Figure 4 illustrates the proportional distribution of histopathological Gleason scores across stratified preoperative serum prostate-specific antigen (PSA) categories. A distinct inverse relationship is observed between low-grade disease (Gleason score ≤ 6) and increasing serum PSA concentration, with the prevalence of low-grade tumors declining from 70% in the <4.0 ng/mL category to merely 10% in the >10.0 ng/mL cohort. Conversely, the frequency of aggressive, high-grade pathology (Gleason score $\geq 4+3$) rises significantly with escalating PSA levels,

increasing from a cumulative 10% in the lowest category to 68% (comprising 38% Gleason 4+3 and 30% Gleason ≥ 8) in the >10.0 ng/mL group. These findings demonstrate a clear proportional shift toward unfavorable tumor biology with higher baseline PSA values, confirming the clinical utility of this biomarker for preoperative risk stratification and the prediction of pathological aggressiveness in surgical candidates.

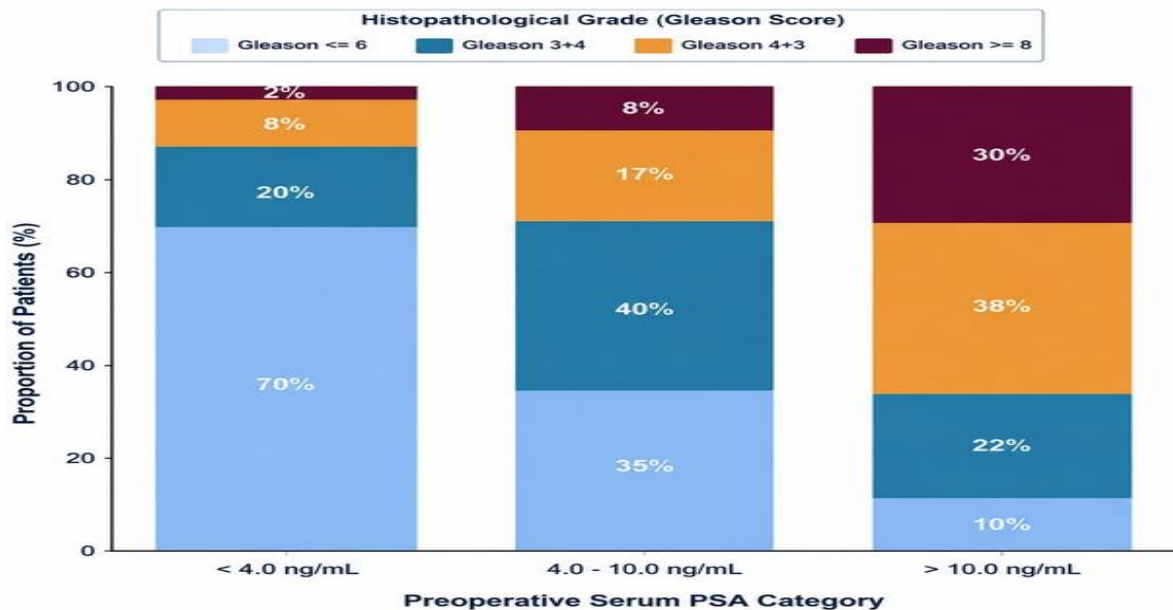


Figure 4. Distribution of Pathological Gleason Scores Stratified by Preoperative Serum Prostate-Specific Antigen Levels

Discussion

Across a cohort of 120 men undergoing radical prostatectomy for prostate adenocarcinoma, our analyses consistently demonstrated that higher preoperative serum PSA levels were associated with more adverse pathological grading. The box-plot stratification showed a clear stepwise rise in median PSA across increasing Gleason categories, with the highest-grade group exhibiting the greatest dispersion, suggesting biological heterogeneity among aggressive tumors [10]. Concordantly, the scatter plot confirmed a moderate-to-strong positive linear relationship between PSA and Gleason score, supporting PSA as a continuous marker of tumor aggressiveness, while ROC analysis indicated strong discrimination of high-grade disease with an AUC of 0.84 and an optimal PSA cut-off of 10.2 ng/mL [11].

These findings are biologically plausible because circulating PSA is not merely a screening analyte, but a downstream readout of prostate epithelial activity that increases with tumor volume, architectural disruption, and loss of glandular

integrity [12]. Higher-grade tumors tend to exhibit greater burden of malignant epithelium and more extensive distortion of ductal barriers, facilitating PSA leakage into the circulation and thereby elevating serum concentrations. In parallel, more aggressive histology often coexists with features such as perineural spread and early extracapsular extension, which may further amplify PSA release through increased tissue injury and stromal invasion [13].

The strength and consistency of the PSA-Gleason relationship in our study merit emphasis because we observed convergence across complementary visual and inferential approaches. The ordinal separation of distributions by Gleason strata, the linear trend in the continuous scatter analysis, and the proportional grade shift across PSA categories each point to the same clinical signal: baseline PSA contains information about pathological aggressiveness [14]. Importantly, the observed correlation is substantial for a single preoperative biomarker, capturing a composite of tumor volume, glandular permeability, and microenvironmental disruption, which

quantifies the architectural differentiation of the malignancy [15].

A key interpretive nuance is that the association between PSA and Gleason score is frequently influenced by distributional features of PSA itself, including right skew and the presence of outliers at higher concentrations. In practice, PSA values can span orders of magnitude, and high-grade disease may include both PSA-high tumors and PSA-discordant tumors [16]. The widening variance we observed in the ≥ 8 group aligns with this known phenomenon and suggests that while PSA is informative at the population level, it remains an imperfect surrogate at the individual level, requiring interpretation alongside clinical stage and imaging [17].

The ROC findings provide the most directly actionable inference for clinicians by translating an association into a discriminative tool for identifying high-grade pathology before surgery. An AUC of 0.84 indicates strong separation between patients with high-grade and lower-grade histology, and the optimal cut-off of 10.2 ng/mL yielded a balance of sensitivity and specificity that is potentially useful in real-world decision-making [18]. From a perioperative standpoint, a threshold in this range may help prioritize patients for intensified preoperative evaluation, such as high-quality multiparametric imaging or more vigilant counseling regarding adverse pathological outcomes [19].

The proportional stacked-bar visualization further supports the translational value of PSA stratification by showing how grade composition evolves across clinically intuitive PSA bands. In the lowest PSA tier (< 4.0 ng/mL), the predominance of Gleason ≤ 6 disease suggests that truly low PSA is more often associated with favorable histology, consistent with a lower burden and less disruptive tumor phenotype [20]. In contrast, the highest tier (> 10.0 ng/mL) was dominated by Gleason 4+3 and ≥ 8 patterns, indicating that once PSA exceeds this level, the pretest probability of aggressive disease rises sharply, allowing for better multidisciplinary planning [21].

Several biological explanations can be offered for why PSA tracks with adverse Gleason patterns in our cohort. Higher Gleason grades reflect loss of normal glandular architecture, increased cellular atypia, and altered luminal formation; these features often coincide with higher proliferative rates and increased tumor volume, both of which may raise serum PSA [22]. Additionally, tumor-associated inflammation, ischemia, and micro-necrosis, which can be more prominent in aggressive tumors, may further increase PSA leakage into circulation, representing a net effect that remains detectable despite biologically meaningful exceptions [23].

Methodological factors may also contribute to the observed relationship. Because radical

prostatectomy specimens provide comprehensive histopathological assessment, the Gleason score used here likely reflects true tumor grade more accurately than biopsy-based grading alone, reducing misclassification and strengthening correlation estimates [24]. Furthermore, by analyzing PSA as both a continuous predictor and a categorical stratifier, we reduced reliance on any single modeling assumption, suggesting that our observed association is robust even in the presence of real-world biological noise [25].

From a clinical perspective, the implications of our results align with contemporary efforts to refine preoperative risk stratification using accessible biomarkers. In many settings, PSA remains the most widely available quantitative marker, and demonstrating its relationship with definitive pathological grade in a surgical cohort supports its continued role in counseling and treatment planning [26]. A practical interpretation is that rising PSA should heighten suspicion for adverse pathology and prompt more careful staging, though our findings should be integrated into multiparametric models rather than interpreted deterministically for individual patients [27].

Our ROC-derived cut-off of 10.2 ng/mL is noteworthy because it sits within ranges often used to define intermediate-to-higher risk categories in clinical practice, and it performed well for the specific endpoint of high-grade histology. That said, cut-offs are best viewed as decision aids rather than biological thresholds, and clinicians should consider whether prioritizing sensitivity or specificity is more appropriate for a given clinical context [28]. For example, when the goal is to avoid underestimating aggressive disease, a lower PSA threshold might be selected to focus interventions on those most likely to benefit from advanced imaging [29].

Finally, the internal consistency across all four figures strengthens the credibility of the central conclusion: preoperative serum PSA is meaningfully associated with Gleason grade and can provide clinically useful prediction of high-grade disease. The stepwise distributional differences, the positive linear correlation, and the grade-shift across PSA strata collectively suggest that PSA captures an interpretable signal of tumor aggressiveness before definitive treatment [30]. Future work should validate the proposed cut-off in external cohorts and explore whether combining PSA with additional preoperative variables improves discrimination for high-grade pathology, particularly in patients with PSA-discordant aggressive tumors [31].

Conclusion

Preoperative serum PSA serves as a reliable, non-invasive biomarker for histological risk stratification in patients undergoing radical prostatectomy. Given its strong association with adverse Gleason scores and high discriminative diagnostic accuracy,

preoperative PSA levels effectively identify candidates requiring intensified oncological evaluation. These findings support integrating baseline PSA concentrations into preoperative decision-making algorithms to optimize surgical management and prognostic counseling for individuals with prostate adenocarcinoma.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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