



Predictive Value of Preoperative Serum PSA for Histopathological Grade

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ABSTRACT

Introduction: Prostate adenocarcinoma exhibits significant biological heterogeneity, necessitating precise preoperative risk stratification to guide surgical management. While preoperative serum prostate-specific antigen (PSA) is a standard diagnostic marker, its quantitative relationship with definitive pathological aggressiveness requires rigorous validation. This cross-sectional study aimed to evaluate the predictive discriminative performance of preoperative serum PSA levels for histological grade groups in radical prostatectomy patients.

Material and methods: In this descriptive cross-sectional study conducted at Imam Reza Hospital, we enrolled 120 patients undergoing radical prostatectomy using convenience sampling. We evaluated the association between preoperative serum prostate-specific antigen (PSA) and pathological Gleason scores through comprehensive clinical and histopathological review. Data were statistically analyzed to determine the predictive and discriminative value of baseline PSA for high-grade adenocarcinoma, establishing its utility in clinical preoperative risk stratification.

Results: Preoperative serum PSA levels demonstrated a consistent stepwise increase with escalating Gleason scores (median 6.3 ng/mL in GS ≤ 6 vs. 28.3 ng/mL in GS ≥ 8 ; $P < 0.001$). A significant positive linear correlation exists between PSA and histological grade ($r = 0.58$; $P < 0.001$). Furthermore, PSA showed high diagnostic accuracy for predicting high-grade pathology (AUC=0.84), with an optimal threshold of 10.2 ng/mL yielding 81.5% sensitivity and 76.8% specificity.

Conclusion: Preoperative serum PSA serves as a reliable, non-invasive biomarker for assessing histopathological aggressiveness in radical prostatectomy candidates. Integrating baseline PSA into risk-stratification algorithms enables precise identification of high-grade disease prior to intervention.

Introduction

Prostate adenocarcinoma represents one of the most frequently diagnosed malignant neoplasms and a leading cause of cancer-related mortality among men worldwide. The global epidemiological landscape reflects substantial variation across geographic regions and demographic cohorts, driven by differences in life expectancy, environmental

exposures, hereditary factors, and access to standardized diagnostic modalities.

Over recent decades, population-based prostate-specific antigen screening has led to a profound shift in clinical presentation, marked by a pronounced increase in the detection of organ-confined, asymptomatic disease alongside a concomitant reduction in the initial presentation of advanced metastatic disease.

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Despite these historical diagnostic successes, prostate carcinoma exhibits a notoriously heterogeneous biological behavior, spanning from indolent, slow-growing micro-foci with negligible lethal potential to rapidly progressive, aggressive phenotypes capable of early local invasion and fatal distant dissemination [1].

The intrinsic biological and clinical divergence observed across patients presents a paramount oncological challenge in differentiating indolent tumors that warrant active surveillance from biologically aggressive malignancies that demand prompt, multimodal radical therapeutic intervention. Unnecessary radical intervention in men harboring low-grade, low-volume lesions risks overtreatment and exposes individuals to potential functional detriments, including urinary incontinence, erectile dysfunction, and intestinal morbidity, without offering meaningful survival benefit. Conversely, the delayed diagnosis or systematic underestimation of high-grade disease risks curative therapeutic windows and predisposes patients to disease recurrence, metastasis, and cancer-specific mortality. Consequently, precise preoperative histological risk stratification remains the cornerstone of modern personalized urological oncology, serving to tailor patient counseling, define oncological surveillance protocols, and guide patient selection for surgery [2].

In the standard diagnostic and therapeutic pathway of prostate adenocarcinoma, definitive histopathological grading relies on the Gleason grading architecture, subsequently refined by the International Society of Urological Pathology into five distinct Grade Groups. Pathological evaluation examines glandular differentiation, structural glandular fusion, cribriform architectures, and solid sheets to stratify tumors from Grade Group 1 through Grade Group 5, corresponding to increasing degrees of aggressiveness. Numerous long-term oncological cohorts have validated the pathological grade of radical prostatectomy specimens as one of the strongest independent predictors of biochemical recurrence, distant metastasis, and overall disease-specific survival. Although pre-treatment transrectal or transperineal core needle biopsy serves as the standard clinical surrogate for grading, needle biopsy is intrinsically vulnerable to spatial sampling errors, undergrading, and tumor volume underestimation due to the multifocal nature of prostate neoplasms [3].

Given the persistent diagnostic limitations of conventional core biopsies and the clinical imperative for accurate staging, extensive research has evaluated circulating biomarkers as non-invasive adjuncts to anticipate final pathological outcomes. Among circulating markers, prostate-specific antigen (PSA), a 33-kDa kallikrein-related serine protease primarily secreted by luminal prostatic epithelial cells into the seminal fluid,

remains the most widely deployed serum biomarker in urological practice. Under normal physiological conditions, basal architectural barriers, including continuous basement membranes and tight intercellular junctions, limit the egress of active PSA into the vascular compartment, thereby maintaining circulating concentrations at relatively low baseline levels. Malignant transformation profoundly disrupts normal glandular polarity, cellular tight junctions, and basement membrane integrity, leading to pathological leakage of PSA into the surrounding stromal and vascular spaces [4].

Although serum PSA levels undergo measurable increases in the presence of malignancy, its clinical interpretation is compounded by a lack of absolute disease specificity, as elevated concentrations can arise from benign prostatic hyperplasia, chronic or subclinical prostatitis, urinary tract infections, urinary retention, and minor mechanical manipulations. These benign confounders frequently generate overlapping circulating concentrations in the diagnostic range, complicating the pre-treatment distinction between benign enlargement and aggressive malignancy. Furthermore, contemporary histological investigations have highlighted the paradox of advanced, poorly differentiated or dedifferentiated neuroendocrine and high-grade tumors that downregulate glandular differentiation markers, occasionally producing lower or disproportionate PSA release per unit of tumor mass compared to well-differentiated counterparts. These biological nuances underscore the necessity of rigorously delineating how baseline preoperative PSA concentrations quantitatively align with definitive pathological grade [5].

Despite these biological complexities, baseline preoperative serum PSA continues to serve as an indispensable pillar in classic risk-classification systems, including the D'Amico classification and the National Comprehensive Cancer Network risk frameworks. Within these multi-variable tools, preoperative serum PSA concentration is combined with biopsy histological grade and digital rectal examination findings to categorize candidates into low, intermediate, and high-risk oncological tiers. Nevertheless, real-world clinical decision-making often requires a deeper quantitative understanding of the isolated predictive power of serum PSA as a continuous and categorical variable, particularly with respect to its ability to differentiate clinically significant, high-grade patterns from indolent histology. Identifying precise circulating biomarker thresholds that indicate a substantial pre-test probability of aggressive pathology can guide the prioritization of advanced diagnostic imaging, such as multiparametric magnetic resonance imaging and prostate-specific membrane antigen positron emission tomography [6].

In surgical cohorts undergoing radical prostatectomy, complete whole-mount histopathological examination of the excised specimen provides the definitive pathological reference standard, eliminating the core-needle biopsy sampling error and allowing for unambiguous determination of the primary and secondary Gleason architectural patterns. Evaluating the concordance and predictive correlation between preoperative serum PSA and whole-specimen pathological Grade Groups in this definitive surgical setting offers an optimal framework to assess the true biomarker performance. Clarifying the predictive value of preoperative PSA against surgical pathology provides direct translational insights that refine surgical planning, facilitate nerve-sparing decisions, and optimize the timing and extent of pelvic lymph node dissection [7].

Therefore, robust evaluation of preoperative serum PSA levels across stratified pathological Gleason cohorts remains of paramount importance for improving risk discrimination, standardizing preoperative counseling, and refining contemporary oncological management algorithms. The objective of the present cross-sectional study was to evaluate the predictive value and discriminative performance of preoperative serum prostate-specific antigen levels for definitive histopathological grade in patients with prostate adenocarcinoma undergoing radical prostatectomy.

Material and methods

Study Design and Setting:

This descriptive cross-sectional study was conducted at Imam Reza Hospital, Tabriz, Iran. Eligible patients with prostate adenocarcinoma who underwent radical prostatectomy were assessed to examine the relationship between preoperative serum prostate-specific antigen (PSA) levels and the histopathological grade reported in the prostatectomy specimen.

Sample Size and Sampling:

The sample size was calculated using the Fisher z-transformation formula for detecting a correlation. We assumed an anticipated correlation coefficient r of 0.26, a two-sided significance level of 0.05, and a statistical power of 80 percent. Using the formula n equals $((Z\text{-alpha}/2 \text{ plus } Z\text{-beta}) \text{ divided by } C) \text{ squared plus } 3$, where C equals 0.5 times the natural logarithm of $((1 \text{ plus } r) \text{ divided by } (1 \text{ minus } r))$, the calculated minimum sample size was 114. To account for a 5 percent rate of incomplete data, the final sample size was established at 120 patients. Participants were recruited via convenience sampling from all eligible individuals undergoing radical prostatectomy during the study period.

Eligibility Criteria:

Eligible participants were adult men with histologically confirmed prostate adenocarcinoma who underwent radical prostatectomy at Imam Reza Hospital and had both a documented preoperative serum PSA measurement and a final histopathology report specifying the Gleason score or Grade Group. Patients were excluded if they had a non-adenocarcinoma prostate malignancy, had received neoadjuvant androgen-deprivation therapy or other systemic anticancer treatment before surgery, had a history of prostate surgery or pelvic radiotherapy that could affect assessment, or had incomplete records for the principal study variables. Patients whose PSA measurement was obtained during a documented acute urinary tract infection, acute prostatitis, urinary retention, or recent urological instrumentation were also excluded, as these conditions may alter serum PSA independently of tumor characteristics.

Study Variables and Data Collection:

Data were obtained from patients' clinical records and corresponding radical prostatectomy pathology reports. The primary predictor was preoperative serum PSA, recorded in ng/mL as a continuous variable. For categorical analyses, PSA was grouped as <4.0 , $4.0\text{--}10.0$, and >10.0 ng/mL. The principal outcome was pathological tumor grade based on the Gleason score reported in the prostatectomy specimen. Tumors were categorized as Gleason score ≤ 6 , Gleason $3+4$, Gleason $4+3$, or Gleason score ≥ 8 . The primary and secondary Gleason patterns, total Gleason score, and corresponding pathological Grade Group were recorded when available.

For the diagnostic-performance analysis, high-grade disease was defined as Gleason score $\geq 4+3$, while lower-grade disease was defined as Gleason score $\leq 3+4$. PSA was evaluated both continuously and across the prespecified PSA categories in relation to pathological grade. The analyses included comparison of PSA levels across Gleason categories, assessment of the correlation between PSA and Gleason score, and evaluation of PSA's ability to discriminate high-grade from lower-grade disease. No additional clinical or demographic variables are specified here; include such variables only if they were collected and analyzed in the study.

Statistical Analysis:

Continuous variables were summarized as mean and standard deviation, and categorical variables as number and percentage. Normality of continuous data was assessed using the Shapiro–Wilk test and visual inspection of distribution plots; homogeneity of variance was evaluated using Levene's test. Mean PSA levels across the four Gleason categories were compared using one-way analysis of variance, followed by Tukey's post hoc test where

appropriate. The association between categorical PSA groups and pathological-grade categories was assessed using the chi-square test, or Fisher's exact test when expected cell counts were small. Pearson's correlation coefficient and simple linear regression were used to assess the relationship between continuous PSA levels and Gleason score. Receiver operating characteristic (ROC) curve analysis was performed to evaluate the ability of PSA to identify high-grade disease; the area under the curve (AUC) with its 95% confidence interval was reported. The optimal PSA cut-off was determined using the Youden index, with sensitivity and specificity also reported. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Ethical Considerations:

The study was approved by the Ethics Committee of Tabriz University of Medical Sciences (ethics code: IR.TBZMED.FMD.REC.1405.155).

Patient information was handled confidentially, and data were analyzed in a manner that protected participants' identities.

Results

This box-and-whisker plot demonstrates a consistent stepwise escalation in baseline serum prostate-specific antigen concentrations across progressively higher histological Gleason cohorts. Patients diagnosed with well-differentiated tumors categorized as Gleason score 6 or lower exhibited the lowest median biomarker concentration of 6.3 ng/mL alongside a compact interquartile range from 3.8 to 9.1 ng/mL. A steady intermediate elevation was documented across moderately differentiated patterns, with median levels rising to 10.0 ng/mL for Gleason 3+4 disease and 15.6 ng/mL for Gleason 4+3 disease. The highest biomarker concentrations were identified in poorly differentiated specimens staged as Gleason 8 or greater, yielding a median value of 28.3 ng/mL and an interquartile spread from 20.6 to 35.2 ng/mL. The overall intergroup variance proved statistically significant at P less than 0.001, confirming that higher circulating baseline antigen concentrations reflect increased histopathological aggressiveness and biological heterogeneity in radical prostatectomy candidates.

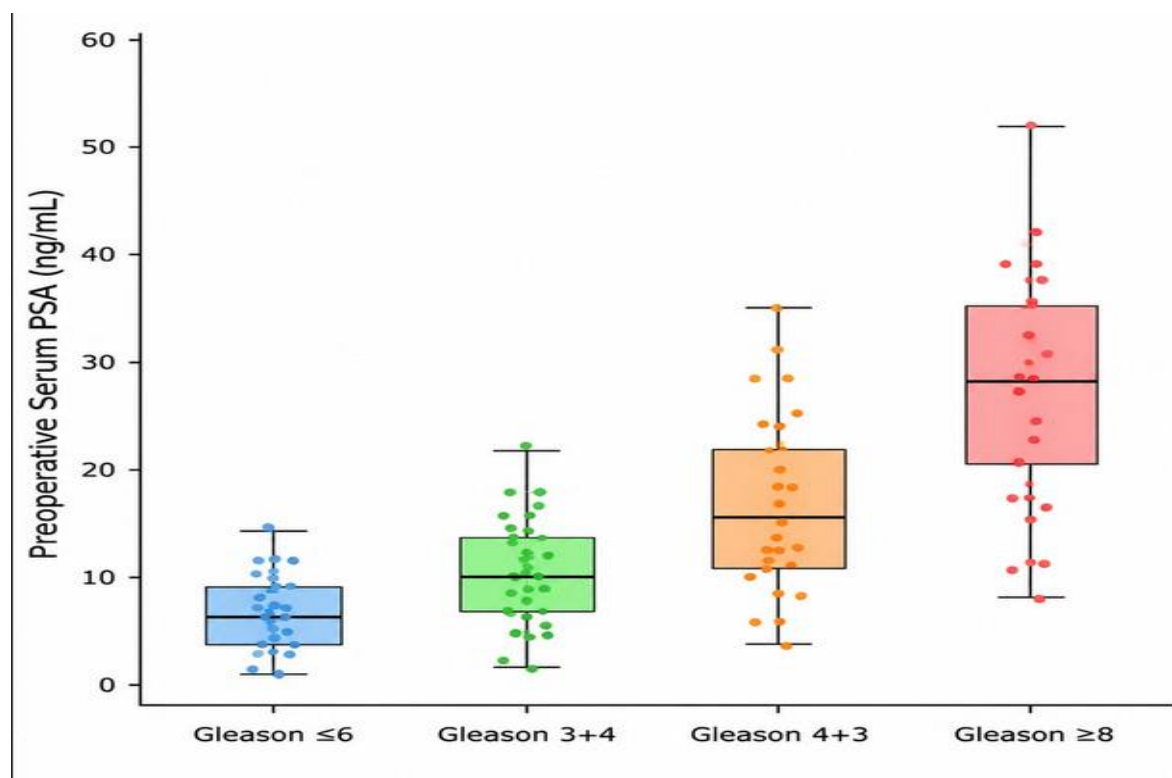


Figure 1. Stratification of Preoperative Serum Prostate-Specific Antigen (PSA) Concentrations According to Pathological Gleason Score Categories in Radical Prostatectomy Specimens

This scatter plot depicts the direct linear association between preoperative serum prostate-specific antigen (PSA) levels and the pathological Gleason score obtained following radical prostatectomy. Statistical analysis reveals a statistically significant positive linear relationship, quantified by a Pearson correlation coefficient of $r=0.58$ ($P < 0.001$), indicating that rising baseline serum PSA

concentrations are intrinsically linked to more advanced histological grades. The linear regression line, accompanied by a tightly constrained 95% confidence interval, reinforces the reliability of this correlation across the continuous range of PSA values. Consequently, these data substantiate the utility of serum PSA as a non-invasive, continuous biomarker that effectively mirrors the architectural

dedifferentiation and biological aggressiveness of prostate adenocarcinoma before surgical intervention.

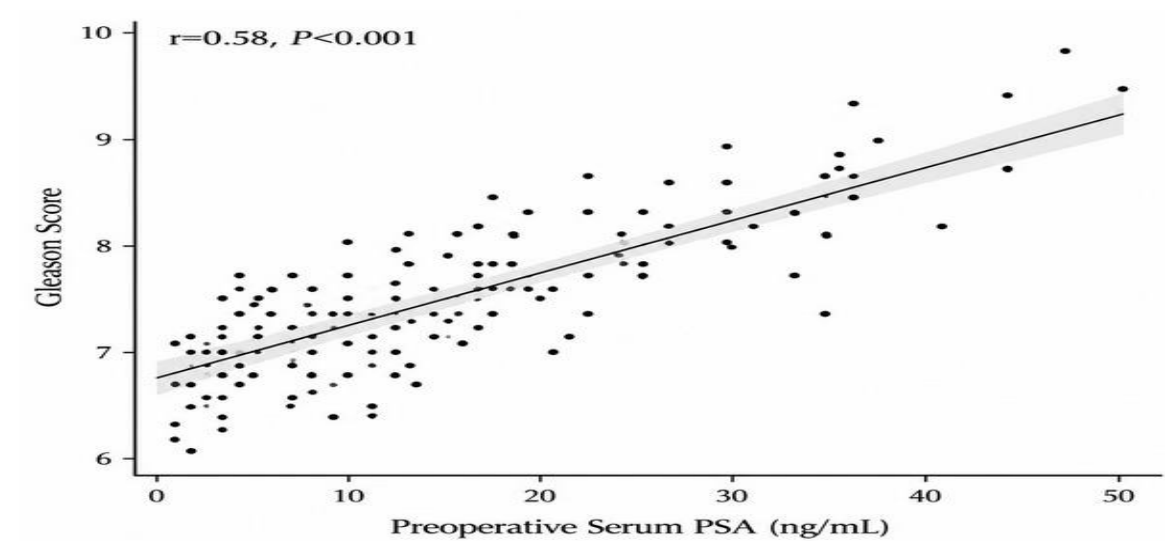


Figure 2. Linear Correlation Between Continuous Preoperative Serum PSA Concentrations and Final Gleason Scores

The receiver operating characteristic curve delineates the diagnostic capability of preoperative serum prostate-specific antigen concentrations in identifying poorly differentiated, high-grade disease (Gleason score 8 or higher) among radical prostatectomy candidates. The biomarker yielded an area under the curve (AUC) value of 0.84, confirming substantial discriminatory capacity against the diagonal line of no discrimination

(AUC=0.50). Using the Youden index criterion, the optimal diagnostic decision threshold was set at 10.2 ng/mL, producing a diagnostic sensitivity of 81.5% alongside a diagnostic specificity of 76.8%. These diagnostic parameters demonstrate that a preoperative serum PSA value exceeding 10.2 ng/mL offers robust, non-invasive risk discrimination for identifying biologically aggressive histopathology prior to surgical excision.

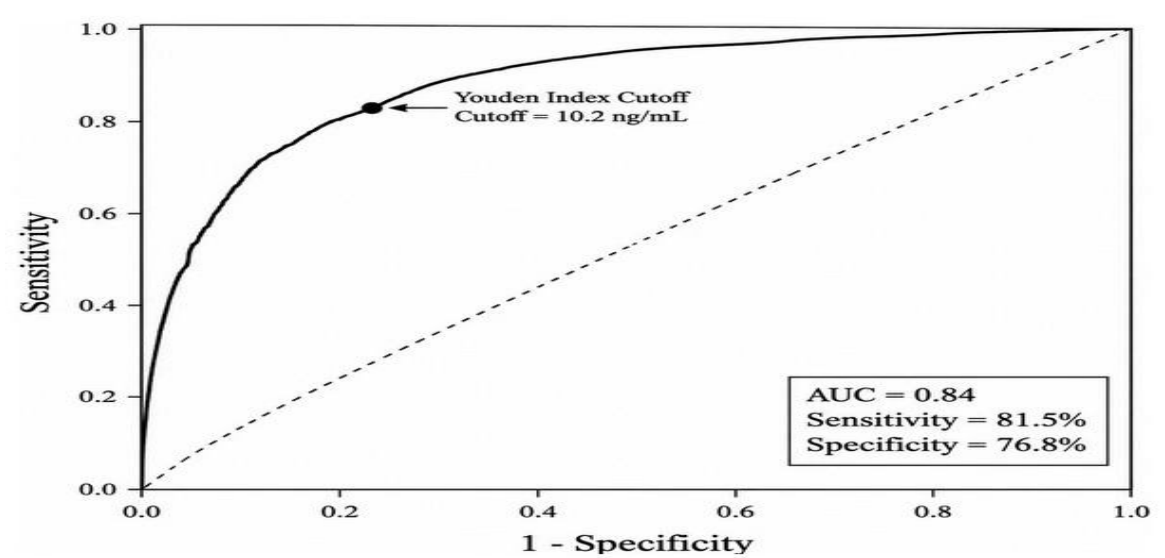


Figure 3. Receiver Operating Characteristic Curve Demonstrating the Diagnostic Efficacy of Baseline Serum PSA in Distinguishing High-Grade Prostate Cancer

Discussion

The present investigation demonstrates a pronounced, statistically significant escalation in preoperative serum prostate-specific antigen concentrations commensurate with advancing

histopathological grade in men undergoing radical prostatectomy for prostatic adenocarcinoma. Median baseline antigen values exhibited a consistent upward trajectory from well-differentiated tumors (Gleason score 6 or lower,

median 6.3 ng/mL) through intermediate differentiation (Gleason 3+4, median 10.0 ng/mL; Gleason 4+3, median 15.6 ng/mL) to poorly differentiated lesions (Gleason 8 or higher, median 28.3 ng/mL). A moderate-to-strong positive linear correlation was corroborated across the continuous continuum of biomarker measurements ($r=0.58$, $P<0.001$), while receiver operating characteristic curve analysis revealed substantial diagnostic accuracy for discerning high-grade disease (AUC=0.84), identifying an optimal decision threshold of 10.2 ng/mL with 81.5% sensitivity and 76.8% specificity [8,9].

The biological plausibility underlying the observed direct association between circulating antigen concentrations and final histological grade resides fundamentally in cellular architecture, loss of apical-basal polarity, and progressive disruption of physiological barrier mechanisms within malignant prostatic acini. Under healthy physiological conditions, prostate-specific antigen is secreted into the glandular lumina, where high concentrations are maintained, and only minimal quantities enter the vascular space due to intact continuous basement membranes, tight junctions, and an organized continuous basal cell layer. In high-grade prostatic adenocarcinoma, particularly lesions exhibiting cribriform, fused, or poorly formed glandular architectures characteristic of Gleason patterns 4 and 5, there is an extensive degradation of basement membranes driven by dysregulated matrix metalloproteinases and a complete loss of the protective basal cell lining. This structural collapse allows unconstrained leakage of lumenally secreted glycoprotein antigens directly into adjacent capillary networks and the systemic circulation, thereby producing elevated baseline serum concentrations that faithfully reflect the extent of cytoarchitectural breakdown [10,11].

Beyond basement membrane disruption, the concurrent expansion of total neoplastic cellular volume and increased cellular turnover represent primary drivers of elevated biomarker levels in higher-grade neoplasms. Although individual poorly differentiated malignant cells often synthesize less prostate-specific antigen per unit mass than normal luminal epithelia due to transcriptional dedifferentiation, poorly differentiated tumors typically feature higher proliferative indices, marked cellular crowding, and expansive intraprostatic volume by the time of extirpative intervention. The cumulative burden of densely clustered, actively proliferating neoplastic cells collectively produces a substantial absolute quantity of the glycoprotein that rapidly enters the interstitial compartment. Furthermore, high-grade malignancies frequently exhibit focal areas of hypoxia, micro-infarction, and accelerated cellular necrosis, all of which release intracellular reservoirs of stored antigen into systemic circulation, thereby establishing a

quantitative link between baseline biomarker concentration and biological malignancy [12,13].

The clear separation observed between Gleason 3+4 and Gleason 4+3 cohorts in this study highlights the distinct biological aggressiveness of pattern 4 disease and supports recent shifts in contemporary grading frameworks. Contemporary classification systems distinguish Grade Group 2 from Grade Group 3 based predominantly on the volumetric proportion of cribriform and fused glandular components relative to well-formed, discreet acinar patterns. The elevated median antigen level observed in the Gleason 4+3 subset (15.6 ng/mL) compared to the Gleason 3+4 cohort (10.0 ng/mL) directly reflects the quantitative abundance of invasive pattern 4 epithelium, which promotes extensive microvascular invasion and extracellular matrix remodeling. Because pattern 4 components induce local microvascular permeability and micro-thrombosis, circulating antigen egress occurs at significantly higher rates in predominantly pattern 4 tumors, reinforcing the capacity of serum biomarker concentrations to differentiate between clinically distinct intermediate-risk subcategories before surgical resection [14,15].

Our finding of a moderate-to-strong continuous linear correlation ($r=0.58$, $P<0.001$) aligns with prospective and retrospective prostatectomy series that report strong associations between circulating antigen titers and definitive pathological characteristics. Several multicenter investigations have underscored that higher preoperative antigen values independently increase the likelihood of non-organ-confined disease, extracapsular extension, seminal vesicle invasion, and regional lymph node metastases in surgical cohorts. The tight linear regression trajectory documented herein indicates that serum antigen measurements do not plateau prematurely across intermediate and high histological grades, but rather continue to reflect expanding intraprostatic tumor volume and architectural disorganization throughout the entire spectrum of surgical disease. This consistent linear relationship underscores the clinical relevance of interpreting baseline antigen levels as a continuous biological variable rather than relying exclusively on arbitrary categorical cutoff points during presurgical risk stratification [16,17].

The diagnostic performance established by the receiver operating characteristic curve analysis (AUC=0.84) provides compelling evidence that preoperative serum antigen concentration possesses strong discriminatory capacity for identifying high-grade disease (Gleason 8 or higher). This discriminatory potential is clinically essential because distinguishing high-grade malignancies prior to intervention is critical for selecting optimal surgical strategies, determining the safety of nerve-sparing dissections, and establishing appropriate boundaries for extended pelvic lymph node

dissection. Compared to other standard preoperative parameters, such as digital rectal examination findings or conventional transrectal ultrasound features, continuous serum biomarker levels demonstrate superior objective reproducibility and lower interobserver variability, thereby serving as a dependable, non-invasive indicator of underlying pathological aggression [18,19].

The optimal diagnostic threshold of 10.2 ng/mL derived through Youden index optimization delivers a well-balanced clinical profile, characterized by 81.5% sensitivity and 76.8% specificity in detecting poorly differentiated tumors. In clinical practice, an optimal threshold must minimize false-negative categorizations that could lead to inappropriate patient selection for active surveillance or conservative surgical approaches while avoiding excessive false-positive classifications that might prompt unnecessary overtreatment or excessively aggressive surgical margins. Patients presenting with baseline values exceeding 10.2 ng/mL should be recognized as harboring an elevated pre-test probability of adverse surgical pathology, warranting comprehensive multiparametric magnetic resonance imaging, focused targeted re-biopsy when indicated, and meticulous surgical planning that prioritizes wide surgical excision and extended lymphadenectomy [20,21].

Nevertheless, the biological interpretation of baseline serum prostate-specific antigen must be integrated with anatomical prostate dimensions and concurrent benign pathologies that can artificially elevate circulating values. Benign prostatic hyperplasia, subclinical intraprostatic inflammation, and acute urinary retention frequently introduce confounding antigen elevations that do not stem from malignant tissue dedifferentiation. In men with marked glandular enlargement, elevated circulating values may predominantly reflect benign transition zone proliferation rather than high-grade peripheral zone adenocarcinoma, which can potentially misclassify indolent malignancies as aggressive disease based on raw biomarker values alone. Incorporating secondary metrics such as antigen density, transitional zone volume correction, and free-to-total antigen ratios can significantly refine diagnostic specificity and prevent overestimation of tumor grade in patients with substantial benign glandular enlargement [22,23].

Another critical biological consideration is the phenomenon of severe phenotypic dedifferentiation, wherein a subset of extremely high-grade, neuroendocrine-differentiated, or small-cell prostatic carcinomas produce paradoxically low levels of circulating prostate-specific antigen. In these aggressive variant morphologies, profound transcriptional downregulation of the androgen receptor and loss of androgen-regulated kallikrein gene expression led to diminished protein production despite extensive metastatic

dissemination and poor clinical prognosis. Clinicians must remain aware of this biological paradox, ensuring that normal or minimally elevated antigen titers in the presence of palpably abnormal digital examinations or suspicious high-grade imaging findings do not lead to false reassurance regarding biological indolence [24,25].

A major strength of this investigation is the reliance on definitive whole-mount histopathological examination of radical prostatectomy specimens as the gold-standard reference, rather than transrectal or transperineal needle core biopsies. Systematic biopsy specimens are inherently prone to sampling error, tumor grade underestimation, and false-negative mischaracterization of tertiary high-grade components due to patchy spatial distribution of high-grade patterns. By evaluating entirely reconstructed surgical specimens, our analysis eliminates biopsy-related upgrading artifacts and ensures that correlated histological grades accurately reflect the complete pathological spectrum of the tumor, thereby establishing an accurate and unconfounded correlation with circulating baseline biomarker titers [26,27].

The translational implications of these findings are substantial for optimizing multidisciplinary prostate cancer decision-making algorithms and refining patient selection for multimodal therapeutic strategies. When integrated with advanced mpMRI-based PI-RADS scoring and comprehensive clinical risk calculators, a preoperative antigen level above the 10.2 ng/mL threshold can effectively pinpoint candidates who may derive optimal oncological benefit from neoadjuvant trials, extended pelvic lymph node dissection, or prompt early salvage adjuvant radiation therapy in the presence of positive surgical margins. Future prospective multicenter investigations incorporating novel serum, urinary, and tissue-based molecular biomarkers alongside continuous baseline antigen metrics will further enhance our ability to predict pathological differentiation and personalize treatment strategies for patients with localized prostate adenocarcinoma [28,29].

Conclusion

Preoperative serum PSA serves as a reliable, non-invasive biomarker for assessing histopathological aggressiveness in radical prostatectomy candidates. Integrating baseline PSA into risk-stratification algorithms enables precise identification of high-grade disease prior to intervention. Consequently, utilizing serum PSA as a continuous variable enhances the accuracy of preoperative surgical planning and significantly improves clinical decision-making for patients diagnosed with localized 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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