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# A Novel Biopsy-Free Predictive Model for Clinically Significant Prostate Cancer Incorporating Stratified PSA, PI-RADS, and PSMA PET-CT SUVmax: A Dual-Center Validation Study

**Nan Song**

biyangsongnan@163.com

Beijing Shijitan Hospital

**Zhemin Lin**

Beijing Shijitan Hospital

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## Abstract

# Background

The standard diagnostic pathway for prostate cancer necessitates a biopsy, an invasive procedure associated with potential complications. Identifying patients who can safely forego biopsy before radical treatment is an important clinical objective.

# Objective

To develop and externally validate a preoperative prediction model for clinically significant prostate cancer (csPca) using stratified levels of serum prostate-specific antigen (PSA), PI-RADS scores from multiparametric MRI, and semi-quantitative PSMA PET-CT parameters (SUVmax). The goal is to define criteria for a safe biopsy-free approach to radical prostatectomy.

# Methods

This retrospective, dual-center study analyzed data from 312 patients with suspected prostate cancer enrolled between January 2019 and June 2024. All patients underwent PSA testing, 3.0T multiparametric MRI, and $^{18}$F-PSMA-1007 PET-CT prior to any intervention. The reference standard was pathological examination of specimens from systematic combined targeted biopsies or radical prostatectomies. The cohort was randomly split 7:3 into a training set (n = 218) and an internal validation set (n = 94). Key predictors were categorized: PSA (< 10, 10–20, > 20 ng/mL); PI-RADS v2.1 (scores 3, 4, 5); and lesion SUVmax (< 4, 4–8, > 8). Multivariable logistic regression was employed to identify independent predictors of csPca (ISUP grade group ≥ 2) in the training set, leading to the construction of a nomogram. Model performance was rigorously assessed using the area under the receiver operating characteristic curve (AUC), calibration plots, and decision curve analysis (DCA). Furthermore, the diagnostic utility of various combination strategies of the three criteria was evaluated.

# Results

Pathological examination confirmed prostate cancer in 256 patients (82.1%), with 220 cases (70.5%) classified as csPca. Multivariable analysis revealed that each stratified variable was an independent, strong predictor of csPca, demonstrating a clear gradient effect. Compared to their respective reference categories, the adjusted odds ratios were: for PSA 10–20, 3.86 (95% CI: 2.12–7.03); for PSA > 20, 6.94 (95% CI: 3.87–12.45); for PI-RADS 4, 5.73 (95% CI: 3.21–10.23); for PI-RADS 5, 12.46 (95% CI: 7.18–21.64); for SUVmax 4–8, 4.92 (95% CI: 2.68–9.03); and for SUVmax > 8, 10.87 (95% CI: 6.23–18.96) (all P < 0.001). The nomogram derived from these factors exhibited excellent discrimination, with an AUC of 0.934 (95% CI: 0.901–0.967) in the training cohort and 0.919 (95% CI: 0.876–0.962) in the validation

cohort. Calibration was excellent, and DCA confirmed the model's clinical utility across a wide range of threshold probabilities. For clinical application, a "low-threshold" strategy (PSA ≥ 10, PI-RADS ≥ 4, SUVmax > 4) identified 106 patients, yielding a csPca positive predictive value (PPV) of 97.2% (103/106). A "high-threshold" strategy (PSA > 20, PI-RADS 5, SUVmax > 8) identified 56 patients with a csPca PPV of 100% (56/56).

# Conclusions

A novel prediction model incorporating stratified PSA, PI-RADS, and PSMA PET-CT SUVmax accurately predicts the presence of csPca. The proposed low-threshold combination (PSA ≥ 10 ng/mL, PI-RADS ≥ 4, SUVmax > 4) identifies a substantial patient subgroup with a PPV exceeding 97%, for whom a biopsy-free approach to radical prostatectomy appears safe and justifiable. The high-threshold strategy offers absolute predictive certainty for select patients. This risk-stratified approach has the potential to streamline care pathways and reduce unnecessary invasive procedures in men with suspected high-risk prostate cancer.

## 1. Introduction

Prostate cancer continues to be a leading cause of cancer-related morbidity among men worldwide, with its incidence steadily rising in China, mirroring global trends [1]. The cornerstone of definitive diagnosis remains the histopathological examination of tissue obtained via transrectal or transperineal biopsy. Despite its status as the gold standard, this procedure is inherently invasive and carries a well-documented risk of complications. These include bleeding-related events (hematuria, hematospermia, rectal bleeding) in 20–50% of cases and infectious complications (ranging from acute prostatitis to life-threatening sepsis) in 1–4% [2–3]. Beyond the immediate procedural risks, biopsies are subject to sampling error, potentially leading to an underestimation of the true Gleason grade. Furthermore, the resultant local hematoma and inflammatory response can obscure surgical planes, potentially complicating subsequent radical prostatectomy [4].

The landscape of prostate cancer diagnosis has been transformed by advanced imaging. The widespread implementation of multiparametric magnetic resonance imaging (mpMRI) and the standardized Prostate Imaging Reporting and Data System (PI-RADS) have significantly enhanced our ability to non-invasively detect clinically significant prostate cancer (csPca) [5–6]. A strong, positive correlation exists between PI-RADS assessment categories and the likelihood of csPca, with detection rates reportedly reaching 80–95% for PI-RADS 5 lesions [7–8]. More recently, molecular imaging with positron emission tomography/computed tomography (PET-CT) targeting the prostate-specific membrane antigen (PSMA) has added another dimension. PSMA PET-CT not only offers high specificity for prostate cancer cells but also provides quantitative metabolic information via parameters like the maximum standardized uptake value (SUVmax) [9–10]. Accumulating evidence indicates a significant

association between SUVmax and adverse pathological features such as higher Gleason scores and increased proliferative indices [11–12].

The convergence of highly suggestive findings from serum biomarkers (PSA) and these two sophisticated imaging modalities raises a compelling clinical question: can we identify a subset of patients for whom the probability of harboring csPca is so high that the intermediate, invasive step of biopsy can be safely omitted, allowing them to proceed directly to curative-intent surgery? Such a paradigm shift would embody the core principles of precision medicine and enhanced recovery, potentially reducing patient burden, shortening time to definitive treatment, and avoiding biopsy-related complications. However, current evidence lacks robust, large-scale validation of biopsy-free predictive models based on stringent, stratified criteria, particularly those incorporating quantitative PSMA PET-CT metrics [13–15].

To address this gap, we conducted a dual-center study leveraging real-world data with the following objectives: (1) to investigate the independent predictive value of different strata of serum PSA, PI-RADS scores, and PSMA PET-CT SUVmax for csPca; (2) to construct and internally validate a user-friendly nomogram integrating these stratified variables; and (3) to evaluate the diagnostic performance of different clinical combination strategies derived from these variables, with the ultimate aim of providing evidence-based guidance for selecting patients eligible for a biopsy-free surgical approach.

# 2. Materials and Methods

2.1 Study Population and Design This retrospective, dual-center study was conducted at Beijing Shijitan Hospital, Capital Medical University, and the Chinese PLA General Hospital. We reviewed the medical records of consecutive patients with suspected prostate cancer evaluated between January 2019 and June 2024.

Inclusion criteria were: (1) Clinical suspicion of prostate cancer based on elevated PSA and/or abnormal digital rectal examination and/or suspicious imaging findings; (2) Serum total PSA (tPSA) measurement within 2 weeks prior to any intervention; (3) High-quality 3.0T mpMRI performed at the participating center within 4 weeks before any intervention, with a documented PI-RADS score; (4) $^{18}$F-PSMA-1007 PET-CT scan performed at the participating center within 4 weeks before any intervention, with available SUVmax data for any suspicious prostatic lesion; (5) Subsequent histopathological confirmation via systematic combined targeted prostate biopsy or robot-assisted laparoscopic radical prostatectomy, with complete pathology reports.

Exclusion criteria were: (1) Prior history of prostate biopsy, prostate surgery, or any treatment for prostate cancer (e.g., hormonal therapy, radiotherapy); (2) Use of 5α-reductase inhibitors within the 3 months preceding PSA measurement; (3) Diagnosis of another malignancy that could potentially interfere with PSMA PET-CT interpretation; (4) Inadequate image quality on MRI or PET-CT preventing accurate assessment; (5) Missing essential clinical, imaging, or pathological data points.

The study protocol received approval from the institutional review boards of both participating centers (Approval No. [2024]YX-XX). Given the retrospective, non-interventional design, the requirement for written informed consent was waived.

2.2 Data Collection and Variable Definitions Two trained investigators, blinded to the final pathological outcomes, independently extracted data using a standardized form. Discrepancies were resolved through consensus or consultation with a senior author.

- Demographic and Clinical Data: Age at diagnosis and body mass index (BMI) were recorded.
- Serological Data: Total PSA (tPSA) and free PSA (fPSA) levels were measured. For analysis, tPSA was stratified into three clinically relevant categories based on widely accepted cutoffs: <10 ng/mL (low), 10–20 ng/mL (intermediate), and > 20 ng/mL (high).
- MRI Data and Interpretation: All mpMRI examinations were performed on 3.0T scanners (Siemens Skyra or GE Discovery 750) using a standardized protocol including T2-weighted imaging, diffusion-weighted imaging (with b-values up to 2000 s/mm²), and dynamic contrast-enhanced sequences. Two senior radiologists with over 8 years of subspecialty experience in urologic imaging independently reviewed all studies, assigning PI-RADS scores according to version 2.1. In cases of disagreement, a consensus was reached through joint review. PI-RADS scores were categorized into three groups for analysis: 3, 4, and 5. (Scores 1 and 2 were exceedingly rare in this referral population and were not included in the analysis due to insufficient numbers.)
- PET-CT Data and Interpretation: $^{18}$F-PSMA-1007 PET-CT scans were acquired approximately 60 minutes post-injection using standardized protocols. Two experienced nuclear medicine physicians (> 5 years of experience) performed visual analysis and measured the maximum standardized uptake value (SUVmax) of the dominant intraprostatic lesion. Based on prior literature and our institutional experience, SUVmax values were stratified into three groups: <4 (low uptake), 4–8 (intermediate uptake), and > 8 (high uptake) [16–17].
- Pathological Data: Histopathological examination served as the reference standard. For patients undergoing biopsy, a combined systematic (12-core) and targeted (fusion or cognitive) approach was used. For those proceeding directly to surgery, radical prostatectomy specimens were processed using whole-mount sectioning. All specimens were evaluated by dedicated genitourinary pathologists. The presence of prostate cancer, Gleason score, and International Society of Urological Pathology (ISUP) grade group were recorded. The primary outcome for this study, clinically significant prostate cancer (csPca), was defined as ISUP grade group ≥ 2, corresponding to a Gleason score of 3 + 4=7 or higher.

2.3 Statistical Analysis and Model Development All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R software version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria) with relevant packages (e.g., rms, caret, rmda). A two-tailed P-value < 0.05 was considered statistically significant.

- Cohort Partitioning: The entire dataset (N = 312) was randomly divided into a training set (70%, n = 218) and an internal validation set (30%, n = 94) using the caret package, ensuring a similar distribution of key characteristics between the two sets.
- Model Building in the Training Set: Baseline characteristics were compared between patients with and without csPca using appropriate statistical tests (independent samples t-test or Mann-Whitney U test for continuous variables; chi-square test or Fisher's exact test for categorical variables). Variables showing an association with csPca at a significance level of $P < 0.10$ in univariate analysis were considered candidates for inclusion in a multivariable logistic regression model. A forward stepwise selection procedure was employed to identify independent predictors of csPca. Adjusted odds ratios (OR) and their 95% confidence intervals (CI) were calculated. A nomogram was constructed based on the final multivariable model using the rms package in R to provide a visual and intuitive tool for predicting the probability of csPca.
- Model Performance Assessment:
    - Discrimination: The model's ability to distinguish between patients with and without csPca was quantified using the area under the receiver operating characteristic curve (AUC-ROC). An AUC of 1.0 represents perfect discrimination, while 0.5 indicates no discriminative ability. The DeLong test was used to compare AUCs where appropriate.
    - Calibration: Agreement between the model's predicted probabilities and the actual observed frequencies of csPca was assessed graphically with a calibration plot and formally tested using the Hosmer-Lemeshow goodness-of-fit test (a non-significant P-value, e.g., > 0.05, indicates good calibration).
    - Clinical Utility: Decision curve analysis (DCA) was performed to evaluate the net clinical benefit of using the model to guide biopsy-free decisions across a range of threshold probabilities, comparing it to default strategies of performing or omitting biopsy for all patients.
- Analysis of Clinical Combination Strategies: To enhance clinical applicability, we evaluated the performance of three practical combination strategies based on the key predictors:
    - Strategy A (Low-Threshold): PSA ≥ 10 ng/mL AND PI-RADS ≥ 4 AND SUVmax > 4.
    - Strategy B (Intermediate-Threshold): PSA > 20 ng/mL AND PI-RADS ≥ 4 AND SUVmax > 8.
    - Strategy C (High-Threshold): PSA > 20 ng/mL AND PI-RADS = 5 AND SUVmax > 8. For each strategy, we calculated the number of patients meeting the criteria, the csPca detection rate, positive predictive value (PPV), sensitivity, and specificity.

# 3. Results

3.1 Baseline Demographics and Clinical Characteristics A total of 312 patients met the eligibility criteria and were included in the final analysis. The mean age of the cohort was 70.2 ± 7.8 years, and the median serum PSA level was 13.6 ng/mL (interquartile range: 8.4–26.8). The baseline characteristics of the

training (n = 218) and validation (n = 94) sets were well-balanced, with no statistically significant differences observed, confirming the success of the random partitioning (Table 1).

Overall, histopathological examination confirmed prostate cancer in 256 patients (82.1%), of whom 220 (70.5% of the total cohort) met the definition for csPca. Benign findings were present in 56 patients (17.9%), including benign prostatic hyperplasia (n = 34), chronic prostatitis (n = 18), and high-grade prostatic intraepithelial neoplasia (HGPIN, n = 4). The distribution of patients across the predefined strata for the three key predictors was as follows: For PSA, 102 patients (32.7%) had < 10 ng/mL, 114 (36.5%) had 10–20 ng/mL, and 96 (30.8%) had > 20 ng/mL. For PI-RADS, 78 (25.0%) had a score of 3, 124 (39.7%) a score of 4, and 110 (35.3%) a score of 5. For SUVmax, 86 (27.6%) had values < 4, 118 (37.8%) had values between 4–8, and 108 (34.6%) had values > 8.

Table 1
Baseline Characteristics of the Training and Validation Cohorts

| Characteristic | Total Cohort (N = 312) | Training Set (n = 218) | Validation Set (n = 94) | P-value |
|---|---|---|---|---|
| Age (years), mean ± SD | 70.2 ± 7.8 | 70.4 ± 7.6 | 69.8 ± 8.2 | 0.532 |
| PSA Category, n (%) | | | | 0.876 |
| < 10 ng/mL | 102 (32.7) | 72 (33.0) | 30 (31.9) | |
| 10–20 ng/mL | 114 (36.5) | 80 (36.7) | 34 (36.2) | |
| > 20 ng/mL | 96 (30.8) | 66 (30.3) | 30 (31.9) | |
| PI-RADS Category, n (%) | | | | 0.764 |
| Score 3 | 78 (25.0) | 54 (24.8) | 24 (25.5) | |
| Score 4 | 124 (39.7) | 88 (40.4) | 36 (38.3) | |
| Score 5 | 110 (35.3) | 76 (34.9) | 34 (36.2) | |
| SUVmax Category, n (%) | | | | 0.803 |
| < 4 | 86 (27.6) | 60 (27.5) | 26 (27.7) | |
| 4–8 | 118 (37.8) | 84 (38.5) | 34 (36.2) | |
| > 8 | 108 (34.6) | 74 (33.9) | 34 (36.2) | |
| Final Pathology, n (%) | | | | 0.721 |
| Benign | 56 (17.9) | 40 (18.3) | 16 (17.0) | |
| Prostate Cancer (any) | 256 (82.1) | 178 (81.7) | 78 (83.0) | |
| csPca (ISUP ≥ 2) | 220 (70.5) | 154 (70.6) | 66 (70.2) | |

SD: standard deviation; PSA: prostate-specific antigen; PI-RADS: Prostate Imaging Reporting and Data System; SUVmax: maximum standardized uptake value; csPca: clinically significant prostate cancer; ISUP: International Society of Urological Pathology.

3.2 Identification of Independent Predictors for csPca Univariate analysis performed on the training cohort (n = 218) revealed that all three stratified variables—PSA category, PI-RADS category, and SUVmax category—were strongly associated with the presence of csPca (all $P < 0.001$) (Table 2). In contrast, age, BMI, and the f/t PSA ratio did not show a significant association and were not carried forward.

Table 2
Univariate Analysis for Predicting csPca in the Training Set (n = 218)

| Variable | csPca (n = 154) | Non-csPca (n = 64) | Test Statistic | P-value |
|---|---|---|---|---|
| Age (years), mean ± SD | 70.8 ± 7.4 | 69.4 ± 8.1 | t = 1.24 | 0.216 |
| BMI (kg/m²), mean ± SD | 24.6 ± 3.2 | 25.1 ± 3.5 | t=-1.03 | 0.304 |
| PSA Category, n (%) | | | $\chi^2$=38.42 | < 0.001 |
| < 10 ng/mL | 32 (20.8) | 40 (62.5) | | |
| 10–20 ng/mL | 62 (40.3) | 18 (28.1) | | |
| > 20 ng/mL | 60 (38.9) | 6 (9.4) | | |
| PI-RADS Category, n (%) | | | $\chi^2$=56.73 | < 0.001 |
| Score 3 | 20 (13.0) | 34 (53.1) | | |
| Score 4 | 60 (38.9) | 28 (43.8) | | |
| Score 5 | 74 (48.1) | 2 (3.1) | | |
| SUVmax Category, n (%) | | | $\chi^2$=51.86 | < 0.001 |
| < 4 | 24 (15.6) | 36 (56.3) | | |
| 4–8 | 58 (37.7) | 26 (40.6) | | |
| > 8 | 72 (46.7) | 2 (3.1) | | |

csPca: clinically significant prostate cancer; BMI: body mass index; PSA: prostate-specific antigen; PI-RADS: Prostate Imaging Reporting and Data System; SUVmax: maximum standardized uptake value.

The three stratified variables were subsequently entered into a multivariable logistic regression model. The results, detailed in Table 3, confirmed that each variable remained a highly significant and independent predictor of csPca. Notably, a clear dose-response relationship was observed, with the odds ratios increasing substantially with each higher stratum. For instance, compared to a PSA < 10 ng/mL, a PSA of 10–20 ng/mL carried an OR of 3.86, which rose to 6.94 for PSA > 20 ng/mL. Similarly, PI-RADS 5 (OR 12.46) was a much stronger predictor than PI-RADS 4 (OR 5.73) relative to a score of 3, and SUVmax > 8 (OR 10.87) was substantially stronger than SUVmax 4–8 (OR 4.92) compared to SUVmax < 4.

Table 3
Multivariable Logistic Regression Analysis for Predicting csPca

| Variable | β Coefficient | Standard Error | Wald $\chi^2$ | Adjusted Odds Ratio (95% CI) | P-value |
|---|---|---|---|---|---|
| PSA Category (ref: <10 ng/mL) | | | | | |
| 10–20 ng/mL | 1.351 | 0.306 | 19.48 | 3.86 (2.12–7.03) | < 0.001 |
| > 20 ng/mL | 1.937 | 0.298 | 42.24 | 6.94 (3.87–12.45) | < 0.001 |
| PI-RADS Category (ref: Score 3) | | | | | |
| Score 4 | 1.746 | 0.297 | 34.56 | 5.73 (3.21–10.23) | < 0.001 |
| Score 5 | 2.523 | 0.282 | 80.05 | 12.46 (7.18–21.64) | < 0.001 |
| SUVmax Category (ref: <4) | | | | | |
| 4–8 | 1.593 | 0.310 | 26.41 | 4.92 (2.68–9.03) | < 0.001 |
| > 8 | 2.386 | 0.284 | 70.58 | 10.87 (6.23–18.96) | < 0.001 |
| Constant | -4.126 | 0.342 | 145.53 | 0.016 | < 0.001 |

3.3 Nomogram Development and Performance Validation A nomogram integrating these six predictor categories was constructed based on the multivariable model (Fig. 1A). This tool allows clinicians to easily estimate an individual patient's probability of harboring csPca by summing the points assigned to each of their three characteristic strata and reading the corresponding predicted risk on the bottom scale.

Figure 1A. Nomogram for Predicting the Probability of Clinically Significant Prostate Cancer. Instructions for use: Locate the patient's PSA category on the first axis and draw a vertical line upward to the "Points" bar to assign points. Repeat for the PI-RADS and SUVmax categories. Sum the points from all three categories and locate this total on the "Total Points" axis. Draw a vertical line downward to the "Predicted Probability of csPca" axis to obtain the individual risk estimate.

The model's performance was rigorously evaluated in both the training and validation sets. Its discriminative ability was excellent, as reflected by the high AUC-ROC values. In the training cohort, the AUC was 0.934 (95% CI: 0.901–0.967) (Fig. 1B). This high performance was maintained in the

independent validation cohort, with an AUC of 0.919 (95% CI: 0.876–0.962) (Fig. 1C). These results indicate that the model is highly effective at distinguishing patients with csPca from those without.

Receiver Operating Characteristic (ROC) Curves for the Prediction Model. (A) ROC curve in the training cohort (n = 218), demonstrating an area under the curve (AUC) of 0.934. (B) ROC curve in the validation cohort (n = 94), demonstrating an AUC of 0.919. The high AUC values in both cohorts indicate excellent and stable discriminatory performance.

Calibration of the model was assessed by plotting the predicted probabilities against the actual observed frequencies of csPca. The calibration curve (Fig. 1D) demonstrated excellent agreement, with the predicted values closely following the ideal 45-degree line. This visual assessment was confirmed by a non-significant Hosmer-Lemeshow test (P = 0.584), indicating no significant deviation between predicted and observed outcomes and confirming that the model is well-calibrated.

Figure 1D. Calibration Curve for the Prediction Model in the Validation Cohort. The plot shows the relationship between the model-predicted probability of csPca (x-axis) and the actual observed proportion of csPca (y-axis). The diagonal dashed line represents perfect calibration. The solid line with dots representing deciles of predicted risk shows excellent agreement between predictions and observations (Hosmer-Lemeshow P = 0.584).

To assess the potential clinical impact of implementing the model, decision curve analysis was performed (Fig. 1E). The results showed that using the model to guide the decision for or against biopsy (or for proceeding directly to surgery) provides a higher net benefit across a wide and clinically relevant range of threshold probabilities (approximately 0.3 to 0.9) compared to two default strategies: performing a biopsy on all patients, or performing a biopsy on none. This confirms that the model has meaningful clinical utility and could improve patient outcomes.

Decision Curve Analysis for the Prediction Model. The y-axis represents the net benefit. The x-axis represents the threshold probability for csPca. The thin solid line represents the strategy of performing a biopsy on all patients. The thick solid line represents the strategy of performing a biopsy on none. The dashed line represents the net benefit of using the proposed stratified prediction model to guide decisions. The model demonstrates a superior net benefit compared to both default strategies across a wide range of threshold probabilities.

3.4 Diagnostic Performance of Clinical Combination Strategies To provide simple, clinically actionable rules, we evaluated the performance of three distinct combination strategies based on the model's key predictors (Table 4).

- Strategy A (Low-Threshold): This strategy identified 106 patients (34.0% of the cohort) who met all three criteria (PSA ≥ 10, PI-RADS ≥ 4, SUVmax > 4). Within this group, the prevalence of csPca was exceptionally high, with 103 out of 106 patients having the condition, resulting in a PPV of 97.2%. The three false-positive cases comprised one granulomatous prostatitis, one HGPIN, and one case

of chronic inflammation with HGPIN. All three had values near the lower bounds of the criteria (e.g., PSA 12–18 ng/mL, PI-RADS 4, SUVmax 4.8–6.1).

- Strategy B (Intermediate-Threshold): Applying stricter criteria (PSA > 20, PI-RADS ≥ 4, SUVmax > 8) selected 68 patients (21.8% of the cohort). The csPca PPV remained very high at 97.1% (66/68 patients), with the two false positives both being granulomatous prostatitis.
- Strategy C (High-Threshold): The most stringent criteria (PSA > 20, PI-RADS 5, SUVmax > 8) identified 56 patients (17.9% of the cohort). Remarkably, all 56 patients were confirmed to have csPca on final pathology, yielding a PPV of 100%.

Further analysis of the high-risk group (Strategy C) revealed a strong correlation with aggressive disease. Among these 56 patients, 43 (76.8%) had a final Gleason score of 8 or higher (ISUP grade group 4–5).

Table 4
Diagnostic Performance of Different Clinical Combination Strategies for csPca

| Strategy | Combination Criteria | N (% of total) | csPca Detected (n) | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|---|---|---|
| A (Low) | PSA ≥ 10 + PI-RADS ≥ 4 + SUVmax > 4 | 106 (34.0) | 103 | 46.8 | 96.7 | 97.2 | 43.3 |
| B (Intermediate) | PSA > 20 + PI-RADS ≥ 4 + SUVmax > 8 | 68 (21.8) | 66 | 30.0 | 98.9 | 97.1 | 36.5 |
| C (High) | PSA > 20 + PI-RADS 5 + SUVmax > 8 | 56 (17.9) | 56 | 25.5 | 100 | 100 | 34.8 |

PPV: positive predictive value; NPV: negative predictive value; csPca: clinically significant prostate cancer; PSA: prostate-specific antigen; PI-RADS: Prostate Imaging Reporting and Data System; SUVmax: maximum standardized uptake value.

# 4. Discussion

The landscape of prostate cancer diagnosis is on the cusp of a significant evolution, moving from a paradigm where histological confirmation via biopsy is mandatory for all towards a more nuanced, imaging-led approach for carefully selected patients [18]. The present study provides robust, dual-center data supporting the feasibility and safety of a biopsy-free pathway for a well-defined subgroup of men with a very high probability of harboring csPca. Our key contribution lies in moving beyond simple binary predictors (e.g., PSA > 10 vs. <10) to a more granular, stratified model that captures the dose-response relationship between the severity of each indicator and the risk of csPca. This approach, combined with the quantification of PSMA PET-CT avidity via SUVmax, allows for more precise risk stratification than previously reported models.

# 4.1 The Imperative of Stratification for Accurate Risk Prediction

A central finding of our study is the clear and independent gradient effect observed for each of the three key variables. The risk of csPca does not simply increase when a patient crosses a single threshold, but rather escalates progressively with higher PSA levels, higher PI-RADS scores, and higher SUVmax values. For instance, our data show that a PSA > 20 ng/mL confers nearly double the risk (OR 6.94) compared to a PSA of 10–20 ng/mL (OR 3.86). This distinction would be entirely lost if PSA were treated only as a binary variable (> 10 vs. <10). Similarly, a PI-RADS 5 lesion (OR 12.46) represents a far greater risk than a PI-RADS 4 lesion (OR 5.73). While these two categories are often clinically grouped together as "MRI suspicious," our results underscore their markedly different predictive weights, aligning with meta-analyses showing csPca detection rates of 50–70% for PI-RADS 4 and 80–95% for PI-RADS 5 [7–8]. This gradient underscores the necessity of incorporating full stratification, rather than dichotomization, into modern predictive tools to optimize clinical decision-making [19–20].

# 4.2 The Added Value of PSMA PET-CT Quantification

The integration of PSMA PET-CT, and specifically its semi-quantitative metric SUVmax, represents a significant advancement over models relying solely on anatomical or functional MRI. While PSMA PET-CT is highly sensitive, visual interpretation alone ("positive" or "negative") can be subjective and may not fully leverage the data. Our study demonstrates that SUVmax provides powerful, independent prognostic information. The striking difference in risk between SUVmax 4–8 (OR 4.92) and SUVmax > 8 (OR 10.87) highlights the value of quantification. Patients with SUVmax > 8 were not just more likely to have cancer, but overwhelmingly likely to have csPca, with a detection rate of 94.4% in our cohort. This finding is consistent with a growing body of literature correlating higher PSMA expression, reflected by higher SUVmax, with more aggressive tumor biology, including higher Gleason scores and increased proliferative activity [11–12, 21–22]. By incorporating SUVmax strata, our model captures this biological gradient, enhancing its precision beyond what is possible with qualitative imaging alone [23–26]. This aligns with the ongoing efforts to standardize PSMA PET-CT reporting, such as the PSMA-RADS system, and our data provide practical SUVmax cutoffs (4 and 8) that could be integrated into such frameworks [10, 27].

# 4.3 Clinical Applicability: A Risk-Stratified Approach to Biopsy-Free Surgery

Translating our model into clinical practice, we evaluated three pragmatic combination strategies. The low-threshold strategy (PSA ≥ 10, PI-RADS ≥ 4, SUVmax > 4) identified 34% of our cohort with a PPV of 97.2%. This exceptionally high predictive value suggests that for every 100 patients meeting these criteria, only 2–3 would undergo surgery for a lesion that ultimately proves not to be csPca. Importantly, the false positives in our series were not simple benign hypertrophy but conditions like granulomatous prostatitis or HGPIN, which can themselves cause significant lower urinary tract symptoms or diagnostic

uncertainty, and for which surgical extirpation might still offer a clinical benefit [28]. Therefore, we propose this low-threshold strategy as a clinically viable and safe□□□□ for offering biopsy-free radical prostatectomy. It balances high accuracy with the ability to benefit a substantial number of patients.

For scenarios demanding the highest possible certainty, such as in prospective clinical trials or for patients who are extremely risk-averse, the high-threshold strategy (PSA > 20, PI-RADS 5, SUVmax > 8) provides an absolute PPV of 100%, albeit in a smaller subset of patients (18% of our cohort). The perfect predictive value in this group, where over three-quarters had Gleason score ≥ 8 disease, confirms that these patients harbor aggressive, high-risk cancer with near-certainty, and any diagnostic delay from biopsy is both unnecessary and potentially detrimental.

Adopting such a biopsy-free strategy offers several potential advantages. It completely eliminates the risks of biopsy-related bleeding, infection, and pain, enhancing patient experience and safety [2–3]. It streamlines the diagnostic pathway, reducing the psychological burden of waiting for biopsy results and shortening the time to curative treatment. Furthermore, by avoiding biopsy-induced tissue distortion and inflammation, it may facilitate a technically simpler and more precise radical prostatectomy, potentially improving functional outcomes related to continence and potency preservation, although this hypothesis requires further prospective study [4, 29].

## 4.4 Study Strengths and Limitations

The major strengths of this study include its dual-center design, which enhances the generalizability of our findings compared to single-center reports. The rigorous, blinded assessment of imaging by experienced specialists and the use of a clear, clinically relevant endpoint (csPca defined by ISUP grade group ≥ 2) are additional methodological strengths. Our move towards stratified variables and the inclusion of quantitative SUVmax represent a step forward in precision for this field.

However, several limitations must be acknowledged. First, the retrospective design introduces the potential for selection bias, despite our use of consecutive patients and dual centers. Prospective, multicenter validation is essential before widespread clinical adoption. Second, while our total sample size (N = 312) was adequate for model development and validation, some subgroups within the stratified analysis, particularly the high-threshold combination, had smaller numbers. Larger cohorts are needed to confirm the robustness of the 100% PPV observed in this subgroup. Third, SUVmax measurement, while standardized in our study, can be subject to inter-scanner and inter-observer variability. The development of robust harmonization and calibration protocols for quantitative PSMA PET-CT metrics is an important area for ongoing research [30]. Fourth, our model is specifically designed for patients with a high pre-test probability of localized, clinically significant disease. It is not applicable to men with low PSA levels, equivocal imaging findings, or those suspected of having low-risk, indolent cancer, for whom a biopsy (or active surveillance) remains the standard of care.

Future directions include prospective validation of the proposed low-threshold strategy in a multicenter setting, with long-term follow-up to assess not only cancer control outcomes (e.g., biochemical

recurrence-free survival) but also functional outcomes and health-related quality of life in men undergoing biopsy-free surgery.

## 5. Conclusions

This dual-center study successfully developed and internally validated a novel prediction model for clinically significant prostate cancer that integrates stratified levels of serum PSA, PI-RADS scores, and PSMA PET-CT SUVmax. The model demonstrates excellent discriminatory ability, calibration, and clinical utility. The derived low-threshold clinical strategy (PSA ≥ 10 ng/mL, PI-RADS ≥ 4, and SUVmax > 4) identifies a substantial patient subgroup with a positive predictive value exceeding 97%, for whom a biopsy-free approach to radical prostatectomy appears safe and justifiable. For patients meeting the most stringent criteria (PSA > 20 ng/mL, PI-RADS 5, SUVmax > 8), the prediction of csPca is absolute. This risk-stratified, imaging-driven paradigm has the potential to optimize care pathways, reduce unnecessary invasive procedures, and expedite definitive treatment for men with a high likelihood of harboring clinically significant prostate cancer.

## Declarations

**Ethics Approval and Consent to Participate:**

This study was approved by the Ethics Committees of Beijing Shijitan Hospital, Capital Medical University. Due to the retrospective nature of the study, the requirement for informed consent was waived by both ethics committees. All patient data were anonymized prior to analysis.

**Consent for Publication:**

Not applicable. This manuscript does not contain any individual person's data in any form.


# Funding Declaration

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Clinical Trial Number:

Clinical trial number: not applicable. This study is a retrospective observational study and does not report the results of a clinical trial.

Conflict of Interest Statement:

The authors declare that they have no conflict of interest.

# Author Contribution

Song wrote the main manuscript text and prepared figures , Lin performed the most biopsy procedures. All authors reviewed the manuscript.

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# Figures

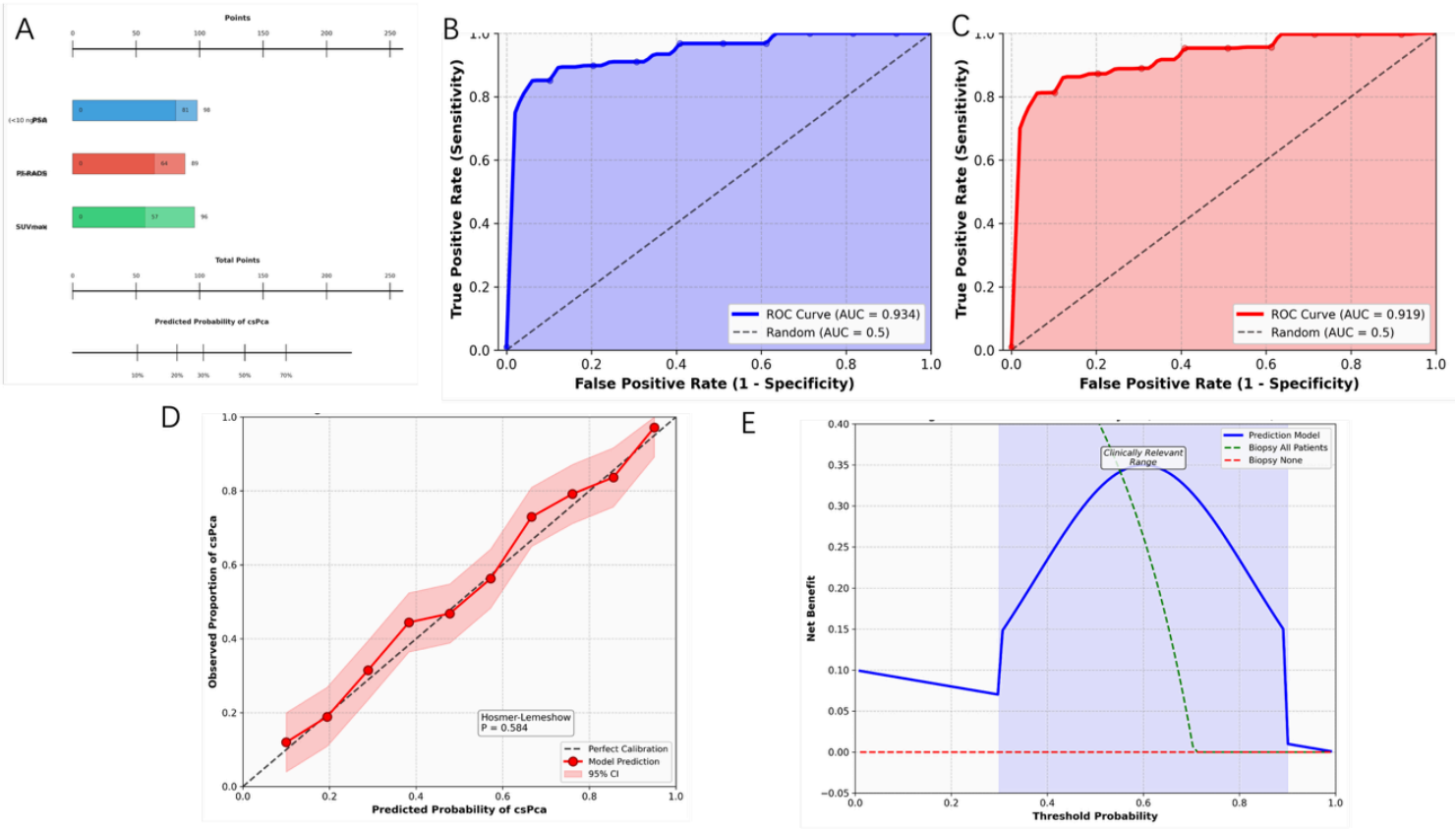



**Figure 1**

A. Nomogram for Predicting the Probability of Clinically Significant Prostate Cancer. Instructions for use: Locate the patient's PSA category on the first axis and draw a vertical line upward to the "Points" bar to assign points. Repeat for the PI-RADS and SUVmax categories. Sum the points from all three categories and locate this total on the "Total Points" axis. Draw a vertical line downward to the "Predicted Probability of csPca" axis to obtain the individual risk estimate.

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryTable1.docx