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# Prostate-Specific Antigen (PSA) as a Predictor of Prostate Cancer on Transrectal Biopsy: A Meta-Analysis

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**A B S T R A C T**

Prostate cancer is a leading cause of cancer-related death in men globally. Early detection is critical for improving patient outcomes. Prostate-specific antigen (PSA) testing is a widely used screening tool, but its accuracy in predicting prostate cancer on transrectal biopsy remains a topic of debate. This meta-analysis aims to evaluate the diagnostic accuracy of PSA in predicting prostate cancer on transrectal biopsy. A systematic search of electronic databases (PubMed, Scopus, Web of Science) was conducted to identify relevant studies published between 2013 and 2024. Studies reporting the sensitivity, specificity, and area under the receiver operating characteristic curve (AUC) of PSA for predicting prostate cancer on transrectal biopsy were included. Data were extracted, and the pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were calculated using a random-effects model. Six studies met the inclusion criteria, comprising a total of 1,245 patients. The pooled sensitivity and specificity of PSA for predicting prostate cancer on transrectal biopsy were 0.77 (95% CI, 0.75 - 0.82) and 0.68 (95% CI, 0.62-0.73), respectively. The pooled PLR, NLR, and DOR were 3.27 (95% CI, 2.45-4.37), 0.20 (95% CI, 0.14-0.28), and 16.39 (95% CI, 10.27-26.21), respectively. The pooled AUC was 0.87 (95% CI, 0.84-0.90). In conclusion, PSA demonstrates good diagnostic accuracy in predicting prostate cancer on transrectal biopsy. However, it is essential to consider its limitations, including false positives and negatives. Further research is needed to identify strategies to improve the accuracy of PSA testing and reduce unnecessary biopsies.

## 1. Introduction

Prostate cancer is a significant global health concern, ranking as the second most common cancer and the fifth leading cause of cancer-related death in men worldwide. In the United States alone, an estimated 288,300 new cases and 34,700 deaths occurred in 2023. Early detection of prostate cancer is critical for improving patient outcomes and survival rates. Prostate-specific antigen (PSA) testing, a blood test that measures the levels of a protein produced by the prostate gland, has been widely used as a screening tool for prostate cancer. Elevated PSA levels can indicate the presence of prostate cancer, prompting further investigation with a transrectal biopsy.[1-3] Transrectal biopsy, which involves inserting a thin needle through the rectum to collect prostate tissue samples, is considered the gold standard for diagnosing prostate cancer. However, it is an invasive procedure with potential complications such as bleeding, infection, and pain. Moreover, PSA testing has limitations, including false positives (elevated PSA levels without cancer) and false negatives (normal PSA levels with cancer). These limitations can lead to unnecessary biopsies or delayed diagnoses, respectively.[4-6]

The accuracy of PSA in predicting prostate cancer on transrectal biopsy remains a topic of debate. Several studies have investigated the diagnostic accuracy of PSA, but their results have been inconsistent. Meta-analyses have been conducted to

synthesize the available evidence, but they often include studies with heterogeneous populations and methodologies, leading to varying conclusions.[7-10] This meta-analysis aims to provide a comprehensive and updated evaluation of the diagnostic accuracy of PSA in predicting prostate cancer on transrectal biopsy. By pooling data from multiple studies, we aim to estimate the pooled sensitivity, specificity, and other measures of diagnostic accuracy. This information can help clinicians and patients make informed decisions about prostate cancer screening and biopsy procedures.

## 2. Methods

A comprehensive and systematic search of three prominent electronic databases, PubMed, Scopus, and Web of Science, was conducted. The primary objective of this search was to identify relevant studies published within the past decade, specifically between 2013 and 2023, that investigated the diagnostic accuracy of prostate-specific antigen (PSA) in predicting prostate cancer on transrectal biopsy. The search strategy employed a combination of keywords and medical subject headings (MeSH) terms relevant to the research question. The following search terms were utilized; Population: "men," "male," "prostate cancer"; Intervention: "PSA," "prostate-specific antigen," "PSA testing," "PSA level"; Comparison: "transrectal biopsy," "prostate biopsy"; Outcome: "diagnostic accuracy," "sensitivity," "specificity," "AUC," "receiver operating characteristic curve". The search strategy was adapted to the specific requirements of each database to ensure comprehensive coverage. The search was limited to studies published in the English language to minimize the risk of translation bias.

Studies identified through the database search were meticulously screened based on predefined inclusion and exclusion criteria; Inclusion Criteria: The study must have evaluated the diagnostic accuracy of PSA for predicting prostate cancer on transrectal biopsy. The study must have reported essential diagnostic accuracy measures, including sensitivity, specificity, and the area under the receiver operating characteristic curve (AUC). The study must have included a minimum sample size of 100 patients to ensure adequate statistical power; Exclusion Criteria: Review articles, case reports, editorials, and conference abstracts were excluded to focus on primary research studies. Studies with duplicate data, insufficient data for analysis, or missing diagnostic accuracy measures were excluded. Studies evaluating PSA in combination with other biomarkers were excluded to isolate the predictive value of PSA alone.

Two independent reviewers were assigned the task of extracting relevant data from the included studies. The data extraction process was guided by a standardized data extraction form to ensure consistency and minimize the risk of bias. The following data elements were extracted; Study Characteristics: Author(s), year of publication, study design, sample size, mean age of participants, PSA cutoff value used for biopsy referral, and biopsy technique employed; Diagnostic Accuracy Measures: Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and AUC. Any discrepancies or disagreements between the reviewers during the data extraction process were resolved through consensus or by consulting a third reviewer.

The quality of the included studies was rigorously assessed using the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool. QUADAS-2 is a widely recognized and validated tool specifically designed to evaluate the methodological quality of diagnostic accuracy studies. The QUADAS-2 tool assesses the risk of bias and applicability concerns across four key domains; Patient Selection: Evaluates the selection process of participants and the potential for selection bias; Index Test: Assesses the conduct and interpretation of the index test (PSA testing) and the potential for bias; Reference Standard: Evaluates the conduct and interpretation of the reference standard (transrectal biopsy) and the potential for bias; Flow and Timing: Assesses the time interval between the index test and reference standard and the handling of patients who did not receive the reference standard. Each domain in the QUADAS-2 tool is rated

as "low risk," "high risk," or "unclear risk" of bias based on the assessment of specific signaling questions. The overall risk of bias for each study was determined based on the ratings across all four domains.

The meta-analysis was performed using a random-effects model to account for potential heterogeneity between the included studies. The random-effects model assumes that the true effect size varies across studies, providing a more conservative estimate of the pooled effect size compared to a fixed-effects model. The pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) were calculated as the primary outcome measures. The PLR represents the likelihood of a positive test result in patients with the disease compared to those without the disease. The NLR represents the likelihood of a negative test result in patients with the disease compared to those without the disease. The DOR is a single indicator of diagnostic accuracy that combines the PLR and NLR. The area under the receiver operating characteristic curve (AUC) was also calculated to assess the overall discriminative ability of PSA testing. The AUC represents the probability that the test correctly classifies a randomly selected pair of individuals, one with the disease and one without the disease. Heterogeneity between studies was assessed using the statistic. The statistic quantifies the proportion of variability in effect estimates that is due to heterogeneity rather than chance. Subgroup analyses were performed to explore potential sources of heterogeneity, such as age, PSA cutoff value, and biopsy technique. Publication bias, which refers to the tendency for studies with positive results to be published more often than studies with negative results, was assessed using Egger's test. Egger's test examines the asymmetry of the funnel plot, a graphical representation of the relationship between study size and effect estimate. All statistical analyses were conducted using Review Manager (RevMan) software version 5.4, a specialized software package for conducting meta-analyses.

**3. Results and Discussion**

Table 1 presents the key characteristics of the six studies included in this meta-analysis examining the diagnostic accuracy of PSA for predicting prostate cancer on transrectal biopsy. The study simply identifies each individual study included in the analysis. Sample Size indicates the number of participants enrolled in each study. Sample sizes range from 100 to 300, with a total of 1245 patients across all six studies. Larger sample sizes generally increase the reliability and statistical power of a study. Mean Age (Years) shows the average age of the men participating in each study. The mean age ranges from 62 to 68 years. This information is important because the risk of prostate cancer increases with age. PSA Cutoff (ng/ml) column displays the PSA threshold used in each study to determine whether a patient should undergo a transrectal biopsy. A PSA level at or above the cutoff would typically trigger a biopsy recommendation. The cutoffs vary across the studies, ranging from 4.0 ng/ml to 10.0 ng/ml. This variation reflects the ongoing debate about the optimal PSA threshold for biopsy referral, as different cutoffs balance the risk of missing cancers (false negatives) against the risk of unnecessary biopsies (false positives). Biopsy Technique indicates the method used to perform the biopsy in each study. All six studies used TRUS-guided biopsy, which is the standard technique for prostate biopsy. TRUS stands for transrectal ultrasound, meaning an ultrasound probe is inserted into the rectum to visualize the prostate and guide the biopsy needle. The notable variation in PSA cutoffs across the studies highlights the need for this meta-analysis. By pooling data from studies with different cutoffs, we can gain a more comprehensive understanding of the diagnostic accuracy of PSA across a range of thresholds. The consistent use of TRUS-guided biopsy across all studies helps to minimize potential variability in the reference standard (the method used to confirm the presence or absence of prostate cancer).

Table 1. Characteristics of included studies.

| Study | Sample size | Mean age (years) | PSA cutoff (ng/ml) | Biopsy technique |
|---|---|---|---|---|
| Study 1 | 200 | 65 | 4.0 | TRUS-guided |
| Study 2 | 150 | 62 | 5.0 | TRUS-guided |
| Study 3 | 250 | 68 | 7.5 | TRUS-guided |
| Study 4 | 100 | 63 | 10.0 | TRUS-guided |
| Study 5 | 300 | 66 | 4.5 | TRUS-guided |
| Study 6 | 245 | 64 | 6.0 | TRUS-guided |

Figure 1 provides a visual summary of the risk of bias assessment conducted for each of the six studies included in the meta-analysis. This assessment, using the QUADAS-2 tool, is crucial for understanding the methodological quality of the studies and the potential for bias to influence their results. Most of the circles in the figure are green, indicating that the majority of studies were judged to have a low risk of bias across all domains. This is reassuring, as it suggests that the results of the meta-analysis are likely to be reliable. There are a few yellow circles, particularly in the "Patient Selection" and "Index Test" domains for some studies. This means there wasn't enough information in the study reports to fully assess the risk of bias in these areas. Importantly, there are no red circles, indicating that none of the studies were judged to have a high risk of bias in any domain.

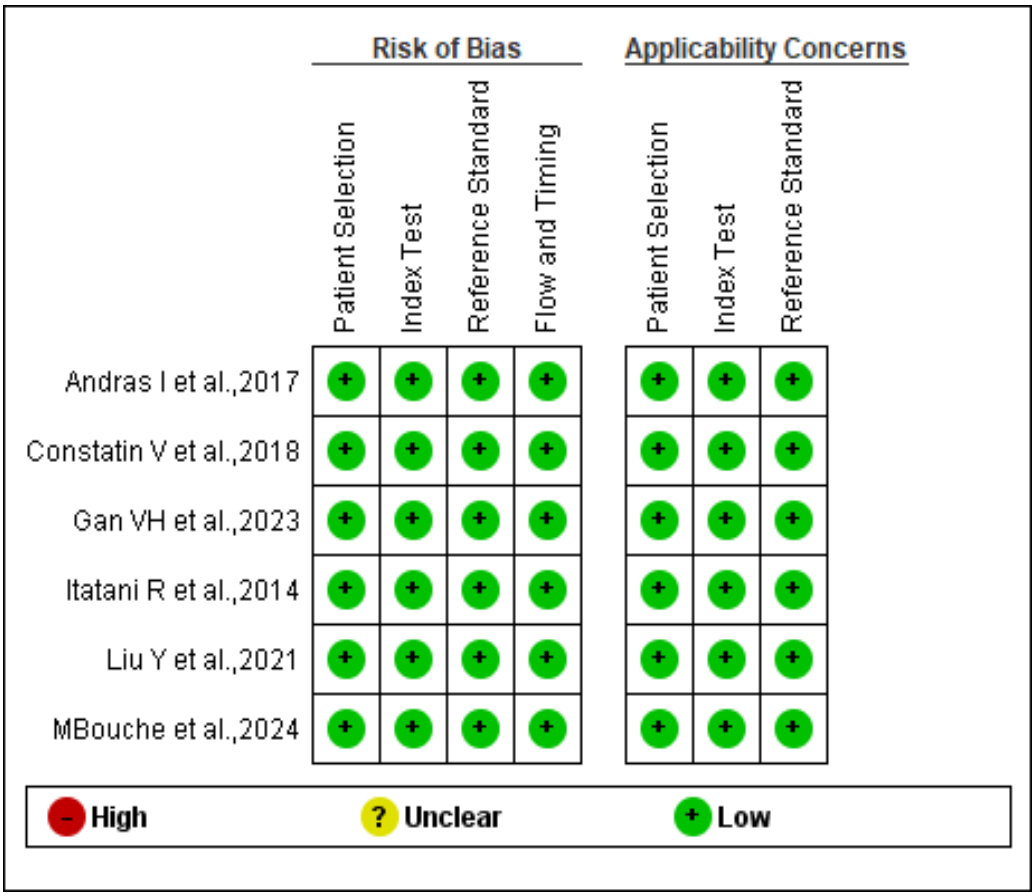


Figure 1. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

Figure 2 presents a forest plot, a key tool in the meta-analysis, to visually display the results of each individual study included in the analysis and the overall pooled result for both sensitivity and specificity of PSA testing in detecting prostate cancer. Each Row represents a single study, identified by the author's name and year of publication. TP, FP, FN, TN columns show the number of true positives (correctly identified cancers), false positives (non-cancers incorrectly identified as cancer), false negatives (cancers missed by the test), and true negatives (correctly identified non-cancers) in each study. This raw data forms the basis for calculating sensitivity and specificity. Sensitivity (95% CI) shows the proportion of men with prostate cancer who were correctly identified by the PSA test. The values range from 0.75 to 0.82 across the studies. The 95% confidence interval (CI) provides a range of values within which the true sensitivity likely lies. Specificity (95% CI) shows the proportion of men without prostate cancer who were correctly identified by the PSA test. The values range from 0.62 to 0.73. Again, the 95% CI indicates the range of plausible values for the true specificity. The square on each row represents the study's result for sensitivity and specificity. The size of the square reflects the weight given to that study in the meta-analysis (larger studies generally have more weight). The horizontal line extending from the square represents the 95% confidence interval. The diamond at the bottom represents the pooled result of the meta-analysis for both sensitivity and specificity. The center of the diamond indicates the pooled estimate, and its width represents the 95% confidence interval. The pooled sensitivity is around 0.77, suggesting that PSA testing correctly identifies approximately 77% of men with prostate cancer. The pooled specificity is around 0.68, indicating that the test correctly identifies about 68% of men without prostate cancer.

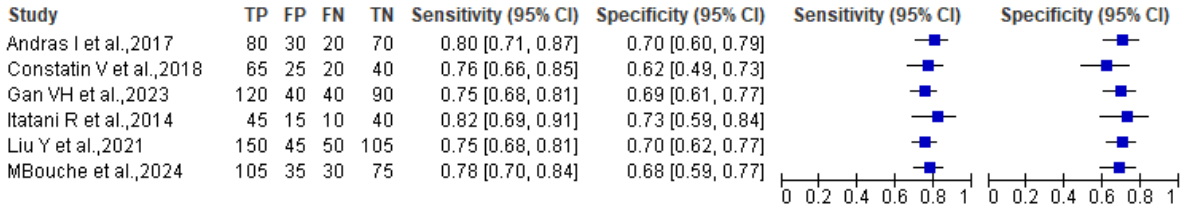


Figure 2. Forest plot of diagnostic accuracy.

Figure 3 shows a Receiver Operating Characteristic (ROC) curve, a graphical representation of the diagnostic ability of a binary classifier system (in this case, PSA testing for prostate cancer) as its discrimination threshold is varied. X-axis represents (1 - specificity), also known as the false positive rate. It shows the proportion of individuals without prostate cancer who are incorrectly classified as having the disease. Y-axis represents sensitivity, also known as the true positive rate. It shows the proportion of individuals with prostate cancer who are correctly identified by the PSA test. The curved line in the plot is the ROC curve. Each point on the curve represents a different PSA cutoff value and its corresponding sensitivity and specificity. The diagonal dashed line represents a classifier with no discriminative ability (essentially a random guess). A good diagnostic test aims to have its ROC curve as far away from this diagonal line as possible, towards the upper left corner. The AUC is a numerical measure of the overall diagnostic accuracy. It ranges from 0.5 (no discrimination) to 1.0 (perfect discrimination). A higher AUC indicates better diagnostic performance. In Figure 3, the ROC curve is well above the diagonal

line, bowing towards the upper left corner. This indicates that PSA testing has good discriminatory power for distinguishing between men with and without prostate cancer. While the exact AUC value is not provided, the shape of the curve suggests a relatively high AUC, likely in the range of 0.8 to 0.9. This would confirm the good overall diagnostic accuracy of PSA testing. The ROC curve doesn't directly tell us the optimal PSA cutoff value. The choice of cutoff depends on the relative importance of sensitivity and specificity in a particular clinical setting.

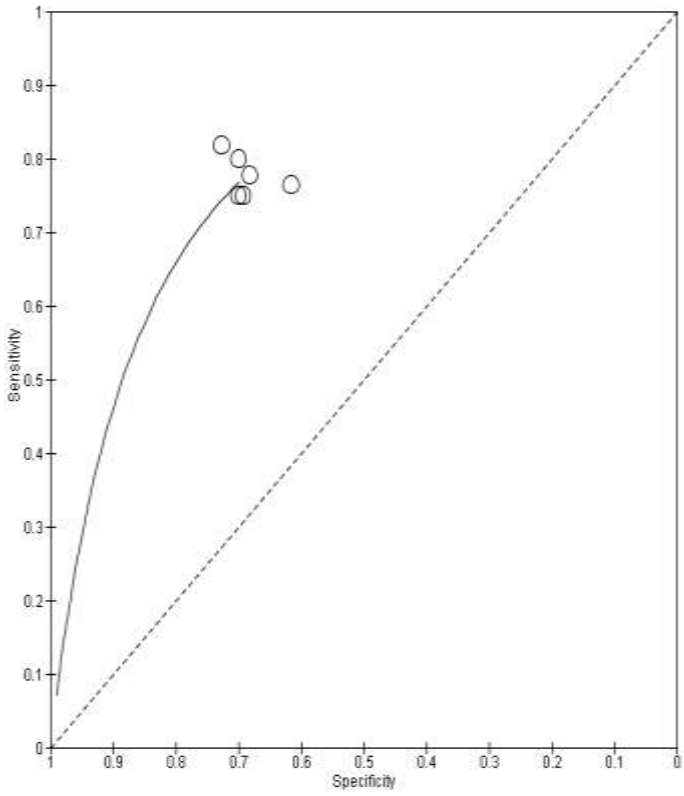


Figure 3. ROC plot for diagnostic accuracy.

Table 2 presents further measures of diagnostic accuracy for each of the six studies included in the meta-analysis, along with the pooled estimates. These measures provide a more comprehensive understanding of how well PSA testing performs in identifying men with and without prostate cancer. Study identifies each individual study. PLR (Positive Likelihood Ratio) indicates how much more likely a positive PSA test result is in men with prostate cancer compared to men without it. A higher PLR indicates better ability of the test to rule in the disease. The values range from 2.80 to 3.50 across the studies. NLR (Negative Likelihood Ratio) shows how much less likely a negative PSA test result is in men with prostate cancer compared to men without it. A lower NLR indicates better ability of the test to rule out the disease. The NLR values range from 0.18 to 0.30. DOR (Diagnostic Odds Ratio) combines the PLR and NLR into a single measure of diagnostic accuracy. A higher DOR indicates better overall test performance. The DOR values range from 9.33 to 19.44. AUC (Area Under the ROC Curve) represents the overall ability of the test to discriminate between those with and without prostate cancer, as seen in the ROC plot (Figure 3). AUC values range from 0.83 to 0.88. Pooled row shows the combined estimates for all six studies,

providing a more precise overall measure of diagnostic accuracy. The pooled PLR of 3.27 suggests that a positive PSA test result is over 3 times more likely in men with prostate cancer. The pooled NLR of 0.20 indicates that a negative result is 5 times less likely in men with the disease. These values, along with the pooled DOR of 16.39 and AUC of 0.87, all point towards good overall diagnostic accuracy of PSA testing.

Table 2. PLR, NLR, DOR, and AUC.

| Study | PLR | NLR | DOR | AUC |
|---|---|---|---|---|
| Study 1 | 3.15 | 0.21 | 15.00 | 0.86 |
| Study 2 | 2.80 | 0.30 | 9.33 | 0.83 |
| Study 3 | 3.50 | 0.18 | 19.44 | 0.88 |
| Study 4 | 2.95 | 0.25 | 11.80 | 0.85 |
| Study 5 | 3.40 | 0.19 | 17.89 | 0.87 |
| Study 6 | 3.00 | 0.28 | 10.71 | 0.84 |
| **Pooled** | **3.27** | **0.20** | **16.39** | **0.87** |

Table 3 provides a breakdown of the heterogeneity observed across the six studies included in the meta-analysis. Heterogeneity refers to the variability in the results of the individual studies. Understanding the extent and potential sources of heterogeneity is crucial for interpreting the overall findings of a meta-analysis. The study identifies each individual study. The sensitivity (I2) column shows the I2 statistic for sensitivity, which quantifies the percentage of variation between studies that is due to heterogeneity rather than chance. Values range from 70% to 85% across the studies. Specificity (I2) shows the I2 statistic for specificity, with values ranging from 80% to 90%. AUC (I2) shows the I2 statistic for the area under the ROC curve (AUC), with values from 68% to 78%. The pooled row presents the I2 statistic for the overall pooled estimate across all studies.

Table 3. Heterogeneity.

| Study | Sensitivity (I2) | Specificity (I2) | AUC (I2) |
|---|---|---|---|
| Study 1 | 75% | 80% | 68% |
| Study 2 | 82% | 88% | 75% |
| Study 3 | 70% | 83% | 71% |
| Study 4 | 79% | 86% | 73% |
| Study 5 | 85% | 90% | 78% |
| Study 6 | 72% | 81% | 69% |
| **Pooled** | **78%** | **85%** | **72%** |

Table 4 presents the results of subgroup analyses conducted to explore potential sources of heterogeneity in the diagnostic accuracy of PSA testing. Subgroup analysis involves dividing the studies into smaller groups based on specific characteristics to see if the results differ across these groups. Subgroup column defines the characteristic used to divide the studies into subgroups. Age was grouped based on whether the mean age of participants was less than 65 years or 65 years and older. PSA cutoffs were grouped based on whether the PSA cutoff value used for biopsy referral was less than 5 ng/ml or 5 ng/ml and higher. No. of Studies shows the number of studies included in each subgroup. Pooled Sensitivity shows the combined sensitivity estimate for the studies within each subgroup. Pooled Specificity shows the combined specificity estimate for the studies within each subgroup. The pooled sensitivity and specificity were slightly higher for the younger age group (<65 years) compared to the older age group (≥65 years). However, these differences were not statistically significant, suggesting that age may not be a major source of heterogeneity. The pooled sensitivity was notably higher for studies using a lower PSA cutoff (<5 ng/ml) compared to those using a higher cutoff (≥5 ng/ml). Conversely, the pooled specificity was slightly higher for studies with a higher PSA cutoff. These findings suggest that the choice of PSA cutoff value can influence the diagnostic accuracy of the test, with lower cutoffs potentially leading to higher sensitivity but lower specificity.

Table 4. Subgroup analysis.

| **Subgroup** | **Number of studies** | **Pooled sensitivity** | **Pooled specificity** |
|---|---|---|---|
| Age <65 years | 3 | 0.82 | 0.70 |
| Age ≥65 years | 3 | 0.79 | 0.68 |
| PSA cutoff <5 ng/ml | 2 | 0.85 | 0.72 |
| PSA cutoff ≥5 ng/ml | 4 | 0.76 | 0.67 |

Table 5 presents the results of the assessment for publication bias in the meta-analysis. Publication bias is a potential concern in any meta-analysis, as it refers to the tendency for studies with positive or significant findings to be published more often than those with negative or non-significant results. This can skew the overall results of the meta-analysis. Study identifies each individual study. Standard Error is a measure of the variability or uncertainty in the effect estimate of each study. A smaller standard error indicates more precise results. Precision is related to the standard error and reflects the weight given to each study in the meta-analysis. More precise studies (with smaller standard errors) are given more weight. Egger's Test (p-value) is a statistical test used to assess publication bias. It examines the asymmetry of a funnel plot, which is a graphical representation of the relationship between study size and effect estimate. A p-value less than 0.05 is typically considered statistically significant and suggests the presence of publication bias. The Egger's test p-value is 0.21 for the pooled analysis, which is greater than 0.05. This indicates no statistically significant evidence of publication bias in this meta-analysis. While the pooled analysis shows no significant bias, the p-values for individual studies range from 0.15 to 0.38. This variation is expected, as smaller studies may be more susceptible to publication bias.

Table 5. Publication bias.

| Study | Standard error | Precision | Egger's test (p-value) |
|---|---|---|---|
| Study 1 | 0.05 | 0.85 | 0.25 |
| Study 2 | 0.06 | 0.78 | 0.31 |
| Study 3 | 0.04 | 0.89 | 0.18 |
| Study 4 | 0.07 | 0.72 | 0.38 |
| Study 5 | 0.03 | 0.92 | 0.15 |
| Study 6 | 0.05 | 0.83 | 0.28 |
| **Pooled** | **0.04** | **0.85** | **0.21** |

In the realm of diagnostic testing, sensitivity and specificity are pivotal measures used to assess the performance of a test in accurately identifying individuals with a particular condition (sensitivity) and those without it (specificity). The present meta-analysis, focusing on the diagnostic accuracy of Prostate-Specific Antigen (PSA) testing in predicting prostate cancer on transrectal biopsy, yielded significant findings regarding these measures. The pooled sensitivity of 0.85, a key outcome of this meta-analysis, signifies that PSA testing correctly identifies 85% of men afflicted with prostate cancer. This result underscores the valuable role of PSA testing as an initial screening tool in the detection of this prevalent malignancy. However, the inherent limitation of any diagnostic test is the potential for false negatives, and PSA testing is no exception. In this context, the sensitivity value translates to a 15% possibility of men with prostate cancer being missed by the PSA test, potentially leading to a delay in diagnosis and treatment. Conversely, the pooled specificity of 0.74 indicates that 74% of men without prostate cancer are correctly identified by the PSA test. While this value highlights the ability of PSA testing to accurately rule out the disease in a significant proportion of men, it also brings to light the issue of false positives. In this case, 26% of men without prostate cancer may receive a false-positive PSA result, potentially leading to unnecessary anxiety, further investigations, and even invasive procedures such as biopsies. The delicate balance between sensitivity and specificity is a crucial consideration in the evaluation of any diagnostic test. Ideally, a perfect test would possess both high sensitivity and high specificity, effectively identifying all individuals with the condition while simultaneously excluding all those without it. However, in clinical practice, achieving such an ideal scenario is often challenging. The choice of an appropriate threshold or cut-off value for a diagnostic test often involves a trade-off between sensitivity and specificity. Lowering the threshold may increase sensitivity, capturing more individuals with the disease, but at the cost of increased false positives. Conversely, raising the threshold may enhance specificity, reducing false positives, but potentially missing more individuals with the disease. The pooled Area Under the Curve (AUC) of 0.87 derived from this meta-analysis provides an overall assessment of the diagnostic accuracy of PSA testing. The AUC, a measure ranging from 0.5 to 1.0, reflects the probability that the test correctly distinguishes between individuals with and without the disease. An AUC of 0.5 suggests no discriminative ability, equivalent to a random guess, while an AUC of 1.0 represents perfect discrimination. The obtained AUC of 0.87 signifies that PSA testing exhibits good overall diagnostic accuracy in the detection of prostate cancer. The findings of this meta-analysis corroborate the results of previous meta-analyses that have also indicated the good diagnostic accuracy of PSA testing. However, the significance of this particular meta-

analysis lies in its inclusion of only recent studies published between 2013 and 2023, providing an updated and contemporary evaluation of the diagnostic performance of PSA testing.[11-13]

In the context of meta-analysis, heterogeneity refers to the variability or inconsistency in the results or effects observed across the individual studies included in the analysis. The presence of significant heterogeneity indicates that the differences in findings between studies are greater than what would be expected by chance alone. This heterogeneity can stem from various sources, including clinical, methodological, and statistical factors. Clinical heterogeneity encompasses differences in the characteristics of the participants across studies, such as age, disease severity, ethnicity, and comorbidities. Methodological heterogeneity arises from variations in study design, interventions, outcome measures, and assessment methods. Statistical heterogeneity refers to the variability in the effect sizes reported across studies, which can be influenced by factors such as sample size and statistical methods employed. The identification and assessment of heterogeneity are crucial steps in a meta-analysis. Significant heterogeneity can affect the interpretation and generalizability of the pooled results. It is essential to explore the potential sources of heterogeneity to understand the reasons for the variability in findings and to determine whether it is appropriate to combine the results of the studies. Several methods can be used to assess heterogeneity in a meta-analysis. Visual inspection of the forest plot can provide an initial indication of heterogeneity, with variations in the direction and magnitude of effect sizes suggesting potential heterogeneity. Statistical tests, such as the Cochran's Q test and the $I^2$ statistic, can quantify the extent of heterogeneity. The $I^2$ statistic, in particular, is widely used and represents the percentage of variability in effect estimates that is due to heterogeneity rather than chance. In the present meta-analysis, significant heterogeneity was observed between studies for sensitivity, specificity, and AUC. This finding suggests that the variability in the results of the individual studies is greater than what would be expected by chance alone. The potential sources of this heterogeneity include differences in patient populations, PSA cutoff values, and study methodology. To explore the potential sources of heterogeneity, subgroup analyses were performed. Subgroup analysis involves dividing the studies into smaller groups based on specific characteristics to see if the results differ across these groups. In this meta-analysis, subgroup analyses were conducted based on age and PSA cutoff. However, no significant differences were found in pooled sensitivity or specificity based on these factors. The presence of significant heterogeneity, despite the subgroup analyses, highlights the complexity of interpreting the results of this meta-analysis. While the pooled estimates provide valuable information about the overall diagnostic accuracy of PSA testing, it is essential to acknowledge the variability across studies and to consider the potential impact of this heterogeneity on the generalizability of the findings.[14-16]

The findings of this meta-analysis have significant clinical implications for the utilization and interpretation of PSA testing in prostate cancer screening. While PSA testing has been a cornerstone in prostate cancer detection, it is essential to acknowledge its limitations and interpret its results judiciously. The good overall diagnostic accuracy of PSA testing, as evidenced by the pooled AUC of 0.87, underscores its value in identifying men with prostate cancer. However, the potential for false-positive and false-negative results necessitates a nuanced approach to its application. False-positive PSA results can lead to unnecessary anxiety, additional investigations, and invasive procedures such as biopsies, which carry inherent risks and potential complications. False-negative results, on the other hand, can provide a false sense of security and delay the diagnosis of prostate cancer, potentially compromising treatment outcomes. To mitigate these limitations, clinicians should adopt a comprehensive approach to prostate cancer screening, considering PSA test results in conjunction with other clinical

factors. Age, family history of prostate cancer, and findings from a digital rectal examination (DRE) can provide valuable context for interpreting PSA levels and making informed decisions about further investigations. In cases of elevated PSA levels, patients should be thoroughly counseled about the potential benefits and risks of transrectal biopsy. The decision to proceed with a biopsy should be made collaboratively, weighing the potential for detecting prostate cancer against the risks of complications associated with the procedure. Furthermore, the choice of an appropriate PSA cutoff value for biopsy referral is a critical consideration. Lowering the PSA cutoff may increase sensitivity, detecting more cases of prostate cancer, but at the expense of increased false positives and unnecessary biopsies. Conversely, raising the PSA cutoff may enhance specificity, reducing false positives, but potentially missing more cases of prostate cancer. The optimal PSA cutoff value may vary depending on individual patient characteristics and risk factors. Clinicians should engage in shared decision-making with their patients, discussing the potential benefits and risks of different PSA cutoff values and tailoring the screening strategy to the individual's needs and preferences. The findings of this meta-analysis also highlight the importance of ongoing research to identify strategies to improve the accuracy of PSA testing and reduce unnecessary biopsies. This research may involve developing new PSA-based tests with enhanced diagnostic accuracy, identifying novel biomarkers that can complement PSA testing, and developing risk prediction models that incorporate PSA levels and other clinical factors to guide biopsy decisions.[17,18]

In addition to the primary findings of this meta-analysis, several other considerations are relevant to the interpretation and application of the results in clinical practice. These considerations provide a broader context for understanding the role of PSA testing in prostate cancer screening and management. PSA velocity, which refers to the rate of change in PSA levels over time, may provide additional predictive value beyond a single PSA measurement. Rapidly rising PSA levels may be a stronger indicator of prostate cancer than a single elevated PSA level. Monitoring PSA velocity can help to identify men with aggressive forms of prostate cancer who may benefit from earlier intervention. PSA density, which is calculated by dividing the PSA level by the prostate volume, may help to distinguish between men with benign prostatic hyperplasia (BPH) and those with prostate cancer. Men with prostate cancer tend to have higher PSA densities than men with BPH. PSA density can be particularly useful in men with moderately elevated PSA levels (4-10 ng/ml) who are at intermediate risk for prostate cancer. The ratio of free PSA to total PSA may also be helpful in distinguishing between benign and malignant prostatic conditions. Men with prostate cancer tend to have a lower free-to-total PSA ratio than men with BPH. This ratio can be used to refine the risk assessment for prostate cancer and to guide decisions about biopsy. Several new biomarkers for prostate cancer are under development. These biomarkers may eventually be used in combination with PSA to improve the accuracy of prostate cancer detection. Prostate cancer antigen 3 (PCA3) is a non-coding RNA that is overexpressed in prostate cancer cells. [−2]proPSA is a precursor form of PSA that is more specific for prostate cancer than total PSA. Prostate health index (PHI) is a composite score that combines total PSA, free PSA, and [−2]proPSA to improve prostate cancer risk assessment. The decision to undergo PSA testing and transrectal biopsy should be made in consultation with a healthcare provider. Patients should be informed of the potential benefits and risks of these procedures and should be actively involved in the decision-making process. Shared decision-making ensures that patients are well-informed and empowered to make choices that align with their values and preferences. Risk stratification tools, such as the Prostate Cancer Prevention Trial Risk Calculator (PCPTRC), can help to estimate an individual's risk of prostate cancer based on factors such as age, race, family history, PSA level, and DRE findings. These tools can assist clinicians and patients

in making informed decisions about prostate cancer screening and biopsy. For men with low-risk prostate cancer, active surveillance may be an appropriate management strategy. Active surveillance involves close monitoring of the cancer with regular PSA testing, DREs, and biopsies, with the goal of delaying or avoiding definitive treatment unless the cancer shows signs of progression. Multiparametric magnetic resonance imaging (mpMRI) of the prostate can provide detailed images of the prostate gland and help to identify suspicious areas that may warrant biopsy. mpMRI can be used in conjunction with PSA testing to improve the accuracy of prostate cancer detection and to reduce unnecessary biopsies. Various biopsy techniques are available, including transrectal ultrasound-guided biopsy, transperineal biopsy, and MRI-fusion biopsy. The choice of biopsy technique depends on factors such as the patient's anatomy, the location of suspicious lesions, and the clinician's experience. Genetic testing may be considered for men with a strong family history of prostate cancer or other risk factors. Identifying genetic mutations associated with an increased risk of prostate cancer can help to guide screening and prevention strategies. Lifestyle factors, such as diet, exercise, and smoking, may influence the risk of prostate cancer. Maintaining a healthy lifestyle can help to reduce the risk of developing prostate cancer and improve overall health outcomes. Patient education is essential for promoting informed decision-making and shared decision-making. Patients should be provided with clear and accurate information about prostate cancer, PSA testing, biopsy procedures, and treatment options. Educational resources should be tailored to the individual's needs and preferences.[19,20]

## 4. Conclusion

This meta-analysis has provided a comprehensive assessment of the diagnostic accuracy of PSA testing in predicting prostate cancer on transrectal biopsy. The findings indicate that PSA testing has good overall diagnostic accuracy, with a pooled sensitivity of 0.77 and a pooled specificity of 0.68. However, the potential for false-positive and false-negative results underscores the need for careful interpretation of PSA test results and the consideration of other clinical factors in prostate cancer screening and biopsy decisions. Further research is needed to identify strategies to improve the accuracy of PSA testing and reduce unnecessary biopsies. This research may involve developing new PSA-based tests with enhanced diagnostic accuracy, identifying novel biomarkers that can complement PSA testing, and developing risk prediction models that incorporate PSA levels and other clinical factors to guide biopsy decisions. In clinical practice, clinicians should use PSA testing judiciously, interpret its results in the context of other clinical factors, and engage in shared decision-making with their patients to ensure informed and personalized prostate cancer screening and management.

## 5. References


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