Abstract

Importance Multiple strategies integrating magnetic resonance imaging (MRI) and clinical data have been proposed to determine the need for a prostate biopsy in men with suspected clinically significant prostate cancer (csPCa) (Gleason score ≥3 + 4). However, inconsistencies across different strategies create challenges for drawing a definitive conclusion.

Objective To determine the optimal prostate biopsy decision-making strategy for avoiding unnecessary biopsies and minimizing the risk of missing csPCa by combining MRI Prostate Imaging Reporting & Data System (PI-RADS) and clinical data.

Data Sources PubMed, Ovid MEDLINE, Embase, Web of Science, and Cochrane Library from inception to July 1, 2022.

Study Selection English-language studies that evaluated men with suspected but not confirmed csPCa who underwent MRI PI-RADS followed by prostate biopsy were included. Each study had proposed a biopsy plan by combining PI-RADS and clinical data.

Data Extraction and Synthesis Studies were independently assessed for eligibility for inclusion. Quality of studies was appraised using the Quality Assessment of Diagnostic Accuracy Studies 2 tool and the Newcastle-Ottawa Scale. Mixed-effects meta-analyses and meta-regression models with multimodel inference were performed. Reporting of this study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.

Main Outcomes and Measures Independent risk factors of csPCa were determined by performing meta-regression between the rate of csPCa and PI-RADS and clinical parameters. Yields of different biopsy strategies were assessed by performing diagnostic meta-analysis.

Results The analyses included 72 studies comprising 36,366 patients. Univariable meta-regression showed that PI-RADS 4 (β-coefficient [SE], 7.82 [3.85]; P = .045) and PI-RADS 5 (β-coefficient [SE], 23.18 [4.46]; P < .001) lesions, but not PI-RADS 3 lesions (β-coefficient [SE], −4.08 [3.06]; P = .19), were significantly associated with a higher risk of csPCa. When considered jointly in a multivariable model, prostate-specific antigen density (PSAD) was the only clinical variable significantly associated with csPCa (β-coefficient [SE], 15.50 [5.14]; P < .001) besides PI-RADS 5 (β-coefficient [SE], 9.19 [3.33]; P < .001). Avoiding biopsy in patients with lesions with PI-RADS category 3 or less and PSAD less than 0.10 (vs <0.15) ng/mL^2 could reduce unnecessary biopsies by 30% or 48%, respectively, while maintaining a sensitivity of 97% or 95%.

Meaning These findings suggest that prostate biopsies may not be necessary for patients with equivocal or negative magnetic resonance imaging results and low PSAD.

Key Points

Question What is the optimal approach to integrating prostate magnetic resonance imaging and clinical parameters for identifying patients requiring prostate biopsy while avoiding unnecessary procedures and minimizing the risk of missing clinically significant prostate cancer (csPCa)?

Findings In this systematic review and meta-analysis of 36,366 patients, Prostate Imaging Reporting & Data System (PI-RADS) category 4 and 5 lesions and prostate-specific antigen density (PSAD) were the only independent imaging and clinical factors associated with csPCa. The strategy to forego biopsy in men lesions with PI-RADS category 3 or less and PSAD less than 0.10 or less than 0.15 ng/mL^2 could reduce unnecessary biopsies by 30% or 48%, respectively, while maintaining a sensitivity of 97% or 95%.

Meaning These findings suggest that prostate biopsies may not be necessary for patients with equivocal or negative magnetic resonance imaging results and low PSAD.
CONCLUSIONS AND RELEVANCE  These findings suggest that in patients with suspected csPCa, patient-tailored prostate biopsy decisions based on PI-RADS and PSAD could prevent unnecessary procedures while maintaining high sensitivity.

Introduction

Prostate cancer is the second most common cancer in men worldwide, with an estimated incidence of 1.4 million in 2020. Several guidelines recommend magnetic resonance imaging (MRI) as a tool to identify clinically significant prostate cancer (csPCa) in all individuals with suspected prostate cancer. Thereby, biparametric or multiparametric MRI is routinely performed in accordance with the Prostate Imaging Reporting & Data System (PI-RADS) in men with suspected csPCa, including biopsy-naive patients or patients with previously negative biopsy results. Patients with focal lesions scored as PI-RADS category 4 or 5 are considered to have a high likelihood of csPCa and should undergo an image-guided targeted biopsy. However, the published literature regarding the association of PI-RADS 3 or less lesions and csPCa is controversial, and there is no consensus on which patients with equivocal (PI-RADS category 3) or negative (PI-RADS categories 1, 2, or no focal lesion) prostate MRI findings could avoid biopsy.

At most institutions, men with suspected csPCa and negative or equivocal MRI results are still referred for systematic prostate biopsy due to the limitation of MRI PI-RADS in excluding csPCa with an overall sensitivity of 85%, consistent with multiple guidelines such as the American Urological Association, European Association of Urology, European Society for Radiotherapy and Oncology, and National Comprehensive Cancer Network. The major challenge of this approach is the low yield of systematic biopsy in this patient cohort and its associated morbidity and health care costs. As such, ancillary clinical data have been proposed to complement MRI to minimize the number of unnecessary biopsies. This concept has been recently expanded by numerous studies, and several MRI-based risk models and strategies have been developed to guide decisions on prostate biopsy. However, it has been challenging to integrate the proposed approaches into clinical practice owing to considerable inconsistencies among them. Previously performed studies were predominantly single institutional, enrolled heterogeneous patient populations, and incorporated different sets of clinical parameters with PI-RADS. The ability to extrapolate broader conclusions from these studies is therefore limited. The purpose of this study was to determine optimal prostate biopsy decision-making by combining MRI PI-RADS with clinical data to avoid unnecessary prostate biopsies while minimizing the risk of missed csPCa.

Methods

Design

This systematic review and meta-analysis was performed and reported in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for searching, diagnostic test accuracy, and harms outcomes.

Literature Search and Studies Selection

A comprehensive search was conducted in PubMed, Ovid MEDLINE, Web of Science, Embase, and the Cochrane Library from inception to July 1, 2022. Bibliographies of the relevant review articles were manually examined for possible inclusion of additional eligible studies. Search terms are presented in eMethods 1 in Supplement 1.
Eligibility criteria were defined based on the population, intervention, comparison, and outcome approach. Studies were considered eligible for inclusion when meeting all of the following criteria: (1) included patients with suspected csPCa, but not patients on active surveillance or patients with previously confirmed or treated prostate cancer; (2) all patients underwent prebiopsy prostate MRI with PI-RADS assessment; (3) all patients had at least 1 relevant clinical parameter available, such as prebiopsy prostate-specific antigen (PSA); (4) all patients underwent systematic and targeted (for PI-RADS ≥3 lesions) transrectal and/or transperineal prostate biopsy; (5) all patients had csPCa defined based on the International Society of Urological Pathology guideline (ie, Gleason score ≥3+4); and (6) the study combined PI-RADS and clinical parameters (eg, PSA) to propose a biopsy decision plan. Exclusion criteria included studies (1) involving nonhuman subjects, (2) not published in English, or (3) not published as an original article. Eligibility criteria details are presented in Methods 2 in Supplement 1.

After removing duplicates, 2 reviewers (A.H.M., a third-year radiology resident, and K.S.B., a fellowship-trained abdominal radiologist with 3 years of experience) independently screened all titles and abstracts in duplicate using Covidence software. The full text of articles that passed initial screening was examined by the same reviewers using a predefined stepwise protocol (eMethods 3 in Supplement 1). Disagreements were resolved by consensus. The interrater agreement between reviewers for the binary decision of inclusion or exclusion was assessed using 200 randomly selected abstracts and showed a strong level of agreement with a Cohen κ of 0.93.

**Data Extraction and Quality Assessment**

Data extraction and quality assessment were conducted by a reviewer (A.H.M.) using standardized extraction forms. Data regarding study design (author, year of publication, number of patients, prospective vs retrospective, consecutive vs nonconsecutive, and inclusion and exclusion criteria), patient characteristics (age, body mass index, race and ethnicity according to their respective study definitions [included because of their potential association with the rate of csPCa], family history of PCa, positive digital rectal examination findings, and prior prostate biopsy), prostate MRI (Tesla, multiparametric vs biparametric), PI-RADS, prostate volume, transitional vs peripheral zone index lesion, clinical parameters (total PSA, free PSA, free/total PSA, and PSA density [PSAD]), biopsy (biopsy method, pathology assessment method, and time interval between MRI and biopsy), and rate of csPCa were recorded.

The quality assessment was conducted using the Quality Assessment of Diagnostic Accuracy Studies 2 tool and the Newcastle-Ottawa Scale. Both tools were modified in accordance with the research question. By combining these tools, studies were rated as having a low, moderate, or high risk of bias. Further details regarding the quality assessment are presented in eMethods 4 and 5, eTables 1 and 2, and eFigure 1 in Supplement 1.

**Statistical Analysis**

The meta-analysis was performed using R Studio, version 1.1.383 (R Project for Statistical Computing) using the meta, version 4.13-0 and metafor, version 2.4-0 packages. The pooled logit-transformed proportions of csPCa were calculated using a random-effects approach and generalized linear mixed-effects model via the metaprop function. Between-study heterogeneity was estimated using I² values with cutoffs of 25%, 50%, and 75% to distinguish low, moderate, and high heterogeneity, respectively. Potential publication bias was assessed using a funnel plot and Egger regression asymmetry test using the metabias function.

Univariable mixed-effects meta-regression was used to assess independent risk factors of csPCa using the metareg function. Multicollinearity of the factors associated with csPCa was evaluated using an intercorrelation matrix and addressed by combining and/or removing close-to-redundant factors with an absolute r greater than 0.6. Multivariable mixed-effects meta-regression was then performed using the multimodel inference that allows examination of all possible
combinations of risk factors and definition of the most important set of variables associated with csPCa (eMethods 6 in Supplement 1).94

Furthermore, we selected studies that assessed the yield of combining PI-RADS and PSAD by reporting patient-level data. The pooled sensitivity, negative predictive value (NPV), number needed to harm (NNH) for not performing a biopsy, and percentage of patients avoiding unnecessary biopsy were calculated using a generalized linear mixed-effects model.89,90 Unnecessary biopsy was defined as performing a biopsy in a patient without csPCa in retrospect. A 2-tailed \( P < .05 \) was considered significant.

Results

Study and Population Characteristics

The median patient age was 65.6 years (range, 61.3-69.3 years). Black race was reported for a median of 14% (range, 1%-29%) of all patients included in the analysis. Median total PSA and PSAD of the patients in the included studies were 7.8 ng/mL (range, 5.1-14.7 ng/mL) and 0.15 ng/mL² (range, 0.10-0.33 ng/mL²), respectively (to convert PSA levels to μg/L, multiply by 1.0). Most of the included patients were biopsy-naive (81%); the rest had a prior negative biopsy (18%) or prior nonsignificant Gleason score 3 + 3 PCa (<1%). A total of 72 studies including 36,366 patients with suspected csPCa who underwent prostate MRI and subsequent biopsy were included (Figure 1).10-81 Details of the included study and patient characteristics are summarized in Table 1 and eTables 3 to 5 in Supplement 1. Studies were published between 2016 and 2022. None of the included studies enrolled patients with prior csPCa. Among the 72 included studies, 19 solely included patients with low to moderate risk of csPCa (ie, PI-RADS 3 and/or transitional zone index lesion and/or total PSA <10 ng/mL).12,17,23,24,28-30,39,49-51,57,59,60,62,63,68,70,761 study solely included high-risk patients with PI-RADS 4 or greater,131 and the remaining 52 studies included all suspected patients regardless of the prostate MRI results or clinical parameters.10,11,13-16,18,19,21,22,25-27,31-38,40-48,52-56,58,61,64-67.
The most frequently used imaging was 3.0 T (92.6%) and multiparametric MRI (80.3%). Pooled percentages of included patients indicated that a median 27% (range, 0%-100%), 21% (range, 0%-100%), and 48% (range, 0%-100%) had a PI-RADS of 2 or less (including no focal lesion), PI-RADS 3, and PI-RADS 4 or more index lesion, respectively. Systematic and targeted (for PI-RADS ≥ 3 index lesions) transrectal or transperineal prostate biopsy was performed in all included patients. Rates of csPCa ranged from 5% to 80% with a median of 35%. The median rate of nonsignificant PCa was 15% (range, 3%-33%).

### Table 1. Patient and Study Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%) or median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients (72 studies[^10-81])</td>
<td>36 (366 patients)</td>
</tr>
<tr>
<td>No. of patients per study</td>
<td>351 (52-2512)</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
</tr>
<tr>
<td>Prospective</td>
<td>31 (43.1)</td>
</tr>
<tr>
<td>Consecutive enrollment</td>
<td>32 (44.4)</td>
</tr>
<tr>
<td>Not reported</td>
<td>9 (12.5)</td>
</tr>
<tr>
<td>Clinical parameters</td>
<td></td>
</tr>
<tr>
<td>Age (70 studies, [10-23,23-58,60-81] 35 949 patients), y</td>
<td>65.6 (61.3-69.3)</td>
</tr>
<tr>
<td>Total PSA (71 studies, [10-58,60-81] 36 211 patients), ng/mL</td>
<td>7.8 (5.1-14.7)</td>
</tr>
<tr>
<td>Free PSA (7 studies, [10,32,60,63,72,74,76] 2348 patients), ng/mL</td>
<td>1.3 (1.1-13.0)</td>
</tr>
<tr>
<td>Free/total PSA (15 studies, [10,16,18,24,31,36,49,68,61,63,68,72,75,76] 6038 patients), %</td>
<td>15 (13-19)</td>
</tr>
<tr>
<td>PSAD (54 studies, [10,13,15-21,23,25-30,32,35-38,40-43,45-47,49-51,54,55,57,58,60-65,67-78,80] 200 patients), ng/mL[^2]</td>
<td>0.15 (0.10-0.33)</td>
</tr>
<tr>
<td>BMI (9 studies, [13,17,18,24,31,39,49,79] 3946 patients)</td>
<td>24.7 (24.2-30.8)</td>
</tr>
<tr>
<td>Positive family history of PCa (16 studies, [12,24,26,38,44,46,49,52,56,62-64,72-74] 10 095 patients), %</td>
<td>17 (1-35)</td>
</tr>
<tr>
<td>Positive DRE (33 studies, [10,15,17,18,21-23,26,31-33,37,38,41,42,44-47,51-53,58,59,62-64,72-74,77,78,81] 19 129 patients), %</td>
<td>23 (7-68)</td>
</tr>
<tr>
<td>Black race (5 studies, [12,15,46,66,79] 1880 patients), %</td>
<td>14 (1-29)</td>
</tr>
<tr>
<td>Biopsy naive (59 studies, [10-14,17,18,21-26,28,29,31-33,37-34,45-63,65,67,70-74,76-81] 28 956 patients), %</td>
<td>81 (0-100)</td>
</tr>
<tr>
<td>Prior nonsignificant Gleason score 3 + 3 PCa (58 studies, [10-13,15,17,18,21-26,28,29,31,33-35,37-43,45-67,69-74,76-78] 30 620 patients), %</td>
<td>0 (0-32)</td>
</tr>
</tbody>
</table>

### MRI

<table>
<thead>
<tr>
<th>MRI Characteristic</th>
<th>No. (%) or median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total No. of patients (72 studies[^10-81])</td>
<td>34 351 patients[^b]</td>
</tr>
<tr>
<td>1.5 T</td>
<td>19 (27.9)</td>
</tr>
<tr>
<td>3.0 T</td>
<td>63 (92.6)</td>
</tr>
<tr>
<td>Sequence (71 studies[^10-61,63-71] 35 902 patients[^b])</td>
<td></td>
</tr>
<tr>
<td>Biparametric</td>
<td>16 (22.5)</td>
</tr>
<tr>
<td>Multiparametric</td>
<td>57 (80.3)</td>
</tr>
<tr>
<td>Prostate volume (58 studies[^10-12,15-18,20,21,23-29,31,32,34,35,37-48,50-55,57,58,60-63,65,66,68-78,80] 29 961 patients), mL</td>
<td>50.5 (28.7-66.0)</td>
</tr>
<tr>
<td>PI-RADS, index lesion (72 studies[^10-81] 36 366 patients), %[^c]</td>
<td></td>
</tr>
<tr>
<td>No focal lesion, 1, or 2</td>
<td>27 (0-100)</td>
</tr>
<tr>
<td>3</td>
<td>21 (0-100)</td>
</tr>
<tr>
<td>4</td>
<td>30 (0-58)</td>
</tr>
<tr>
<td>5</td>
<td>18 (0-42)</td>
</tr>
<tr>
<td>Location of index lesion (8 studies[^11,20,25,29,39,50,75,76] 3549 patients), %[^c]</td>
<td></td>
</tr>
<tr>
<td>Peripheral zone</td>
<td>44 (0-65)</td>
</tr>
<tr>
<td>Transitional zone</td>
<td>54 (19-100)</td>
</tr>
</tbody>
</table>

### Biopsy

<table>
<thead>
<tr>
<th>Biopsy Characteristic</th>
<th>No. (%) or median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>csPCa (72 studies[^10-81] 36 366 patients), %</td>
<td>35 (5-80)</td>
</tr>
<tr>
<td>Non-csPCa (62 studies[^11,12,14-19,21-28,31,37,39-47,51-54,56-81] 31 408 patients), %</td>
<td>15 (3-33)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index (measured as weight in kilograms divided by height in meters squared); csPCa, clinically significant prostate cancer; DRE, digital rectal examination; MRI, magnetic resonance imaging; PI-RADS, Prostate Imaging Reporting & Data System; PSA, prostate-specific antigen; PSAD, prostate-specific antigen density.

SI conversion factor: To convert PSA levels to μg/L, multiply by 1.0.

[^10-81]: Specified per row. Values in parentheses represent the full range of reported data across studies.
[^b]: Some studies used both a 1.5- and 3.0-T scanner and both bi- and multiparametric approaches.
[^c]: Pooled percentages were calculated using random- and mixed-effects meta-analysis and may not sum to 1.
Quality Assessment and Publication Bias

Eight studies (11%) were judged to have a moderate risk of bias. No potential source of bias was identified for the other 64 (89%) studies. Retrospective study design and concern regarding the selection domain (ie, studies only noted that patients with suspected csPCa were included rather than providing detailed inclusion and/or exclusion criteria) were the main sources of bias. Details of the quality assessment are presented in eTables 1 and 2 and eFigure 1 in Supplement 1. A funnel plot in which the P value of the weighted linear regression test was 0.65 demonstrated the absence of publication bias (eFigure 2 in Supplement 1).

Meta-Regression: Independent Determinants of csPCa

On univariable meta-regression, the following continuous or categorical variables were associated with a higher risk of csPCa (Figure 2; eFigures 3-5 in Supplement 1): age, years (β-coefficient [SE], 1.28 [0.31]; P < .001); total PSA (β-coefficient [SE], 1.18 [0.26]; P < .001); PSAD (β-coefficient [SE], 72.76 [16.57]; P < .001); PI-RADS 4 (β-coefficient [SE], 7.82 [3.85]; P = 0.045); and PI-RADS 5 (β-coefficient [SE], 23.18 [4.46]; P < .001). The following variables were associated with a lower risk of csPCa (Figure 2; eFigures 3-5 in Supplement 1): free/total PSA (β-coefficient [SE], −662.97 [253.14]; P = .02); prostate volume (β-coefficient [SE], −0.39 [0.08]; P < .001); and PI-RADS 2 or less, including no focal lesion (β-coefficient [SE], −8.19 [2.36]; P = .001). However, PI-RADS 3 was not associated with a lower risk of csPCa (β-coefficient [SE], −4.08 [3.06]; P = .19).

The intercorrelation matrix showed a significantly high level of correlation among total PSA (|r|>0.6; P < .001 for the correlation between PSA and PSAD, and |r|>0.6; P < .001 for the correlation between PSA and free/total PSA), free/total PSA (|r|>0.6; P < .001 for the correlation between free/total PSA and PSAD), PSAD (|r|>0.6; P < .001 for the correlation between PSAD and prostate specific antigen density).

Figure 2. Univariable Meta-Regression for the Association Between the Rate of Clinically Significant Prostate Cancer (csPCa) and Imaging and Clinical Parameters
volume), and prostate volume (eFigure 6 in Supplement 1). Moreover, a moderate level of correlation was noted between PI-RADS 2 or less and PI-RADS 4 (|r|>0.6; P < .001). To avoid multicollinearity, each multivariable model was built based on a distinct set of noncollinear variables (|r|<0.6). For instance, PSAD was chosen to use solely in the multivariable models as it contains all components of other clinical parameters, including total PSA and prostate volume.

On multivariable meta-regression with multimodel inference, the following variables showed the highest importance with a significant independent association with a higher risk of csPCa (PI-RADS 5: β-coefficient [SE], 9.19 [3.33]; PSAD: β-coefficient [SE], 15.50 [5.14]; both P < .001) (Figure 3). Limiting multivariable meta-regression to studies (1) with no risk of bias, (2) including all suspected patients regardless of the prostate MRI results or clinical parameters, and (3) only including biopsy-naive patients showed similar results with the same independent risk factors of csPCa (eTable 6 in Supplement 1).

**Diagnostic Meta-Analysis: Yield of Combining PI-RADS and PSAD**

In patients with PI-RADS 2 or less, including no focal lesions (7-11 studies including 1499-2970 patients), avoiding prostate biopsy if PSAD was less than 0.10 ng/mL² (vs <0.15 and <0.20 ng/mL²) showed sensitivity of 83% (vs 66% and 36%), NPV of 95% (vs 94% and 92%), NNH of 19 (vs 16 and 13), and avoidance of unnecessary biopsy in 39% (vs 67% and 89%) of men (by comparing performing biopsy in all suspected patients) (Table 2). Limiting to patients with PI-RADS of 3 (8-10 studies comprising 1386-1644 patients), avoiding prostate biopsy if PSAD was less than 0.10 ng/mL² (vs <0.15 and <0.20 ng/mL²) showed sensitivity of 85% (vs 70% and 44%), NPV of 93% (vs 90% and 87%), NNH of 15 (vs 10 and 8), and avoidance of unnecessary biopsy in 43% (vs 66% and 84%) of men (by comparing performing biopsy in all suspected patients) (Table 2).

Overall, avoiding prostate biopsy in patients with PI-RADS 3 or less and PSAD less than 0.10 ng/mL² (vs <0.15 and <0.20 ng/mL²) resulted in an NNH of 3 (vs 2 and 2) (Table 2). Similarly in patients with PI-RADS 4 or greater (6-7 studies comprising 2716-3114 patients), avoiding prostate biopsy even if PSAD was less than 0.10 ng/mL² (vs <0.15 and <0.20 ng/mL²) resulted in an NNH of 3 (vs 2 and 2) (Table 2).

To avoid multicollinearity, each model was built based on a distinct set of noncollinear variables. Multimodel inference analysis represents models and variables with the highest importance in estimating csPCa. Variables with a risk factor importance of 1 represent the highest significance. The horizontal blue line indicates the cutoff value of 0.8, differentiating between important and less important risk factors; PI-RADS, Prostate Imaging Reporting & Data System; and PSAD, prostate-specific antigen density.
Discussion

The aim of our meta-analysis exploring the independent risk factors of csPCa and assessing the added value of combining PI-RADS and clinical parameters was to improve biopsy decision-making for men with suspected csPCa. The findings of this analysis suggest that PI-RADS 4 and 5 lesions, but not PI-RADS 3 lesions, are significant imaging risk factors of csPCa. Among clinical parameters, only PSAD-related factors (i.e., total PSA and prostate volume) were found to be independent risk factors of csPCa when considered together with PI-RADS category. The strategy to forego biopsy in men with PI-RADS 3 or less and PSAD less than 0.10 ng/mL$^2$ or less than 0.15 ng/mL$^2$ would avoid 30% or 48% of unnecessary biopsies, respectively, while maintaining sensitivity of 97% or 95%.

The literature search yielded narrative review articles on MRI-based strategies in prostate cancer diagnosis. These articles discussed the variable diagnostic performance of the proposed strategies, with an overall area under the receiver operating characteristic curve of 0.64 to 0.93 for detecting csPCa. Our study was strengthened by implementing robust inclusion and exclusion criteria, minimizing verification bias since all included patients in our meta-analysis underwent prostate biopsy even after a negative prebiopsy MRI, performing a comprehensive meta-analysis and quality assessments, generating a simplified practical conclusion from a large number of studies, and having a lack of significant publication bias.

Many of the included studies in our meta-analysis combined MRI and clinical data by creating either (1) risk calculators using nomogram regression equations and/or machine learning models or (2) biopsy strategies using a stepwise approach. Despite the promising performance, the proposed approaches could not be integrated into clinical practice owing to several limitations. First, output of the risk calculators is on a sliding scale representing the likelihood of csPCa, which should be categorized into low vs high likelihood in order to identify patients requiring biopsy. However, the suggested risk threshold for performing a biopsy varied among studies and needs to be adjusted based on the net benefit trade-off between improving diagnostic accuracy and reducing unnecessary biopsies. Second, these models mostly require further external validation and recalibration to ensure their satisfactory performance prior to implementation in clinical practice. Deniell et al found that the overall net benefit of risk calculators ranged from not useful to harmful if used without recalibration. Third, variable sets of clinical parameters were deployed to develop models. Fourth, Table 2. Yield of Combining PI-RADS Categories and PSAD Using Different Cutoffs

<table>
<thead>
<tr>
<th>PSAD measure for avoiding biopsy, ng/mL$^2$</th>
<th>No. of studies (patients)</th>
<th>Sensitivity (95% CI), %</th>
<th>NPV (95% CI), %</th>
<th>NNH (95% CI)</th>
<th>Unnecessary biopsy avoided (95% CI), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>In patients with PI-RADS ≤2 index lesion (including no focal lesion)</td>
<td>&lt;0.10</td>
<td>8 (1724)</td>
<td>83 (69-91)</td>
<td>95 (91-97)</td>
<td>19 (11-33)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.15</td>
<td>11 (2970)</td>
<td>66 (45-83)</td>
<td>94 (88-97)</td>
<td>16 (9-30)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.20</td>
<td>7 (1499)</td>
<td>36 (28-46)</td>
<td>92 (88-95)</td>
<td>13 (8-21)</td>
</tr>
<tr>
<td>In patients with PI-RADS ≥3 index lesion</td>
<td>&lt;0.10</td>
<td>8 (1386)</td>
<td>85 (79-90)</td>
<td>93 (86-97)</td>
<td>15 (7-34)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.15</td>
<td>10 (1454)</td>
<td>70 (49-84)</td>
<td>90 (84-94)</td>
<td>10 (6-16)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.20</td>
<td>8 (1644)</td>
<td>44 (26-65)</td>
<td>87 (82-92)</td>
<td>8 (5-12)</td>
</tr>
<tr>
<td>In patients with PI-RADS ≥4 index lesion</td>
<td>&lt;0.10</td>
<td>6 (2733)</td>
<td>86 (81-90)</td>
<td>64 (59-69)</td>
<td>3 (2-3)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.15</td>
<td>7 (2716)</td>
<td>75 (52-89)</td>
<td>55 (49-60)</td>
<td>2 (2-2)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.20</td>
<td>7 (3114)</td>
<td>49 (38-60)</td>
<td>53 (43-63)</td>
<td>2 (2-3)</td>
</tr>
<tr>
<td>In patients with PI-RADS ≥3 index lesion (including no focal lesion)</td>
<td>&lt;0.10</td>
<td>6 (5288)</td>
<td>97 (95-98)</td>
<td>94 (89-96)</td>
<td>17 (9-27)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.15</td>
<td>7 (5225)</td>
<td>95 (90-98)</td>
<td>93 (87-97)</td>
<td>15 (8-29)</td>
</tr>
<tr>
<td></td>
<td>&lt;0.20</td>
<td>6 (5288)</td>
<td>87 (85-92)</td>
<td>90 (84-94)</td>
<td>10 (6-16)</td>
</tr>
</tbody>
</table>

Abbreviations: NNH, number needed to harm; NPV, negative predictive value; PI-RADS, Prostate Imaging Reporting & Data System; PSAD, prostate-specific antigen density.
given the growing number of risk calculators and biopsy strategies, it is challenging for clinicians to choose one over the others. Finally, studies showed a probable superiority of a combined MRI and PSAD strategy by comparing risk calculators in terms of reducing unnecessary biopsies without missing csPCa.15 Thereby, pooling results of previously published studies sheds light on the optimal approach of combining MRI and clinical data for prostate biopsy decision-making.

To date, the clinical importance of PI-RADS 3 or less lesions is conflicting, and it is uncertain whether patients with PI-RADS 3 or less or no focal lesions require a biopsy.7 At most institutions, men with suspected csPCa still undergo prostate biopsy even after negative MRI results.2-4,9 The Prospective Assessment of Image Registration in the Diagnosis of Prostate Cancer trial found that 15% of patients with negative MRI results had csPCa.97 In other studies, the range of csPCa in men with PI-RADS 3 and PI-RADS 1 or 2 lesions ranged from 3% to 46% and 0% to 17%, respectively.7,98,99 The observed variation could be due to several factors, including heterogeneous patient populations and suboptimal interobserver agreement of PI-RADS.100-102 Our results suggest that combining PI-RADS with PSAD would reduce the number of unnecessary biopsies and improve the diagnostic yield. Although the stepwise approach based on PI-RADS and PSAD has been used in some institutions to drive decision-making toward prostate biopsy, the current guidelines do not advise against biopsies in patients with a low PSAD and equivocal MRI findings given a lack of level 1 evidence. This meta-analysis provides evidence that could potentially influence the evolution of these guidelines.

Limitations
This analysis has some limitations. First, this study-level meta-analysis was based on published data rather than individual patient data; thus, we were unable to adjust our findings for patient-level confounders. Second, some clinical variables were assessed and reported by only a few studies, which limited our ability to investigate the importance of those factors, such as family history of csPCa, race and ethnicity, genomic analysis, PCA antigen 3 test, and other novel serum and urine biomarkers, in estimating csPCa. Third, regarding stepwise biopsy strategies, the published literature has mainly focused on the yield of combining PI-RADS with PSAD and/or total PSA; we did not have sufficient evidence-based literature on all other clinical parameters to perform a further diagnostic meta-analysis. Exploring other PSAD cutoff points and additional variables like age may have some added value in reducing unnecessary biopsies; however, the current lack of studies on these approaches limits our ability to conduct meta-analyses. Furthermore, the results of pooled analysis for the stepwise biopsy strategy combining PI-RADS with PSAD were driven by 6 to 11 studies comprising 1454 to 5288 patients. Fourth, several PSA-related analyses, such as the Four Kallikrein score,103 the Prostate Health Index,104 ConfirmMDx,105 and SelectMDx,106 have been proposed to guide prostate decision-making. Since these scores and indices have been developed by combining clinical factors, including total PSA, we did not include them separately in our model. Fifth, we observed high between-study heterogeneity in the rate of csPCa due to different patient populations, which was addressed by using random-effects models and performing meta-regression analyses. Sixth, non-English-language articles were excluded, which may have resulted in some studies being missed.

Conclusions
The need to identify men requiring a prostate biopsy remains a key issue in the diagnosis of PCA. Results of our systematic review and meta-analysis suggest that prostate biopsy might be avoided in men with negative or equivocal MRI results and low PSAD. Despite the high sensitivity, 3% to 5% of csPCa cases may still be missed with this approach. This concern can be addressed by future prospective studies using a lower threshold for PSAD and incorporating additional variables for further risk stratification. In addition, we can assess effective follow-up approaches after a decision
not to perform a biopsy is made, especially since this decision-making process would need to occur over a person's lifetime.

**REFERENCES**


30. Han C, Liu S, Qin XB, Ma S, Zhu LN, Wang XY. MRI combined with PSA density in detecting clinically significant prostate cancer in patients with PSA serum levels of 4-10 ng/mL: biparametric versus multiparametric MRI. *Diagn Interv Imaging.* 2020;101(4):235-244. doi:10.1016/j.diii.2020.01.014


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SUPPLEMENT 2.
Data Sharing Statement