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A New Risk-Stratified Pathway Based on Internally Validated Pre- and Post- MRI Prediction Models for Clinically Significant Prostate Cancer

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Abstract

Purpose

To develop and internally validate two pre- and post-MRI prediction models (COR-PM1 and COR-PM2) and evaluate a sequential risk-stratified pathway (COR-RSP) for reducing MRI examinations and prostate biopsies during the early detection of clinically significant prostate cancer (csPCa).

Methods

COR-PM1 and COR-PM2 were developed using logistic regression in 943 men who underwent MRI and biopsy (2016–2023). COR-PM1 incorporated age, serum PSA, DRE findings, prior negative biopsy, and qualitative DRE-derived prostate volume (PV). COR-PM2 incorporated PI-RADS score, with MRI-PV instead of DRE-PV. Calibration, discrimination, net benefit, and clinical performance were assessed after correction by optimism. COR-RSP sequentially applied both models at thresholds corresponding to 95% sensitivity.

Results

CsPCa was detected in 501 men (53.1%). Optimism-corrected AUC were 0.765 (95% CI 0.737–0.796) for COR-PM and 0.819 (95% CI 0.793–0.845) for COR-PM 2 (p = 0.001). Both models showed good calibration and net benefit. At 95% sensitivity thresholds, COR-PM1 could have avoided 139 MRI examinations (14.7%), whereas COR-PM2 could have avoided 180 biopsies (19.1%), particularly among men with PI-RADS ≤ 3. COR-RSP could have avoided 139 MRI examinations (14.7%), and 240 biopsies (25.5%), while missing 40 csPCa missed (8.0%). Biopsy yield could have increased from 53.1% to 65.6%.

Conclusions

COR-PM1 and COR-PM2 may help predict csPCa risk before and after MRI. COR-RSP may reduce MRI use and biopsies while increasing biopsy yield, although some csPCa cases may be missed. External validation is needed to confirm its clinical utility.

Introduction

Prostate cancer (PCa) is a commonly diagnosed malignancy in men worldwide and a leading cause of cancer-specific mortality [1]. Early detection of clinically significant PCa (csPCa) can reduce PCa-specific mortality [2]. In 2022, the European Union recommended evaluating the feasibility of organized PCa screening programs [3].

Opportunistic PCa screening has traditionally relied on serum prostate-specific antigen (PSA) testing and digital rectal examination (DRE) findings, followed by systematic biopsy. This approach has been criticized because of low csPCa detection and overdiagnosis of insignificant PCa (iPCa) [4–6]. Integrating magnetic resonance imaging (MRI) into the diagnostic pathway improves detection by identifying suspicious lesions and enabling risk stratification using the Prostate Imaging-Reporting and Data System (PI-RADS) [7]. This approach can reduce biopsies in men with PI-RADS < 3 and increase diagnostic yield through targeted biopsy of PI-RADS ≥ 3 lesions. Active surveillance is standard for iPCa, while the transperineal approach is increasingly used to reduce infectious complications [8]. However, unnecessary biopsies and overdiagnosis remain, particularly for PI-RADS 3 lesions [9]. The European Association of Urology recommends risk-stratified pathways incorporating csPCa prediction models (PMs) to reduce MRI use and biopsies [10].

Implementing PMs requires accessible risk calculators and external validation [11]. Developed in 2022, the Barcelona (BCN)-PMs addressed limitations of the European Randomized Study of Screening for Prostate Cancer (ERSPC) calculator, including restricted ranges of age, PSA, and prostate volume, and development using PI-RADS version 1 [12, 13]. BCN-PM1 (pre-MRI) aims to reduce MRI use, whereas BCN-PM2 (post-MRI) improves biopsy selection. Both include age, PSA, DRE findings, previous negative biopsy, and family history, a variable absent from ERSPC models. BCN-PM1 incorporates DRE-derived prostate volume (small, intermediate, or large) [12], whereas BCN-PM2 uses MRI-derived prostate volume (mL) and PI-RADS version 2.0 [13]. An online calculator is available (http://bcnrc.com). BCN-PM2 has been externally validated in men receiving 5-alpha-reductase inhibitors (5-ARIs) [14], men assessed using PI-RADS version 2.1 and undergoing transperineal biopsy [15], and European and Ibero-American cohorts [16, 17]. The BCN risk-stratified pathway (BCN-RSP), which sequentially applies both models, can reduce MRI use and biopsies while increasing biopsy diagnostic yield [18, 19].

Because missing family history data precluded retrospective validation of BCN-PMs in the Córdoba csPCa early detection cohort, we hypothesized that Córdoba (COR)-PMs can be developed and internally validated, along with a corresponding COR-RSP.

The primary objective was to develop and internally validate COR-PM1 and COR-PM2 and evaluate COR-RSP performance. Secondary objectives were to assess calibration, discrimination, net benefit, and clinical performance; evaluate COR-PM2 across PI-RADS categories; and compare COR-RSP with the current diagnostic approach.

Methods

Study design, setting, and participants

This retrospective study included 943 men with suspected prostate cancer (PCa) who underwent MRI and targeted and/or systematic biopsy at a tertiary academic hospital between 2016 and 2023. Eligibility required a complete dataset. Men with a previous PCa diagnosis were previously excluded. We

developed and internally validated pre- and post-MRI prediction models (COR-PM1 and COR-PM2). COR-RSP performance was compared with that on the applied diagnostic approach. Reporting followed the TRIPOD + AI guidelines [20]. The study was approved by the Córdoba Ethics and Research Committee (SICEIA-2026-001749).

Diagnostic approach and definition of csPCa

In biopsy-naïve men, PCa suspicion was based on serum PSA levels, and/or suspicious digital rectal examination (DRE) findings. After a previous negative biopsy, suspicion was based on persistently elevated or rising PSA, suspicious DRE, PSA density, and MRI findings. [8]. All men underwent multiparametric MRI at 1.5 or 3 T, using a pelvic surface coil and T2-weighted, diffusion-weighted, and dynamic contrast-enhanced sequences, according to European Society of Urogenital Radiology recommendations [21]. Experienced radiologists interpreted images using PI-RADS version 2.0 or 2.1, introduced locally in late 2019 [22, 23]. The most experienced radiologist (> 500 MRI reports annually) reviewed all images before biopsy, and the PI-RADS score of index lesion guided clinical decisions. Only men with PI-RADS < 3 and high risk of csPCa underwent biopsy [24].

Most biopsies were transrectal; a minority were transperineal. Software-based MRI–transrectal ultrasound fusion was performed using LOGIQ E9, Hitachi, or BiopSee platforms. PI-RADS > 3 lesions underwent targeted biopsy (2–5 cores per lesion, up to three lesions), alongside systematic biopsy. Experienced urologists performed biopsies, and specialized uropathologists assessed specimens. Clinically significant PCa (csPCa) was defined as International Society of Urological Pathology (ISUP) Grade Group ≥ 2 [25].

Development of COR-PM1, COR-PM2, and COR-RSP

Both models were developed using logistic regression. COR-PM1 included age (years), previous negative biopsy (yes/no), DRE findings (normal/suspicious), PSA (ng/mL), and DRE-derived prostate volume (small, intermediate, or large). COR-PM2 included the same variables, replacing DRE-derived volume with MRI-derived volume (mL) and adding PI-RADS category (2–5). Predicted csPCa probabilities were expressed as percentages.

COR-RSP first stratified men using COR-PM1 at the risk threshold corresponding to 95% sensitivity. Men at or below this threshold were classified as low risk and did not undergo MRI or biopsy. The remaining men underwent MRI and were reassessed using COR-PM2 at the risk threshold corresponding to 95% sensitivity tin the full cohort to guide biopsy decisions.

Statistical analysis

An anonymized dataset was compiled in Microsoft Excel. Reporting of diagnostic accuracy components followed STARD recommendations [26]. Continuous variables are reported as medians and interquartile

ranges (IQRs), and categorical variables as counts and percentages. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. McNemar's and Pearson's tests compared paired and independent binary outcomes, respectively. Internal validation used 2000 bootstrap resamples to estimate optimism and correct apparent performance estimates. In each resample, the models were refitted and their performance evaluated in both the bootstrap sample and the original cohort. Average optimism was estimated for each performance measure and subtracted from its apparent value to obtain optimism-corrected estimates. Calibration was assessed using calibration plots, the Brier score, calibration-in-the-large (CITL), and calibration slope. Discrimination was evaluated using receiver operating characteristic (ROC) curves and area under the curve (AUC), with apparent AUCs compared using DeLong's test. Net benefit was assessed by decision curve analysis (DCA), and clinical utility curves (CUCs) quantified MRI or biopsy avoidance and missed csPCa cases across risk thresholds. At a fixed 95% sensitivity, the models were compared in terms of specificity, positive and negative predictive values, OR, accuracy, MRI or biopsy avoidance, and missed csPCa cases. COR-RSP was compared with the applied diagnostic approach regarding MRI and biopsy avoidance, missed csPCa cases, and biopsy diagnostic yield. Two-sided p values < 0.05 were considered statistically significant. Analyses were performed using R 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria), and SPSS 29 (IBM, Armonk, NY, USA).

Results

Characteristics of development cohort

Baseline characteristics of predictive variables included into COR-PMs within the 943 participants are described in Table 1. Forty-five men (4.8%) were receiving 5-ARI treatment, and only 1.9% had PI-RADS < 3. Overall csPCa detection was 53.1%, with rates of 5.6% in PI-RADS 2, 21.2% in PI-RADS 3, 55.6% in PI-RADS 4, and 84.0% in PI-RADS 5 (Supplementary Table 1).

Table 1
Characteristics of men included in the development cohort of COR-PMs.

Characteristic	Measurement
Number of men, n	943
Median age, years (IQR)	64 (59–70)
Median serum PSA, ng/mL (IQR)	6.0 (4.6-9.0)
Suspicious DRE, n (%)	96 (10.2)
Prior negative biopsy, n (%)	683 (72.4)
Prostate volume derived from DRE, n (%)	
Small, n (%)	106 (11.2)
Intermediate, n (%)	543 (57.6)
Large, n (%)	294 (31.2)
Median prostate volume derived from MRI, mL (IQR)	54 (39–77)
PI-RADS score	
1, n (%)	0 (0.0)
2, n (%)	18 (1.9)
3, n (%)	212 (22.5)
4, n (%)	507 (53.8)
5, n (%)	206 (21.8)
Overall detection of csPCa, n (%)	501 (53.1)

Table 2
Clinical performance of COR-PM1 and COR-PM2 at thresholds corresponding to 95% sensitivity for csPCa.

Statistic	COR-PM1	COR-PM2
95% sensitivity threshold, %	26.3	22.7
Specificity, % (95% CI)	25.8 (21.9–30.1)	35.1 (30.8–39.6)
Positive predictive value, % (95% CI)	59.2 (55.8–62.5)	62.4 (58.9–65.8)
Negative predictive value, % (95% CI)	82.0 (74.8–87.5)	86.1 (80.3–90.4)
Odds ratio (95% CI)	6.62 (4.64–9.45)	10.28 (7.05–14.99)
Accuracy, % (95% CI)	62.6 (59.4–65.6)	66.9 (63.8–69.8)
Avoided MRI/biopsies, n (%; 95% CI)	139/943 (14.7; 12.6–17.1)	180/943 (19.1; 16.7–21.7)
Missed csPCa, n (%)	25/501 (5.0)	25/501 (5.0)

Development of COR-PM 1 and COR-PM 2

Logistic regression results for COR-PM1 and COR-PM2 are presented in Supplementary Table 2. Nomograms for both models are presented in Supplementary Figs. 1 and 2.

Bootstrap internal validation

Internal validation used 2000 bootstrap resamples to estimate and correct for optimism. Calibration plots are shown in Fig. 1A. The optimism-corrected Brier score (95% CI) was 0.198 (0.185–0.212) for COR-PM 1 and 0.172 (0.159–0.186) for COR-PM 2. The corrected calibration slope was 0.912 (0.842–0.983) and 0.956 (0.902–1.021), respectively. Corrected CITL was − 0.015 (-0.089 to 0.058) for COR-PM1 and − 0.010 (-0.074 to 0.053) for COR-PM2.

Discrimination of COR-PM1 and COR-PM 2 for csPCa

The apparent AUCs were 0.771 (95% CI 0.740–0.801) for COR-PM1 and 0.824 (95% CI 0.796–0.851) for COR-PM2. After bootstrap correction for optimism, the AUCs were 0.766 (95% CI, 0.737–0.796) and 0.819 (95% CI, 0.793–0.845), respectively (p = 0.001; Fig. 1B).

Net benefit of COR-PM1 and COR-PM2

Decision curve analysis corrected by optimism showed that COR-PM1 provided a greater net benefit than the biopsy-all strategy at threshold probabilities above 18%, whereas COR-PM2 provided a greater net benefit at threshold probabilities above 12% (Fig. 1C).

Clinical performance of COR-PM1 and COR-PM2

CUCs illustrated the trade-off between avoided biopsies and missed csPCa cases across risk thresholds for both models (Fig. 1D). At the 95% sensitivity threshold of 26.3%, COR-PM1 showed a specificity of 25.8% (95% CI 21.9–30.1), corresponding to 139 avoided MRI examinations (14.7%). At a threshold of 22.7%, COR-PM2 showed a specificity of 35.1% (95% CI 30.8–39.6), corresponding to 180 avoided biopsies (19.1%; p = 0.011).

Clinical utility of COR-PM2 at the overall threshold of 22.7%, stratified by PI-RADS category, is summarized in Suoolementary Table 3. Among men with PI-RADS 2, 94.4% of biopsies would have been avoided, at the cost of missing the only detected case of csPCa. Among those with PI-RADS 3, 62.7% of biopsies would have been be avoided, with 15 missed csPCa cases (33.3%). Among men with PI-RADS 4, 5.9% of biopsies would have been avoided, while 9 cases of csPCa (3.2%) would be missed. No biopsies would have been avoided among men with PI-RADS 5. Overall, 25 cases of csPCa would have been missed (5.0%).

Clinical performance of COR-RSP

The COR-RSP flowchart is shown in Fig. 2. In the first step, COR-PM1 was applied to all 943 men at 26.3% risk threshold. MRI could have been avoided in 139 men (14.7%), with 25 csPCa cases missed (5.0%). In the second step, 804 men were stratified using COR-PM2 at 22.7% threshold. This step identified 101 men (10.7% of the initial cohort) in whom biopsy could have been avoided, with 15 csPCa cases missed (3.0%). Overall, 703 men (74.6%) would have undergone biopsy, detecting 461 of the 501 csPCa cases (92.0%).

Compared with the applied diagnostic pathway, COR-RSP could have avoided 139 MRI examinations (14.7%) and 240 biopsies (25.5%), while missing 40 csPCa cases (8.0%). Biopsy diagnostic yield could have increased from 53.1% to 65.6% (p < 0.001).

Discussion

Our main objective was to design a new RSP and compare its performance with the current diagnostic approach based on MRI and PSA density [24]. The newly developed and internally validated pre- and -post MRI prediction models aimed to reduce MRI use (COR-PM1), and avoid unnecessary biopsies (COR-PM2).

Both models underwent bootstrap internal validation, providing optimism- corrected performance estimates while retaining the full cohort for model development [20]. Models showed good calibration and discrimination, although AUCs were slightly lower than those reported with BCN-PMs in their development cohorts [12, 13]. Net benefit and clinical performance were broadly comparable. COR-RSP improved the current diagnostic pathway relying on MRI and PSA density [8, 24]. An important difference between this cohort and BCN-PMs development cohort was the distribution of PI-RADS categories. Fewer than 5% of men had PI-RADS < 3, compared with approximately 20% in the BCN cohorts. This difference likely reflects the current strategy of biopsy only high-risk cases [8, 24]. COR-PM2 showed

clinical utility in men with PI-RADS ≤ 3, limited benefit in those with PI-RADS 4, and no meaningful utility in PI-RADS 5, where biopsy remains clearly indicated [13].

COR-RSP could educed MRI examinations by 14.7% and biopsies by 25.5%, while missing 8.0% of csPCa cases and increasing biopsy diagnostic yield from 53.1% to 65.6%. These results are comparable to those reported for BCN-RSP [18, 19] and suggest potentially greater reductions in MRI use and biopsies than those achieved by ERSPC-based pathways [27]. Overall, a sequential, risk-adapted strategy may improve diagnostic efficiency while reducing resource use.

A further strength was the agreement between csPCa detection rates across PI-RADS categories and those reported in a meta-analysis of PI-RADS version 2.1 [23], supporting the cohort's clinical representativeness. However, this study has limitations. This retrospective, single-center study may be subject to selection bias and limited generalizability. The low proportion of men with PI-RADS < 3 limits subgroup estimates. External validation and prospective studies are needed to confirm the models' performance and clinical utility.

First, the small proportion of men with PI-RADS < 3 may limit generalizability, particularly to lower-risk populations. Second, the single-center design may restrict external validity. External validation is required before clinical implementation.

These findings support locally tailored prediction models as a pragmatic approach to clinical decision-making. Differences in patient populations, MRI interpretation, and diagnostic pathways may limit the transportability of existing models. Locally developed models may therefore offer better calibration, discrimination and clinical utility in specific healthcare settings. Accessible risk calculators are essential for clinical implementation [28]. However, dynamic model updating remains challenging [29]. Machine-learning approaches may facilitate ongoing updating and validation [30]. Future prospective, multicenter studies should externally validate COR-PM1, COR-PM2, and COR-RSP to confirm these results, and compare with other recognized pathways.

Conclusions

COR-PM1 and COR-PM2 may help optimize the diagnostic pathway for csPCa by reducing MRI examinations and unnecessary biopsies, respectively. Their sequential application through COR-RSP may improve biopsy diagnostic yield while reducing MRI use and biopsies, although some csPCa cases may be missed. External validation is needed to confirm these findings and establish clinical utility.

Declarations

Author contributions: Juan Morote had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Morote, Recio, Gómez-Gómez.

Acquisition of data: Recio, Chamorro, López-Ruiz, Gómez-Gómez, Campos, Cruz, Valero, Carrasco.

Statistical analysis: Miró, Morote, Recio, Gómez-Gómez.

Analysis and interpretation of data: Recio, Morote, Gómez-Gómez.

Drafting of the manuscript: Morote, Recio.

Critical revision of the manuscript for important intellectual content: Miró, Gómez-Gómez, Chamorro, Moranderira-Rivas.

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Administrative, technical, or material support: None.

Supervision: Morote, Gómez-Gómez.

Other: None.

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Data Availability

Data is available on request.

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Figures

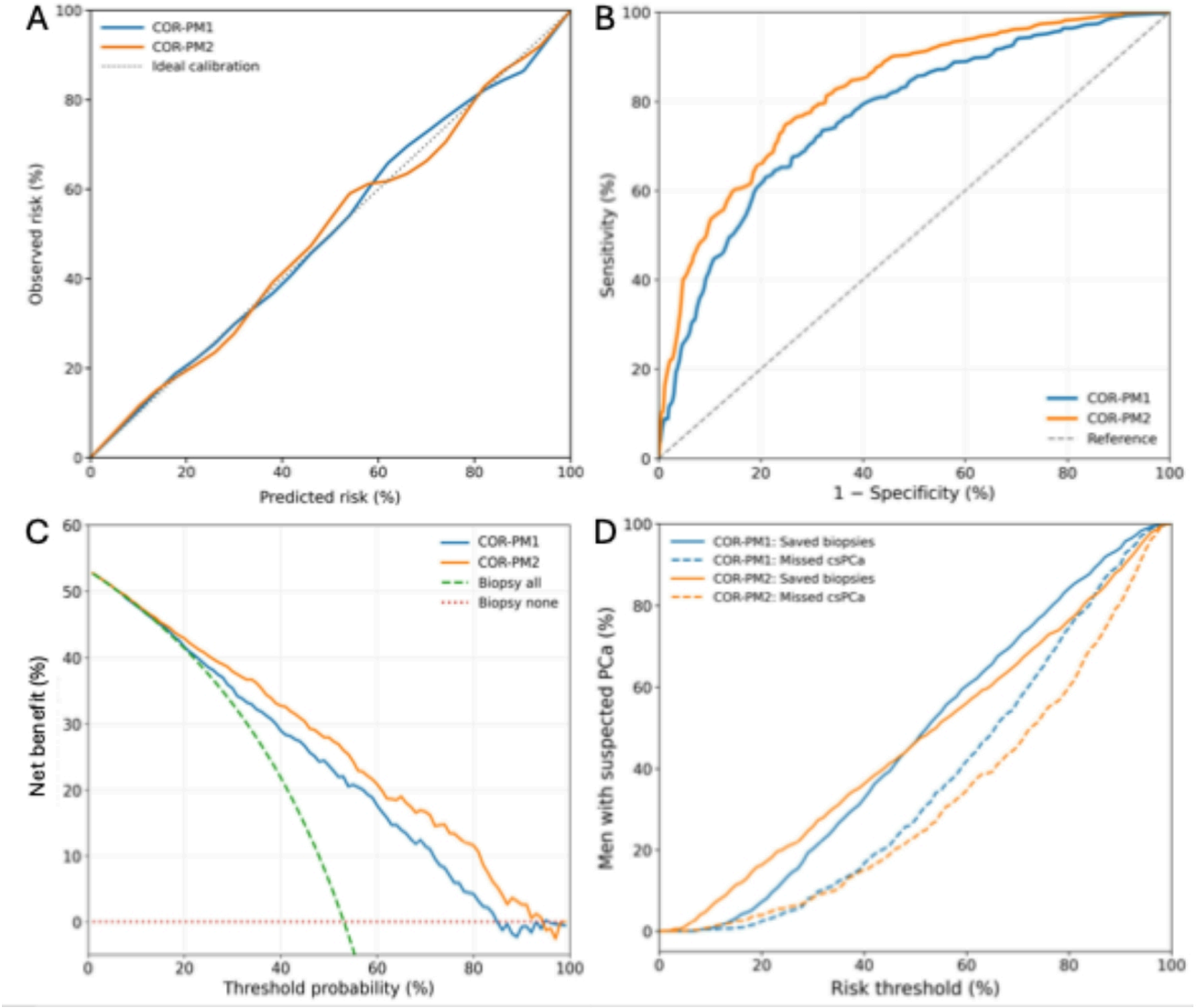
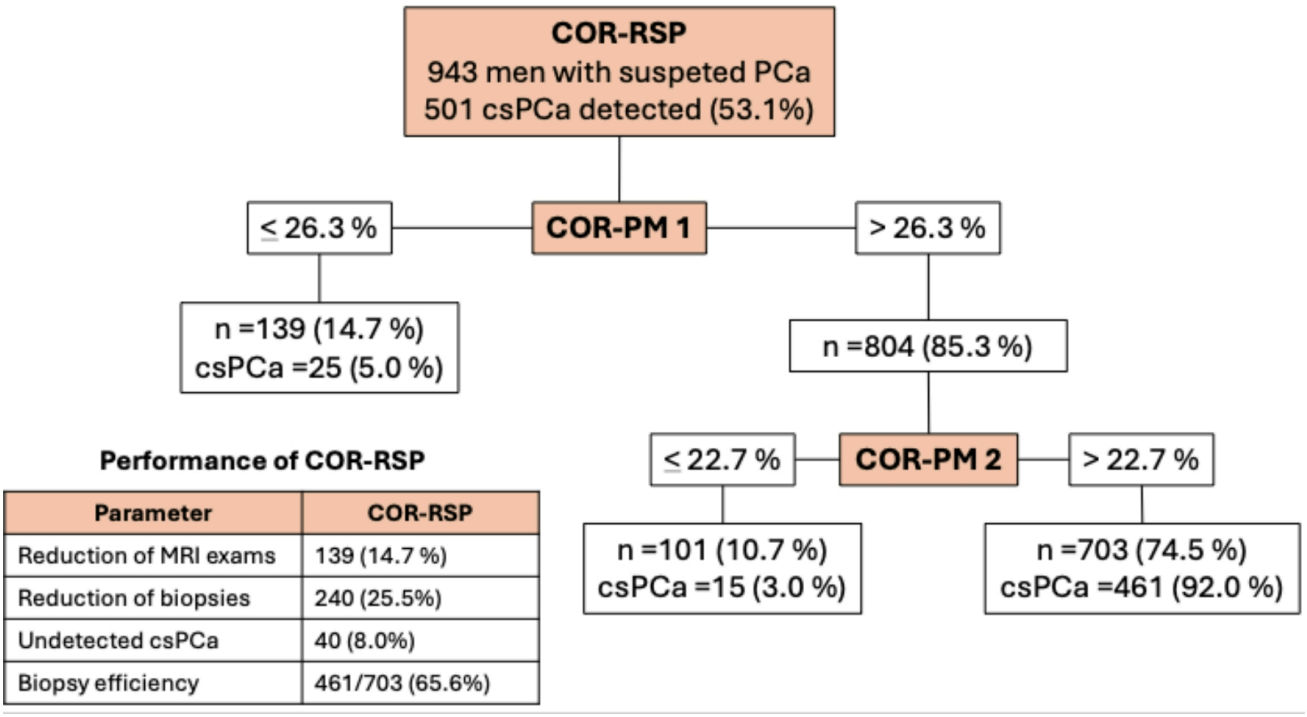


Figure 1

Calibration plot of COR-PM1 and COR-PM2 showing the agreement between predicted and observed risks (A). Receiver Operating Characteristic curves showing the discrimination of COR-PM1 and COR-PM2 (B). Decision Curve Analysis showing the net benefit of COR-PM1 and COR-PM2 compared with biopsy-all and biopsy-none strategies (C). Clinical Utility Curves showing the trade-off between rates of saved biopsies and missed csPCa cases across risk threshold of COR-PM1 and COR-PM1-PM2.



Performance of COR-RSP

Parameter	COR-RSP
Reduction of MRI exams	139 (14.7 %)
Reduction of biopsies	240 (25.5%)
Undetected csPCa	40 (8.0%)
Biopsy efficiency	461/703 (65.6%)

Figure 2

Flowchart and performance of COR-RSP, based on sequential application of COR-PM1 and COR-PM2 applying risk thresholds corresponding to the overall 95% sensitivity.

Supplementary Files

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

- SupplementaryMaterialV1..docx