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Who with suspected prostate cancer can benefit from Proclarix after multiparametric magnetic resonance imaging?

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Abstract

Proclarix is a new blood-based test to assess the likelihood of clinically significant prostate cancer (csPCa) defined as ≥2 grade group. In this study, we analyzed whether Proclarix and PSA density (PSAD) could improve the selection of candidates for prostate biopsy after multiparametric magnetic resonance imaging (mpMRI). Proclarix and PSAD were assessed in 567 consecutive men with suspected PCa in whom pre-biopsy 3 Tesla mpMRI, scoring with Prostate Imaging-Report and Data System (PI-RADS) v.2, and guided and/or systematic biopsies were performed. Proclarix and PSAD thresholds having csPCa sensitivity over 90% were found at 10% and 0.07 ng/(mL*cm^3), respectively. Among 100 men with negative mpMRI (PI-RADS <3), csPCa was detected in 6 cases, which would have been undetected if systematic biopsies were avoided. However, Proclarix suggested performing a biopsy on 70% of men with negative mpMRI. In contrast, PSAD only detected 50% of csPCa and required 71% of prostate biopsies. In 169 men with PI-RADS 3, Proclarix avoided 21.3% of prostate biopsies and detected all 25 cases of csPCa, while PSAD avoided 26.3% of biopsies, but missed 16% of csPCa. In 190 men with PI-RADS 4 and 108 with PI-RADS 5, Proclarix avoided 12.1% and 5.6% of prostate biopsies, but missed 4.8% and 1% of csPCa, respectively. PSAD avoided 18.4% and 9.3% of biopsies, but missed 11.4% and 4.2% csPCa, respectively. We conclude that Proclarix outperformed PSAD in the selection of candidates for prostate biopsy, especially in men with PI-RADS ≤3.

Keywords

Clinically significant prostate cancer, magnetic resonance imaging, proclarix, thrombospondin-1, cathepsin D, prostate-specific antigen density

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Introduction

Early detection of clinically significant prostate cancer (csPCa) decreases the specific mortality of PCa.[1] Currently, suspicion of PCa is established from a persistent elevation of serum prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE) and then followed up with systematic prostate biopsies;[2] however, this approach has been disapproved due to the high rates of unnecessary biopsies and the overdetection of

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insignificant PCa (iPCa).[3] Multiparametric magnetic resonance imaging (mpMRI) and guided biopsies have enabled recent improvements in the early detection of csPCa.[2] Nevertheless, the efficacy of this new strategy could be further improved with a more accurate selection of candidates for prostate biopsy, especially when low or moderate likelihood of csPCa is suggested by mpMRI.[2] A Prostate Imaging-Reporting and Data System (PI-RADS) score of <3 indicates a negative mpMRI, and the current negative predictive value of mpMRI is 80%–95%.[4] Additionally, PI-RADS category 3 suggests a moderate risk of csPCa that does not exceed 20%.[5] In these challenging scenarios where the rate of csPCa detection is low, PSA density (PSAD), modern markers, or predictive models can be helpful.[6,7]

Proclarix is a blood-based marker test that was recently introduced.[8] Proclarix provides a multivariate risk score for csPCa to guide biopsy decision making. This risk score is based on the combination of age and serum measurements of thrombospondin-1 (THBS1), cathepsin D (CTSD), total PSA (tPSA), and free PSA (fPSA).[9,10] THBS1 and CTSD were initially identified using a discovery mass spectrometry–based proteomics approach[11] and were subsequently observed in a PTEN knockout mouse model silencing the PI3 K/PTEN cancer pathway that is involved in the carcinogenesis and progression of PCa[12] and in human serum of men with and without PCa.[13] Clinical testing of individual immunoassays for the quantification of several glycoproteins was performed, and THBS1 and CTSD were ultimately selected because their measurement improved the accuracy of the percentage of fPSA in distinguishing men with and without csPCa.[14] This novel diagnostic test has been developed and validated to distinguish men without PCa or iPCa from those with csPCa among men with serum PSA between 2 and 10 ng/mL, prostate volume ≥35 cc, and normal DRE, with a recommended threshold of 10%.[9,10,15] Moreover, PSAD, which is a classic tool to improve the specificity of PSA, has been reinforced because MRI provides the most accurate measurement of prostate volume without additional cost.[16]

Because the performance of Proclarix according to the PI-RADS category has not yet been studied, our objective is to compare the performance of Proclarix and PSAD in the selection of candidates for prostate biopsy after mpMRI.

Materials and methods

Design, setting, participants, and intervention

This was a prospective head-to-head evaluation of Proclarix in a frozen serum collection (https://biobancos.isciii.es/; Reference collection: 0003439) and PSAD in 567 consecutive men with PSA >3 ng/mL and/or abnormal DRE in whom pre-biopsy 3-Tesla mpMRI was performed (Magnetom Trio, Siemens Corp., Germany). From January 2018 to March 2020 at a single academic institution, men with tumors with a score of ≥3 on PI-RADS v.2 received 2- or 3-core transrectal ultrasound (TRUS)-guided cognitive fusion biopsies to all detected lesions plus a 12-core TRUS systematic biopsy, while those with a PI-RADS v.2 score of <3 received only a 12-core TRUS systematic biopsy (BK Focus 400 ultrasound scanner, BK Medical Inc., Denmark). Blood samples were obtained immediately prior to prostate biopsy, and serum was stored at −80°C. This project was approved by the institutional ethics committee (PRAG129/2020) and informed consent was signed by all participants.

Laboratory method for Proclarix evaluation and prostate-specific antigen density assessment

THBS1 and CTSD were measured using the Proclarix kit (Proteomedix, Zürich-Schlieren, Switzerland) as previously described.[8] Serum tPSA and fPSA were re-analyzed for all samples using the Roche Cobas immunoassay system (Roche Diagnostics, Rotkreuz, Switzerland). All measurements were performed in the Proteomedix laboratory in Zürich-Schlieren, Switzerland, with Proteomedix bearing the costs for measurements and reagents. Serum THBS1, CTD, tPSA, percent fPSA, and age were entered into an algorithm that reported a score from 0% to 100%.[10]

PSAD was estimated from the MRI-derived prostate volume and the tPSA measured in Proclarix evaluation.

Endpoint measurements and definition of clinically significant prostate cancer

The endpoint measurements were csPCa detection rates, rates of avoided prostate biopsies, and rates of overdetection of iPCa. Tumors with an International Society of Uro-Pathology grade group of ≥2 were defined as csPCa.[17]

Statistical analysis

Comparisons were performed with the Mann–Whitney U test for quantitative variables and with the Chi square and Kruskal–Wallis tests for qualitative variables. Receiver operating characteristic (ROC) curves and areas under the curve (AUCs) were used to analyze efficacies, and the DeLong test for their comparisons. Decision curve analysis (DCA) was used to evaluate net benefits. SPSS v.25 (IBM Corp., Armonk, NY, USA) and R programming language v.3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) were used.

Results

PCa was detected in 298 men (52.6%), of whom 232 (40.9% of all participants) were diagnosed with csPCa and 66 (11.6%) had iPCa. The characteristics of the entire study cohort and a comparison of these characteristics in men without PCa or with iPCa and those with csPCa are presented in Table 1. We note that men with csPCa had significantly higher age, serum PSA, and PSAD; a lower percentage of fPSA; and higher rates of abnormal DRE, PCa family history, and positive mpMRI (PI-RADS $\geq$3). The median Proclarix score was 20.9% in men without PCa or with iPCa and 43.5% in those with csPCa ($P<0.001$). ROC curves of mpMRI, Proclarix, and PSAD for csPCa detection in the overall study cohort are presented in Figure 1(a). The AUC of Proclarix in the overall study cohort was slightly higher than that of PSAD (0.745 vs. 0.740; $P=0.465$). The morphologies of ROC curves suggest that Proclarix was more specific than PSAD at high sensitivities. This was more pronounced in men with PI-RADS scores of 1–3, for whom Proclarix outperformed mpMRI and PSAD (Figure 1(b) to (d)). A 10% risk score of Proclarix and 0.07 ng/(mL*cm^3) of PSAD were selected as thresholds with sensitivities for csPCa over 90%, and they were used across PI-RADS categories.

Table 2 shows the performance of Proclarix and PSAD both in all men and according to the PI-RADS categories. We note that Proclarix was able to detect all the 6% of csPCa detected in the systematic biopsies performed in the 100 men with negative mpMRI, although prostate biopsy was required in 70% of them. In contrast, PSAD detected 50% of csPCa and required 71% of systematic biopsies. In the subset of 169 men with a PI-RADS of 3, Proclarix avoided 21.3% of biopsies and detected all 25 cases of csPCa, while PSAD avoided 26.2% of biopsies, but missed 16.0% of csPCa. In men with PI-RADS of 4 and 5, Proclarix avoided 12.1% and 5.6% of biopsies, but misdiagnosed 4.8% and 1.0% of csPCa, respectively. PSAD avoided 18.4% and 9.3% of biopsies and misdiagnosed 11.4% and 4.2% of csPCa, respectively. The net benefit of Proclarix and PSAD on the biopsy of all men is presented in DCAs of Figure 2(a) and according to the PI-RADS categories in Figure 2(b) to (e).

Discussion

The present study confirms that Proclarix is a very sensitive marker of csPCa (grade group of $\geq$2).[8–10] Proclarix outperformed PSAD and improved the negative predictive value of mpMRI from 94% to 100%.[4,6] In men with tumors in the equivocal PI-RADS category 3, in whom at least 70% of prostate biopsies are not required,[5,7] Proclarix was able to avoid more than 20% of prostate biopsies without missing csPCa. PSAD was able to avoid 26% of prostate biopsies, but it missed 16% of csPCa. To miss csPCa detection in men with tumors in PI-RADS categories >3 is dangerous due to the higher aggressiveness of the tumors detected compared to those in lower PI-RADS categories. This is why clinicians usually refuse to avoid prostate biopsies in this setting.[5,7] Thus, only tools with 100% sensitivity for csPCa in these settings should be offered to

Table 1. Characteristics of the study cohort and comparison between the characteristics of men without PCa or iPCa and that of those with csPCa (>2 grade group).

Characteristic	All men	Without PCa or iPCa	With csPCa	*P* value
Number of cases	567	335	232	—
Median age, years (IQR)	69 (63–74)	67 (61–72)	72 (67–76)	0.001
Median total PSA, ng/mL (IQR)	7.0 (4.9–11.2)	6.1 (4.5–9.8)	8.0 (5.9–14.2)	0.001
Abnormal DRE, n (%)	109 (19.2)	30 (9.0)	79 (34.1)	0.001
Median free PSA, ng/mL (IQR)	1.1 (0.7–1.7)	1.1 (0.7–1.7)	1.1 (0.7–1.8)	0.832
Median prostate volume, mL (IQR)	55 (40–76)	63 (45–85)	48 (35–63)	0.001
Median percent free PSA, % (IQR)	15.1 (10.7–20.6)	17.2 (12.4–23.4)	12.1 (8.8–17.3)	0.001
Median PSA density, ng/(mL*cm^3) (IQR)	0.13 (0.09–0.21)	0.10 (0.07–0.16)	0.19 (0.12–0.34)	0.001
Repeat biopsy, n (%)	133 (23.5)	88 (26.3)	45 (19.4)	0.035
Family history of PCa, n (%)	48 (8.6%)	24 (7.9)	25 (10.8)	0.089
Proclarix, % (IQR)	28.7 (15.5–50.0)	20.9 (10.1–34.7)	43.5 (26.6–67.2)	0.001
PI-RADS, n (%)				
1–2	100 (17.6)	94 (28.1)	6 (2.6)	0.001
3	169 (29.8)	144 (43.0)	25 (14.8)	
4	190 (33.5)	85 (25.4)	105 (45.3)	
5	108 (19.0)	12 (3.5)	96 (41.4)	
Overall PCa detection, n (%)	298 (52.6)			
csPCa detection, n (%)	232 (40.9)			
iPCa detection, n (%)	66 (11.6)			

iPCa: insignificant PCa; IQR: interquartile range; PCa: prostate cancer; PI-RADS: Prostate Imaging-Report and Data System.

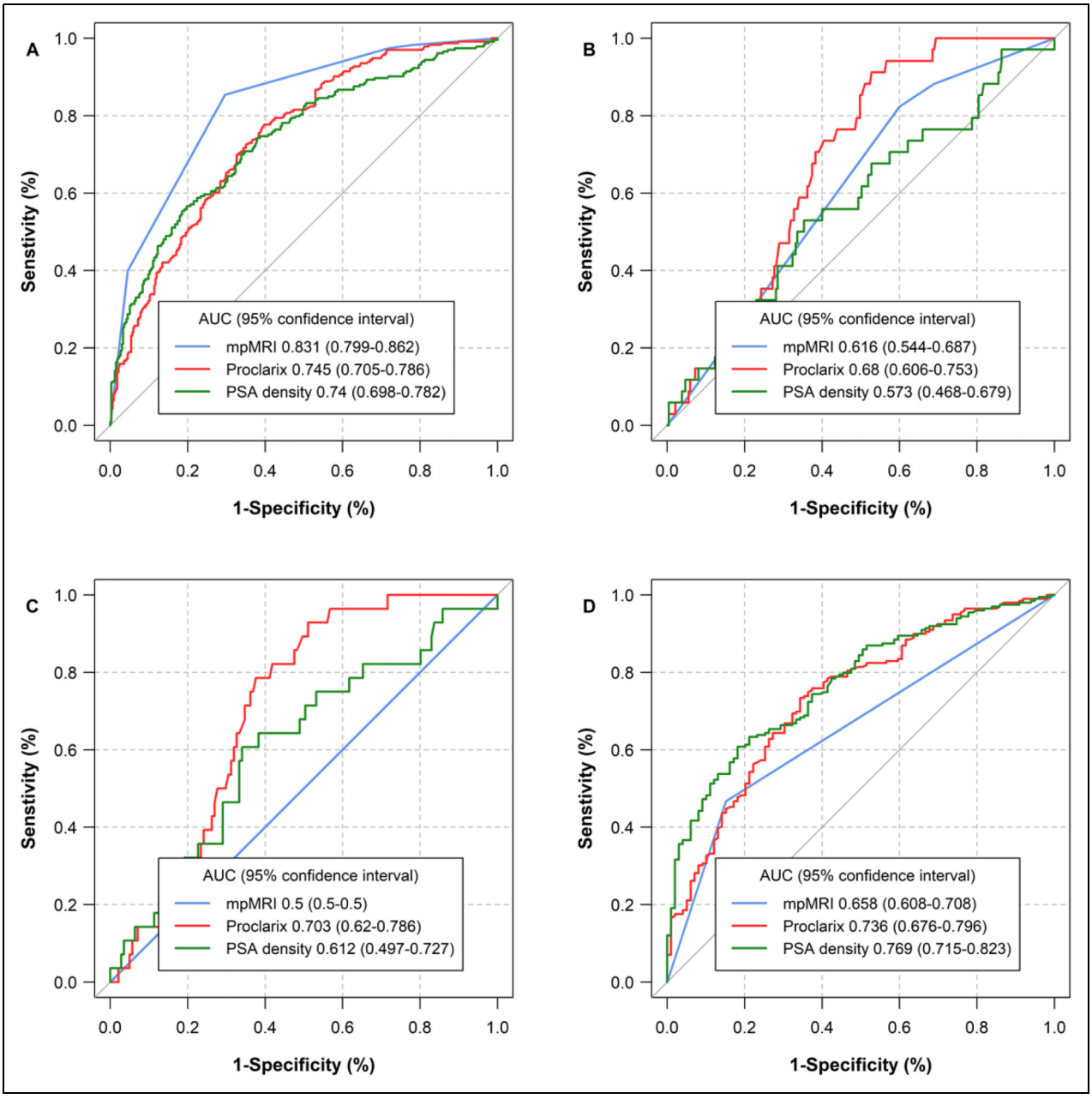

Figure 1. Efficacy of proclarix, PSAD and mpMRI for the detection of csPCa (≥ grade group) in the entire study cohort (a), in men with negative mpMRI (b), PI-RADS 3 (c), and PI-RADS >3 (d).
csPCa: clinically significant prostate cancer; mpMRI: multiparametric magnetic resonance imaging; PI-RADS: Prostate Imaging-Report and Data System; PSAD: Proclarix and PSA density.

clinicians. Therefore, we believe that neither Proclarix nor PSAD should be recommended in men with PI-RADS scores above 3.

PROPOSe was the first study analyzing Proclarix in men with pre-biopsy mpMRI. The authors reported results from 108 men with positive mpMRI in whom guided and systematic biopsies were performed.[14] After fixing a sensitivity for ≥2 grade group PCa at 97%, the specificity of Proclarix was 26% and that of PSAD was 8%, and their negative predictive values were 96% and 88%, respectively. Unfortunately, men with negative mpMRI were not biopsied and the analysis according to the PI-RADS categories was not performed. The authors concluded that Proclarix outperformed PSAD. We believe that additional analyses regarding the PI-RADS categories are important because the overall results do not represent the specific efficacies in every PI-RADS category. Moreover, the

Table 2. Performance of proclarix at 10% threshold and PSAD at 0.07 ng/(mL*cm^3) threshold for csPCa (≥2 grade group) detection in all population study and according to the PI-RADS categories.

	Proclarix (threshold 10%)					PSA density (threshold 0.07 ng/(mL*cm3))				
Parameter	All men (n = 567)	PI-RADS 1–2 (n = 100)	PI-RADS 3 (n = 169)	PI-RADS 4 (n = 190)	PI-RADS 5 (n = 108)	All men (n = 567)	PI-RADS 1–2 (n = 100)	PI-RADS 3 (n = 169)	PI-RADS 4 (n = 190)	PI-RADS 5 (n = 108)
Sensitivity	97.4 (226/232)	100 (6/6)	100 (25/25)	95.2 (100/105)	99.0 (95/96)	90.1 (209/232)	50 (3/6)	84.0 (21/25)	88.6 (93/105)	95.8 (92/96)
Specificity	26.6 (89/335)	31.9 (30/94)	25.0 (36/144)	21.2 (18/85)	41.7 (5/12)	28.7 (96/335)	27.7 (26/94)	28.5 (41/144)	27.1 (13/85)	50.0 (6/12)
Negative PV	93.7 (89/95)	100 (30/30)	100 (36/36)	78.3 (18/23)	83.3 (5/6)	80.7 (96/119)	89.7 (26/29)	91.1 (41/45)	65.7 (23/35)	60.0 (6/10)
Positive PV	47.9 (226/472)	8.6 (6/70)	19.8 (25/133)	59.91 (00/167)	93.1 (95/102)	46.7 (209/448)	4.2 (3/71)	16.0 (21/124)	60.0 (93/155)	93.9 (92/98)
Accuracy	55.6 (315/567)	36 (36/100)	36.1 (61/169)	62.1 (118/190)	92.6 (100/108)	53.8 (305/567)	29.0 (29/100)	36.7 (62/169)	61.1 (116/190)	90.7 (98/108)
Avoided biopsies	16.8 (95/567)	30 (30/100)	21.3 (36/169)	12.1 (23/190)	5.6 (6/108)	21.0 (119/567)	29.0 (29/100)	26.2 (45/169)	18.4 (35/190)	9.3 (10/108)
Missed csPCa	2.6 (6/232)	0 (0/6)	0 (0/25)	4.8 (5/105)	1.0 (1/96)	9.9 (23/232)	50.0 (3/6)	16.0 (4/25)	11.4 (12/105)	4.2 (4/96)

csPCa: clinically significant prostate cancer; PI-RADS: Prostate Imaging-Report and Data System; PV: predictive value.

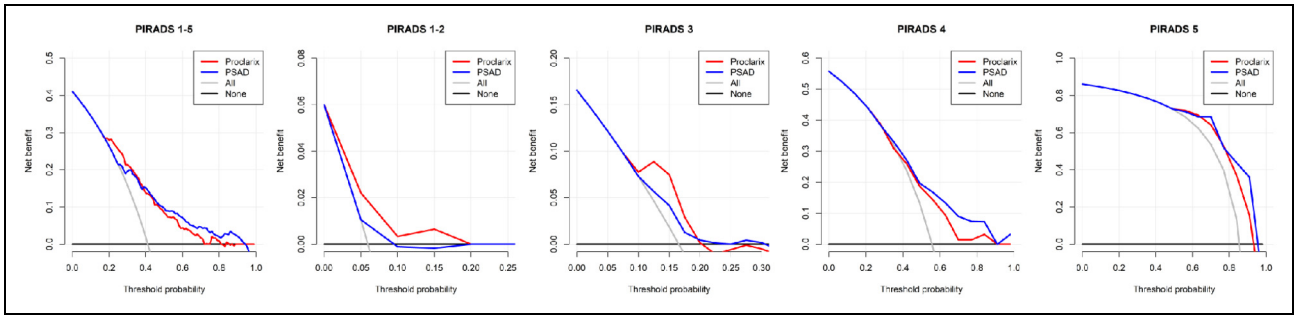

Figure 2. Net benefit of proclarix and PSAD instead of biopsy all men in the entire study cohort (PI-RADS 1–5), and according to the PI-RADS categories.
PI-RADS: Prostate Imaging-Report and Data System; PSAD: Proclarix and PSA density.

case-mix of PI-RADS in every series can change depending on the characteristics of the analyzed population and the interpretation of mpMRI.[7]

Comparisons between Proclarix and other markers are needed.[18–20] In our opinion, a major strength of Proclarix is its high sensitivity for tumors with a grade group of ≥2, which guarantees the detection of most of these tumors. Nevertheless, a cost-benefit analysis must be performed to determine the final benefit of markers as complementary tools of mpMRI.[20]

The limitations of our study include its partially retrospective design and the lack of external validation. Prospective and multicenter studies mimicking real clinical practice are needed, especially studies comparing the existing markers. However, a common limitation of these studies is measuring the rate of csPCa in prostate biopsies, which does not represent the true pathology observed in the whole prostate gland. A strength of our study was to perform systematic biopsies in men with negative mpMRI (PI-RADS <3) which allowed the possibility to know that Proclarix increased the negative predictive value of mpMRI from 94% to 100%.

Finally, we note that Proclarix can improve the selection of candidates for prostate biopsy after mpMRI, especially in men with low or moderate risk of csPCa defined by a PI-RADS score ≤3.

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Declaration of conflicting interests

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