Original Article
Prostate cancer

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The Efficacy of Proclarix to Select Appropriate Candidates for Magnetic Resonance Imaging and Derived Prostate Biopsies in Men with Suspected Prostate Cancer

Juan Morote[1,3,5], Miriam Campistol[1], Anna Celma[1,3], Lucas Regis[1,3], Inés de Torres[2,3,5], María E. Semidey[2,3,5], Sarai Roche[4], Richard Mast[4], Anna Santamaría[3], Jacques Planas[1,3], Enrique Trilla[1,3,5]

[1]Department of Urology and Renal Transplantation, Vall d´Hebron Hospital, [2]Department of Pathology, Vall d´Hebron Hospital, [3]Prostate Cancer Research Group, Vall d´Hebron Research Institute, [4]Department of Radiology, Vall d´Hebron Hospital, [5]Department of Surgery, Universitat Autònoma of Barcelona, Barcelona, Spain

Purpose: To analyze how Proclarix is valuable to appropriately select candidates for multiparametric magnetic resonance imaging (mpMRI) and derived biopsies, among men with suspected prostate cancer (PCa). Proclarix is a new marker computing the clinically significant PCa (csPCa) risk, based on serum thosmbospondin-1, cathepsin D, prostate-specific antigen (PSA) and percent free PSA, in addition to age, that has been developed in men with serum PSA 2 to 10 ng/mL, prostate volume ≥35 mL, and normal digital rectal examination (DRE).

Materials and Methods: Proclarix score (0%–100%) is analyzed in a prospective frozen serum collection of 517 correlative men scheduled for guided and/or systematic biopsies after mpMRI. Outcome variables were csPCa detection (grade group ≥2), insignificant PCa (iPCa) overdetection and avoided mpMRIs.

Results: The area under the curve of Proclarix was 0.701 (95% CI 0.637–0.765) among 281 men with serum PSA 2 to 10 ng/mL, prostate volume ≥35 mL, and -normal DRE, and 0.754 (95% CI 0.701–0.807) in the others, p=0.038. Net benefit of Proclarix existed in all men. After selecting 10% threshold, Proclarix was integrated in an algorithm which also used the serum PSA level and DRE. A reduction of 25.4% of mpMRIs request was observed and 17.7% of prostate biopsies. Overdetection of iPCa was reduced in 18.2% and 2.6% of csPCa were misdiagnosed.

Conclusions: Proclarix is valuable in all men with suspected PCa. An algorithm integrating Proclarix score, serum PSA, and DRE can avoid mpMRI requests, unnecessary prostate biopsies and iPCa overdetection, with minimal loss of csPCa detection.

Keywords: Clinically significant; Diagnosis; Multiparametric magnetic resonance imaging; Proclarix; Prostate cancer

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Correspondence to: Juan Morote https://orcid.org/0000-0002-2168-323X
Department of Urology and Renal Transplantation, Vall d´Hebron Hospial, Passeig Vall d'Hebron, 119-129, Barcelona 08035, Spain.
Tel: +34-932746009, **Fax:** +34-934893129, **E-mail:** jmorote@vhebron.net

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INTRODUCTION

Early detection of clinically significant prostate cancer (csPCa) can decrease the specific mortality of PCa [1]. PCa is suspected through the elevation of serum prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE), and classically systematic biopsies have confirmed the diagnosis [2]. This approach has been criticised for the high rate of unnecessary biopsies and the overdetection of insignificant PCa (iPCa) [3]. Many tools have been used to increase the specificity of PCa suspicion; however, the true improvement of early detection of csPCa has come from multiparametric magnetic resonance imaging (mpMRI) and guided biopsies [2]. mpMRI can achieve a negative predictive value of up to 90%, while guided biopsies increase the sensitivity for csPCa, especially when they are associated with systematic biopsies [4]. However, this approach is hampered by the cost and access to imaging in many sites. Therefore, an appropriate selection of candidates for mpMRI and derived biopsies may contribute to this strategy [5,6], by using appropriate biomarkers and risk calculators possible tools [7].

Proclarix (Proteomedix, Schlieren, Switzerland) is a new blood-based CE-marker test based on the combination of serum thrombospondin-1 (THBS1), cathepsin D (CTSD), total PSA, and percent free-PSA in addition to age, providing a risk score of csPCa [8-10]. THBS1 and CTSD were identified from a mass spectrometry-based proteomics discovery approach [11] in a PTEN knockout mouse model of the PI3K/PTEN cancer pathway, which is involved in the carcinogenesis and progression of PCa [12,13]. Both glycoproteins, determined through specific immunoassays, improve the accuracy of percent-free PSA and age to distinguish men with csPCa [14]. Proclarix was developed in men with serum PSA between 2 and 10 ng/mL, prostate volume ≥35 mL, and normal DRE, and 10% threshold has been recommended due to its 90% sensitivity for csPCa [10]. The current challenge is how to make the best use of Proclarix in the current setting of csPCa diagnosis.

Our primary endpoint is to analyze the role of Proclarix to select suitable candidates for mpMRI and derived prostate biopsies among men with suspected PCa. Secondary endpoints are (1) to analyse associations of Proclarix with clinicopathological features of men with suspected PCa, (2) to know if Proclarix is valuable in men with suspected PCa and serum PSA outside the 2 to 10 ng/mL range, or prostate volume <35 mL, or abnormal DRE, and (3) to design an algorithm with Proclarix and clinical data to appropriately select candidates for mpMRI and derived prostate biopsies.

MATERIALS AND METHODS

1. Design, setting, and participants

A retrospective analysis was carried out in a prospective database and frozen serum collection of 567 men with suspected PCa, 433 (76.4%) biopsy naïve, scheduled for prostate biopsy after mpMRI [2], in Vall d´Hebron University Hospital, from 11 January 2018 to 12 March 2020. Blood samples were obtained immediately before prostate biopsy, and serum was stored at -80°C (Collection 0003439; https://biobancos.isciii.es). Men with PCa on active surveillance and those with symptomatic benign prostatic hyperplasia on 5-[Symbol - a]-reductase inhibitors were previously excluded. The clinicopathological characteristics of this cohort study are summarized in Supplement Table 1.

2. Intervention

THBS-1, CTSD, total PSA, and free PSA were determined with specific immunoassays at Proteomedix (Zurich-Schlieren, Switzerland). Then, THBS-1 and CTD levels, percent free PSA, and age were computed in an algorithm that reported a score ranging from 0% to 100%.

3. MpMRI technique and evaluation

Magnetic resonance was acquired on a 3-T scanner, using a surface phased-array coil (Magneton Trio; Siemens Corp., Erlanger, Germany). The acquisition protocol included T2-weighted imaging, diffusion-weighted imaging and dynamic contrast-enhanced imaging, according to the European Society of Urogenital Radiology guidelines [15]. Two expert radiologists analysed images and reported them according to Prostate Imaging-Reporting and Data System (PI-RADS) v.2.0 [16].

4. Prostate biopsy procedure and pathologic analysis

Guided biopsies obtained 2 to 3 cores from each PI-RADS v.2.0 ≥3 lesion through the TRUS-MRI cognitive-fusion technique [17]. A 12-core systematic biopsy was also performed in all men. All biopsies were performed through transrectal approach by one experienced urol-

Table 1. Behaviour of Proclarix, and univariate analysis regarding to clinical characteristics of the study population and its pathologic features

Characteristic	Men	Proclarix (%)	p-value
Biopsy result	567 (100.0)		
Benign	271 (47.8)	21.3 (9.5–34.6)	-
Prostate cancer	296 (52.2)	39.6 (24.9–65.7)	<0.001[a]
Grade group in biopsy	296 (100.0)		
1	66 (22.3)	26.6 (14.6–40.6)	0.026[a]
2	87 (29.4)	39.1 (23.2–56.0)	<0.001
3	61 (20.6)	38.4 (25.5–53.6)	0.861
4	51 (17.2)	53.6 (31.2–51.0)	0.018
5	31 (10.5)	74.5 (46.3–98.0)	0.047
Clinical stage (TNM)	296 (100.0)		
Localized (cT1-2 N0 M0)	263 (88.9)	37.3 (22.6–57.1)	<0.001[a]
Locally advanced (cT3-4 N0 M0)	22 (7.4)	60.1 (36.1–94.9)	<0.001
Disseminated (cT1-4 N0-1 M0-1)	11 (3.7)	97.4 (51.6–100)	<0.001
Localized prostate cancer recurrence risk	263 (100.0)		
Low	56 (21.3)	24.8 (14–4–37.7)	0.198[a]
Intermediate	136 (51.7)	34.1 (23.6–53.4)	<0.001
High	71 (27.0)	57.3 (31.4–80.9)	<0.001
Type of prostate cancer	296 (100.0)		
Insignificant	66 (22.2)	26.5 (14.6–40.6)	0.024[a]
Clinically significant	230 (77.8)	45.8 (28.3–70.5)	<0.001
Type of pathology	80 (100.0)		
Favorable	8 (10.0)	14.9 (6.1–38.7)	0.258[a]
Unfavorable	72 (90.0)	30.3 (20.0–47.2)	0.048

Values presented as number (%) or median (interquartile range).
[a]p-value referred to benign biopsy result.

ogist (A.C.) using a BK Focus 400 ultrasound scanner (BK Medical Inc., Herlev, Denmark). Biopsy samples were sent separately to the pathology department, where two expert pathologists analysed them (M.E.S. and I.T.). The International Society of Urological Pathology (ISUP) grade groups (GG) were used for grading tumours [18]. csPCa was defined when GG ≥2 [19]. In men subjected to radical prostatectomy, favorable pathology was defined when GG <2 and pT <3, and unfavorable pathology was defined when GG ≥2 or pT ≥3.

5. Endpoint variables

csPCa detection, iPCa overdetection, avoided mpMRIs, avoided prostate biopsies, misdiagnosis of csPCa.

6. Populations included in the study

The development population was defined as those men who had the same characteristic as those included in the development of Proclarix, PSA 2 to 10 ng/mL, and prostate volume ≥35 mL, and normal DRE (Subset 1). An additional population was men who did not meet any of these conditions (Subset 2).

7. Statistical analysis

Quantitative variables were expressed as medians and interquartile ranges. Qualitative variables were expressed as rates. Comparisons between quantitative variables were performed with the Mann–Whitney U-test and the Kruskal–Wallis test. Qualitative variables were compared with the chi-square test and the Fisher correction if necessary. Receiver operating characteristic (ROC) curves were constructed and areas under the curve (AUC) were evaluated and compared with the DeLong test. Binary logistic regression analysis was performed to assess predictors of csPCa and generate predictive models. Decision curve analyses (DCAs) were generated to assess net benefits between predictors. Significant differences were assessed when the p-value was less than 5%. SPSS v.25 (IBM Corp., Armonk, NY, USA) and R programming language v.3.3.1 (The R Statistical Foundation, Vienna, Austria) were used.

Table 2. Analysis of predictors for clinically significant prostate cancer detection in the entire study population

Predictor	Univariate analysis		Multivariate analysis	
	Odds ratio (95% confidence interval)	p-value	Odds ratio (95% confidence interval)	p-value
Age (ref. previous year)	1.079 (1.052–1.106)	<0.001	1.040 (0.879–1.069)	0.186
Prostate cancer family history (ref. no)	1.344 (0.708–2.550)	0.366	1.534 (0.794–2.963)	0.203
Type of biopsy (ref. initial)	0.785 (0.502–1.225)	0.286	0.757 (0.477–1.201)	0.237
Digital rectal examination (ref. normal)	2.607 (1.290–4.682)	<0.001	1.980 (0.785–3.717)	0.094
Prostate-specific antigen (ref. previous ng/mL)	1.028 (1.013–1.053)	<0.001	1.001 (0.991–1.011)	0.858
Proclarix (ref. previous percent value)	1.034 (1.023–1.044)	<0.001	1.042 (1.028–1.057)	<0.001

8. Ethics statement

Our study was conducted in line with Good Clinical Practice guidelines and the ethical principles laid down in the latest version of the Declaration of Helsinki (2013). Before inclusion, all participants signed a written informed consent about the collection and storage of material and personal data in accordance with national bylaws. All anamnestic, clinical and laboratory data containing sensitive information about patients were de-identified in order to ensure analysis of anonymous data only. The present study protocol was reviewed and approved by Vall d´Hebron Ethics Commitee (Reg. No. PR-AG129/2020).

RESULTS

1. Behaviour of Proclarix regarding the clinicopathological characteristics of men with suspected PCa

The associations between Proclarix and clinical and pathological features of the study cohort are summarized in Table 1. The median score of Proclarix in men with a benign result of prostate biopsy was 21.3%, which is significantly lower than the median of 39.6% observed in men with PCa, p<0.001. The median score of Proclarix in men with GG1 PCa was 26.6%, which is significantly higher than that observed in men with benign prostate biopsy, p=0.026. Therefore, the Proclarix score increased with GG, p<0.05, except between GG2 and GG3 tumours, p=0.861. The median Proclarix score in clinically localized PCa was 37.3%, 60.1% in locally advanced PCa, and 97.4% in metastatic PCa, p<0.001. The median Proclarix score in low-risk, clinically localized PCa was 24.8%, which is similar to the median in men without PCa, p=0.198. The median Proclarix score increased to 34.1% in intermediate-risk PCa and 57.3% in high-risk PCa, p<0.001. The median Proclarix score was 45.8% in men with csPCa and 26.5% in iPCa, p<0.001. Among 80 men subjected to radical prostatectomy, the median Proclarix score was 14.9% when the pathology was favorable, being it similar to that observed in men with benign tissue at prostate biopsy, and the median Proclarix score was 30.3% when the pathology was unfavorable, p=0.048.

2. Analysis of Proclarix as a predictor of csPCa in men with suspected PCa before mpMRI

Univariate analysis including age, PCa family history, type of biopsy (initial *versus* repeat), DRE, serum PSA, and Proclarix as potential predictors of csPCa, showed age, DRE, serum PSA, and Proclarix were significantly associated with csPCa, Table 2. Thereafter, a logistic regression analysis showed that the quantitative Proclarix score was the only independent predictor of csPCa, odds ratio (OR) 1.042 (95% confidence interval [CI] 1.028–1.057), p<0.001, Table 2. The ROC curve of the Proclarix score presented in Fig. 1A, had an AUC of 0.767 (95% CI 0.730–0.805). DCA showing the net benefit of Proclarix is presented in Fig. 1B.

In our entire study cohort, the recommended 10% threshold of Proclarix presented a sensitivity for csPCa of 97.4%, specificity of 26.7%, a negative predictive value of 93.8%, and a positive predictive value of 47.6%. In summary, 16.9% of mpMRI requests and derived prostate biopsies will be avoided, as will 2.6% of csPCa misdiagnosis, Table 3. The characteristics of six men, identified with false-negative Proclarix results, are summarized in Supplement Table 2: two men had GG 2, one had GG 3, two men had GG4, and one had GG5.

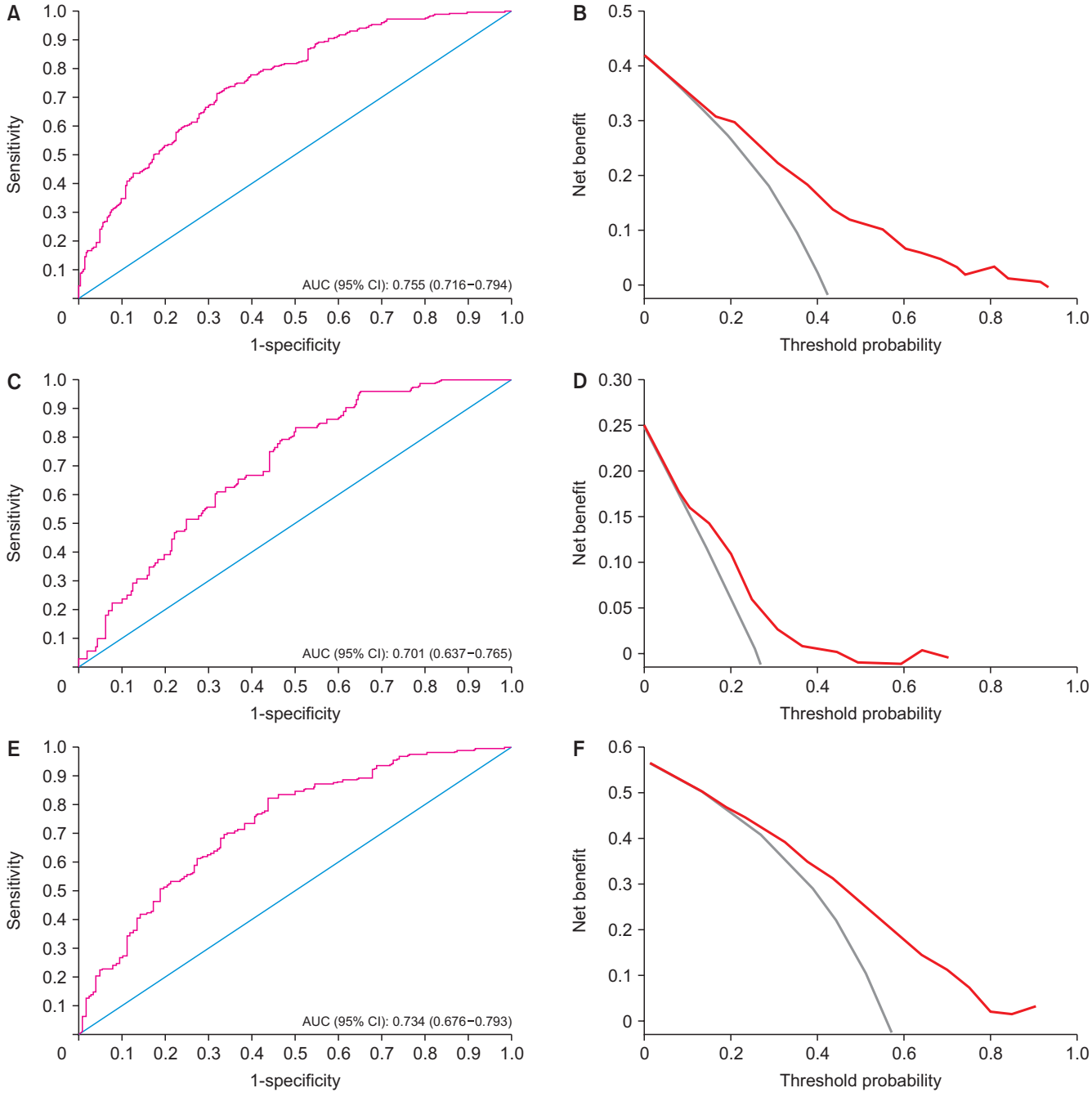

Fig. 1. Receiver operating characteristic curves of Proclarix score for clinically significant prostate cancer, and decision curve analysis showing its net benefit in front of biopsying all men with suspected prostate cancer in the overall population (A, B), in men with serum prostate-specific antigen 2 to 10 ng/mL, prostate volume ≥35 mL, and normal digital rectal examination (Subset 1) (C, D), and men with serum prostate-specific antigen out of the interval 2 to 10 ng/mL, or prostate volume <35 mL, or abnormal digital rectal examination (Subset 2) (E, F). AUC: areas under the curve.

3. Behaviour of Proclarix as a predictor of csPCa in men with suspected PCa regarding the level of serum PSA, prostate volume, and DRE

Among our correlative series of 567 men with suspected PCa, 281 (49.6%) had serum PSA between 2 and 10 ng/mL, prostate volume ≥35 mL, and normal DRE (Subset 1), while 286 (50.4%) has serum PSA outside the 2 to 10 ng/mL range, or prostate volume <35 mL, or abnormal DRE (Subset 2). The characteristics of both subsets are presented in Supplement Table 3. We highlight that the median Proclarix score was 21.0% in Subset 1 and 41.0% in Subset 2, p<0.001, and the rate of csPCa was 25.6% in Subset 1 and 55.2% in Subset 2, p<0.001.

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Table 3. Parameters of efficacy of Proclarix score (threshold 10%) to detect clinically significant prostate cancer in overall study population

Parameter	Value
Sensitivity	224/230 (97.4)
Specificity	90/337 (26.7)
Negative predictive value	90/96 (93.8)
Positive predictive value	224/471 (47.6)
Accuracy	314/567 (55.4)
Avoided magnetic resonance imaging	96/567 (16.9)
Undetected clinically significant prostate cancer	6/230 (2.6)
Odds ratio (95% confidence interval)	13.603 (5.838–31.698)
p-value	<0.001

Values are presented as number (%).

Logistic regression analysis for csPCa was performed in both subsets of men and is shown in Table 4. We highlight that Proclarix score was the only significant and independent predictor of csPCa, OR 1.037 (95% CI 1.018–1.056), p<0.001, in Subset 1, and OR 1.057 (95% CI 1.022–1.083), p<0.001, in Subset 2. The ROC analyses of the Proclarix score in the men of Subset 1 is presented in Fig. 1C, with AUC=0.701 (95% CI 0.637–0.765). DCA showing the net benefit of Proclarix is presented in Fig. 1D. Among men of Subset 2, the ROC analyses of Proclarix score is presented in Fig. 1E, with AUC=0.754 (95% CI 0.701–0.807; p=0.038). DCA showing the net benefit of Proclarix is presented in Fig. 1F (p=0.038).

The parameters of the efficacy of Proclarix using the threshold of 10% in both subsets of men are summa-

Table 4. Logistic regression analysis of candidate predictors for clinically significant prostate cancer detection regarding the characteristic of men with suspected prostate cancer

Predictor	Subset 1		Subset 2	
	Odds ratio (95% confidecne interval)	p-value	Odds ratio (95% confidence interval)	p-value
Age (ref. previous year)	1.005 (0.960–1.051)	0.845	1.032 (0.945–1.102)	0.189
Prostate cancer family history (ref. no)	1.397 (0.541–3.602)	0.490	1.707 (0.654–4.455)	0.274
Type of biopsy (ref. initial)	1.225 (0.619–2.422)	0.560	0.510 (0.270–0.963)	0.138
Digital rectal examination (ref. normal)	-		1.637 (0.980–3.610)	0.089
Prostate-specific antigen (ref. previous ng/mL)	0.957 (0.817–1.120)	0.581	1.001 (0.990–1.011)	0.912
Proclarix (ref. previous percent)	1.037 (1.018–1.056)	<0.001	1.057 (1.022–1.083)	<0.001

-: not available.
Subset 1 (men with serum prostate-specific antigen 2 to 10 ng/mL, and prostate volume ≥35 mL, and normal digital rectal examination), and Subset 2 (men who do not meet any of the previous characteristics).

Table 5. Parameters of efficacy for Proclarix, using a threshold of 10%, regarding the characteristics of men

Parameter	Subset 1	Subset 2
Sensitivity	69/72 (95.8)	155/158 (98.1)
Specificity	68/209 (32.5)	22/128 (17.2)
Negative predictive value	68/71 (95.8)	22/25 (88.0)
Positive predictive value	69/219 (31.5)	155/261 (59.4)
Correct classification	137/281 (48.8)	177/286 (61.9)
Avoided magnetic resonance imaging	71/281 (25.3)	25/286 (8.7)
Undetected clinically significant prostate cancer	3/72 (4.2)	3/158 (1.9)
Odds ratio (95% confidence interval)	11.092 (3.369–36.519)	10.720 (3.130–36.735)
p-value	<0.001	<0.001
Prostate cancer detection	117/281 (41.6)	179/286 (62.6)
Clinically significant prostate cancer detection	72/281 (25.6)	158/286 (55.2)
Insignificant prostate cancer detection	45/281 (16.0)	21/286 (7.3)

Values are presented as number (%).
Subset 1 (men with serum prostate-specific antigen 2 to 10 ng/mL, and prostate volume ≥35 mL, and normal digital rectal examination), and Subset 2 (men who do not meet any of the previous characteristics).

rized in Table 5. We highlight that Proclarix presented a sensitivity of 95.8% in Subset 1 and 98.1% in Subset 2, and specificities of 32.5% and 17.2%, respectively. From the clinical point of view, Proclarix will avoid 25.3% of mpMRI and derived prostate biopsies in Subset 1 with 4.2% misdiagnosis of csPCa, while in Subset 2, these rates were 8.7% and 1.9%, respectively.

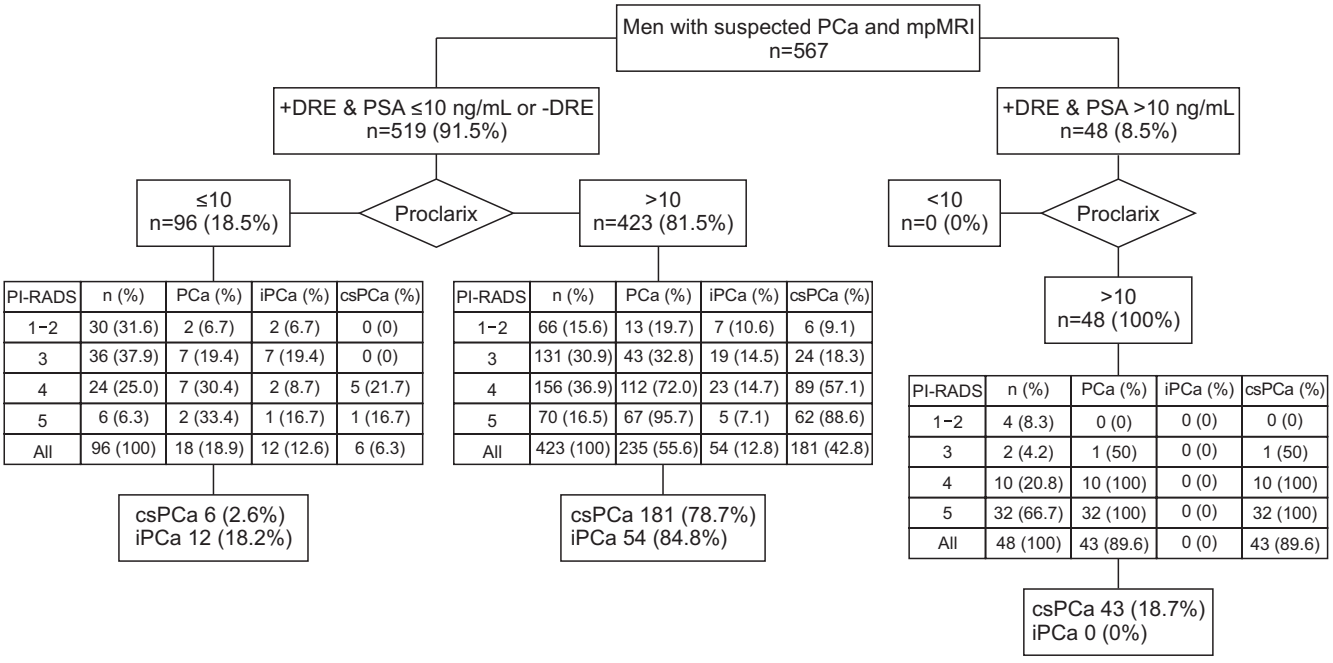
4. Design of an algorithm integrating the characteristics of serum PSA, DRE, and Proclarix to select appropriate candidates for mpMRI and derived prostate biopsies

We detected 48 men (8.5%) with +DRE and PSA >10 ng/mL in whom mpMRI and guided biopsies do not increase the efficacy of systematic biopsies [20]. Proclarix was >10% in all these men and csPCa was detected in 43 (89.6%); Fig. 2. We also confirmed that guided biopsies did not increase the rate of csPCa detection. Both systematic and guided biopsies detected 8 men with GG=2, 10 with GG=3, 11 with GG=4, and 14 with GG=5. Therefore, we propose that men with +DRE and PSA >10 ng/mL will be directly schedule for systematic biopsies (Fig. 3). Among the remaining 519 men who had normal DRE, or abnormal DRE with serum PSA ≤10 ng/mL, Proclarix was ≤10% in 96 (18.5%). iPCa was detected in 12 (18.2% of all iPCa) and csPCa was detected in 6 (2.6% of all csPCa). Proclarix was >10% in 423 men (81.5%). iPCa was detected in 54 (84.8% of all iPCa), and csPCa was detected in 181 (78.7% of all csPCa) (Fig. 2). We propose avoiding mpMRI and derived prostate biopsies among men with Proclarix <10% and performing guided and/or systematic prostate biopsies in those with Proclarix >10% (Fig. 3). This algorithm will avoid 25.4% of mpMRIs, 17.5% of prostate biopsies, and 18.2% of iPCa overdiagnosis, with 2.6% misdiagnoses of csPCa (Fig. 3).

Among 423 men with PI-RADS ≥3 in whom guided and systematic biopsies were performed, csPCa was detected in 181 (42.8%). In 121 men, both biopsies identified csPCa (66.9%), only the guided biopsies identified csPCa in 31 (17.1%), and only the systematic biopsies identified csPCa in 28 (15.5%), p=0.458.

DISCUSSION

The new marker Proclarix has been associated with PCa grading, but used to compare men without PCa or GG 1 with those with GG 2 or 3 and those with GG 4 or 5 [10,21]. The present study confirms that Proclarix score is associated with the GG, but it cannot



PI-RADS	n (%)	PCa (%)	iPCa (%)	csPCa (%)
1–2	30 (31.6)	2 (6.7)	2 (6.7)	0 (0)
3	36 (37.9)	7 (19.4)	7 (19.4)	0 (0)
4	24 (25.0)	7 (30.4)	2 (8.7)	5 (21.7)
5	6 (6.3)	2 (33.4)	1 (16.7)	1 (16.7)
All	96 (100)	18 (18.9)	12 (12.6)	6 (6.3)

PI-RADS	n (%)	PCa (%)	iPCa (%)	csPCa (%)
1–2	66 (15.6)	13 (19.7)	7 (10.6)	6 (9.1)
3	131 (30.9)	43 (32.8)	19 (14.5)	24 (18.3)
4	156 (36.9)	112 (72.0)	23 (14.7)	89 (57.1)
5	70 (16.5)	67 (95.7)	5 (7.1)	62 (88.6)
All	423 (100)	235 (55.6)	54 (12.8)	181 (42.8)

PI-RADS	n (%)	PCa (%)	iPCa (%)	csPCa (%)
1–2	4 (8.3)	0 (0)	0 (0)	0 (0)
3	2 (4.2)	1 (50)	0 (0)	1 (50)
4	10 (20.8)	10 (100)	0 (0)	10 (100)
5	32 (66.7)	32 (100)	0 (0)	32 (100)
All	48 (100)	43 (89.6)	0 (0)	43 (89.6)

Fig. 2. Multiparametric magnetic resonance imaging reports (PI-RADSv.2) and prostate biopsy results regarding the proposed algorithm in men with suspected PCa, based on serum PSA >3.0 ng/mL and/or abnormal DRE, in whom mpMRI and guided and/or systematic biopsies were performed. PCa: prostate cancer, mpMRI: multiparametric magnetic resonance imaging, DRE: digital rectal examination, PSA: prostate-specific antigen, csPCa: clinically significant PCa, iPCa: insignificant PCa.

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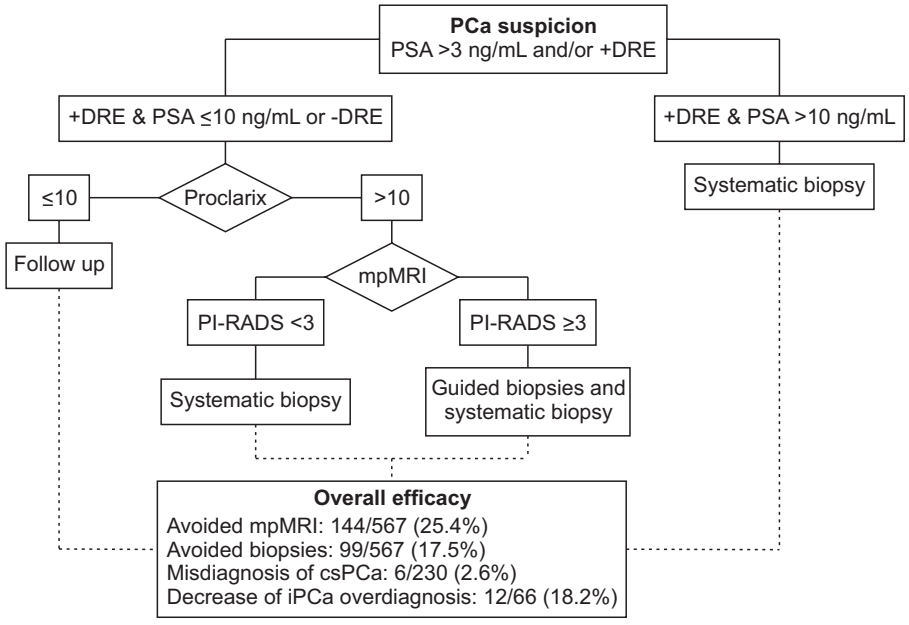

Fig. 3. Overall efficacy of a proposed algorithm, which uses Proclarix evaluation, after PCa suspicion, in men with abnormal DRE and serum PSA ≤10 ng/mL, and those with normal DRE. Men with abnormal DRE and serum PSA >10 ng/mL are directly scheduled to systematic biopsy without previous mpMRI. PCa: prostate cancer, PSA: prostate-specific antigen, DRE: digital rectal examination, mpMRI: multiparametric magnetic resonance imaging, csPCa: clinically significant PCa, iPCa: insignificant PCa.

distinguish between GG 2 and GG 3. We also report that Proclarix is associated with the clinical stage of PCa and the risk of recurrence of treated localized PCa. Nowadays, only the recently published PROPOSe study has analyzed the relationship between Proclarix score and the results of mpMRI. The authors analyze the biopsy results in 121 men with positive mpMRI, suggesting that Proclarix represents a valuable rule-out test in the diagnostic algorithm for PCa, alone or in combination with mpMRI [21].

Proclarix has been used in men with PSA between 2 and 10 ng/mL, prostate volume <35 mL, or abnormal DRE [10-14,21]. We have tested Proclarix in men outside of these characteristics, representing half of our correlative case mix of men with suspected PCa. This is especially relevant with the prostate volume, which is currently not known before mpMRI because transrectal ultrasonography is not usually performed for this purpose [22]. Both populations are different in terms of csPCa incidence, which was 25.3% and 55.5%, respectively. The sensitivity of Proclarix was very high in both subsets of men, 95.8% in men with PSA between 2 and 10 ng/mL, prostate volume <35 mL, or abnormal DRE and 98.1% in the others. However, the specificities were 32.5% and 17.2% respectively. To summarize, Proclarix showed net benefit in both subsets of men with suspected PCa; however, Proclarix was able to reduce 25.3% of mpMRI and derived prostate biopsies in men with serum PSA 2 to 10 ng/mL, and prostate volume ≥35 mL, and normal DRE, while it reduced 8.7% of mpMRI request in those men who did not meet any of these characteristics. The misdiagnosis rate of csPCa was 4.2% and 1.9%, respectively.

We intended to analyze how Proclarix can be used to select appropriate candidates for mpMRI. Because there is evidence that men with abnormal DRE and serum PSA >10 ng/mL do not benefit from mpMRI and guided biopsies [20,23], we propose that these men be scheduled directly for systematic prostate biopsy. The rate of csPCa in these men, who represents around 10% of all men with suspected PCa, was 89.6%; that is, 18.7% of all detected csPCa. Then, we propose that Proclarix will be evaluated in men with normal DRE, and those with abnormal DRE and serum PSA ≤10 ng/mL. Among these men, around 20% had a Proclarix of ≤10%, which was our target for avoiding mpMRI and derived prostate biopsies. Here, the misdiagnosis of csPCa represented 2.6% of all csPCa detected, and the overdiagnosis of iPCa was 18.2% of all iPCa detected. Finally, all men with Proclarix >10% will be scheduled for guided and/or systematic prostate biopsy. This overall approach will reduce the request for mpMRIs by 25.4%, the number of prostate biopsies by 17.5%, the overdetection of iPCa by 18.2%, and the misdiagnosis of csPCa will be 2.6%.

The comparison between Proclarix and other markers is difficult [24-28]. SelectMDx seems more sensitive than mpMRI but less specific [24]. In a cohort of 599 biopsy naïve men scheduled to guided and/or systematic biopsies, SelectMDx will avoid 38% of prostate biopsies

with 10% of csPCa misdiagnosis [25]. 4K test has been shared with mpMRI and clinical variables in a predictive nomogram [26]. In a study of 266 biopsy-naïve men in whom 74 csPCa were detected (27.8%), 4K <7.5 will avoid 32 (12%) mpMRI and 1 csPCa between 74 (1.4%) csPCa will be misdiagnosed [27]. Prostate Health Index has been analyzed only in biopsied men with PI-RADS ≥3 [28]. Comparisons between markers can be only effective in head-to-head studies. We believe that the major strength of Proclarix when used to select appropriate candidates for mpMRI and derived prostate biopsies, is its high sensitivity for csPCa. Nevertheless, the final benefit of any strategy for csPCa detection should be analyzed in terms of health benefit, through appropriate studies of cost-effectiveness analyzing the quality-adjusted life years and healthcare cost [29].

Limitations of our study are its retrospective design and the definition of csPCa used in prostate biopsies which may not represent the true pathology. External and multicenter validation of these results is necessary.

CONCLUSIONS

Proclarix is associated with the clinical stage and grading of PCa, the risk of biochemical recurrence of treated localized PCa, and the type of pathology from surgical specimens. Proclarix is valuable for csPCa detection in all men with suspected PCa, independently of their PSA level, prostate volume, or DRE. Proclarix can be integrated into an algorithm to select appropriate candidates for mpMRI and derived prostate biopsies.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: JM, MC. Data curation: AC, LR, SR, LdT, M.S,. Formal analysis: JM. Methodology: JM, AS, JP. Software: Filemaker14, SPSS 25, Bookends13.2.3. Supervision: JM, ET. Writing – original draft: JM. Writing – review & editing: JM, ET.

Supplementary Materials

Supplementary materials can be found *via* https://doi.org/10.5534/wjmh.210117.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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