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Mobile phone apps for the prediction of prostate cancer: External validation of the Coral and Rotterdam apps

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ABSTRACT

Objective: To analyze the performance of two mobile phone apps—the Rotterdam prostate cancer risk app and the Coral app—in a cohort of patients undergoing prostate biopsies.
Methods: A consecutive series of men undergoing prostate biopsies were enrolled in two centers. Indications for prostate biopsy included abnormal prostate-specific antigen levels (PSA >4 ng/mL) and/or an abnormal digital rectal examination (DRE). Prostate cancer risk and high-grade prostate cancer risk were assessed using the Rotterdam prostate cancer risk app (iOS) and the Coral app (iOS). The usability of the apps was also assessed and compared using the Post-Study System Usability Questionnaire (PSSUQ) developed by IBM.
Results: Overall, 1682 patients with a median age of 68 (62–73) years were enrolled. The Rotterdam app outperformed the Coral app in the prediction of prostate cancer (AUC: 0.70 versus 0.631, $p = 0.001$) and of high-grade prostate cancer (0.75 versus 0.69, $p = 0.001$) (Fig. 1). PSSUQ data revealed that both Rotterdam and Coral applications were comparable in terms of usefulness (87% versus 83%, $p = 0.708$), information quality (74% versus 72%, $p = 0.349$), interface quality (79% versus 74%, $p = 0.216$) and satisfaction (76% versus 76%, $p = 0.935$), respectively. In terms of preferences, 26/50 (54%) preferred the Rotterdam app, while 24/50 (46%) preferred the Coral app.
Conclusion: In our experience the Rotterdam App outperformed the Coral App for the prediction of prostate cancer or high-grade cancer diagnosis. In particular we confirmed, using the Rotterdam app, that only one out of ten patients with a low Rotterdam score will harbor high-grade prostate cancer on biopsy.

Introduction

Prostate cancer (PCa) is the second most commonly diagnosed malignancy in men, with an estimated 1.1 million diagnoses worldwide in 2012 [1]. Diagnosis of PCa is driven mostly by a persistent elevation in serum levels of prostate-specific antigen (PSA), and this triggers a prostate biopsy. However, PSA is far from ideal as a tumor marker as its accuracy is low, leading to a large number of unnecessary prostate biopsies. Among patients with PSA levels between 2 and 10 ng/mL only 20–40% will have a diagnosis of PCa [2,3].

In order to overcome the diagnostic limitations of PSA testing, the European Association of Urology guidelines recommend an individualized risk assessment of the patient [4]. According to the literature, family history of PCa, age, abnormal digital rectal examination, serum markers, urine markers, and multiparametric MRI (mpMRI) are useful tools, combined with PSA levels, to accurately predict PCa. Recently, many authors have developed PCa risk calculators, including some of these risk factors to enhance the diagnostic accuracy of PSA. However, none has clearly shown superiority, so which one to use remains a personal decision [5].

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A recent meta-analysis evaluated all the available calculators. The most studied nomograms/calculators include the European Randomised Study of screening for PCa calculator (ERSPC) [6] and the North American prostate cancer prevention trial-based risk calculator (PCPT) [7]. To make these calculators more accessible to physicians and patients, the Rotterdam app and the Coral app have recently been developed to calculate PCa and high-grade PCa risk based on the ERSPC and PCPT risk calculators, respectively. According to a recent review, these apps are the only two available that predict pre-biopsy PCa risk; however, no external validation or comparison has been performed [8].

Although there is growing interest in mpMRI, genomic testing and fusion biopsies for the diagnosis of PCa, these are still not widely available. Mobile phone calculators, which present the advantage of being cheaper, less time-consuming, and available worldwide, are strongly recommended by the latest EAU guidelines as a valid alternative to serum/urine-based testing—e.g. Prostate Health Index (PHI) test, four kallikrein (4 K) score, prostate cancer gene 3 (PCA3), HOXC6/DLX1—or mpMRI.

With this knowledge in mind, the aim of our study is to validate the diagnostic performance and test the usability of the two mobile phone apps in a cohort of patients at increased risk of PCa undergoing prostate biopsies.

Materials and methods

After Internal Review Board approval, a consecutive series of patients with no history of PCa undergoing initial prostate biopsy because of an abnormal finding on digital rectal examination (DRE) and/or an elevation of serum levels of PSA (>4 ng/mL) were enrolled in two centers. All patients signed a dedicated informed consent, and the study was conducted in accordance with the principles of the declaration of Helsinki. Patients with a previous diagnosis of PCa, previous biopsies, PSA <0.4 ng/mL or >30 ng/mL, or prostate volume (PV) <10 mL or >110 mL were excluded (PSA and PV boundaries were defined by the admitted input). DRE was performed by a senior staff urologist and judged positive if suggestive of cancer. Body mass index (BMI) was calculated as kg/m^2. Every patient underwent 12-core TRUS (transrectal ultrasound) biopsy with the same scheme, following our department's protocol [9]. All biopsies were performed and pathologically reviewed in the same institute by a single dedicated pathologist in each center. Low-grade disease was defined as Gleason $\leq$6 and high-grade disease as Gleason $\geq$7 as defined by the mobile apps. Total PSA was measured the day of the biopsy. Before the biopsy, two independent investigators (RL and GT) calculated prostate cancer risk and high-grade prostate cancer risk according to two different phone applications. The Rotterdam Prostate Cancer Risk app includes mandatory data on age, previous negative biopsies, DRE outcome, PSA, and prostate volume. The Coral app includes data on race, age, PSA, DRE outcome, previous negative biopsies, and family history of PCa. Prostate biopsy was carried out independently of the app results. Both apps were developed in a population of patients undergoing 12-core random prostate biopsies.

The usability of the apps was also assessed and compared using the Post-Study System Usability Questionnaire (PSSUQ), developed by IBM, in a group of 50 participants not involved in the study; this group comprised urologists, oncologists, radiotherapists and medical students. An alpha value of 5% was considered as the threshold for significance.

Statistical analysis

Statistical analysis was performed using SPSS 24 (IBM, statistical software) and STATA software (Stata software version 14, StataCorp 2015 *Stata Statistical Software: Release 14*, College Station, TX: StataCorp LP). Continuous variables are presented as median and interquartile ranges (IQRs) and were compared by the Student independent *t*-test, the Mann–Whitney *U* test or Kruskal–Wallis one-way based on their normal or not-normal distribution, respectively (normality of the distribution of variables was tested by the Kolmogorov–Smirnov test). Categorical variables were tested with the chi-square test.

Using multiple logistic regression with the enter method, the statistically significant variables as assessed in univariate analysis were entered and investigated as predictors of presence versus absence of prostate cancer, and in a separate model comparing high-grade versus low-grade disease among men with cancer at biopsy. Low-grade disease was defined as Gleason $\leq$6 and high-grade disease as Gleason $\geq$7 as defined by the mobile apps. The logistic regression analysis was carried out using complete data. Receiver operator characteristic curves (ROCs) were produced to evaluate the area under the curve (AUC) and the diagnostic performance of the two nomograms; comparisons were made using DeLong's method. Performance characteristics of the apps were assessed by calibration plots, where the x axis represents the predicted probability and the y axis represents the actual observed accuracy of the biopsy. Significance of an observed miscalibration was tested via the Hosmer–Lemeshow test. For this test, a p value < 0.05 indicates a poor agreement between predicted probabilities and observed outcome. Decision curves were generated to compare the net benefit of each risk calculator.

Results

Overall, 636/1682 patients (39.8%) were diagnosed with prostate cancer and 366/636 (57%) had high-grade cancer (Gleason score $\geq$7). Characteristics of the patient cohort according to the presence or absence of cancer are listed in Table 1. Patients with positive biopsies, and particularly those with high-grade cancer, were older, had smaller prostates, had higher levels of PSA, and were more likely to have a positive DRE. Age, TRUS volume, PSA and DRE were found to be significant predictors of cancer and high-grade cancer in univariate and multivariate analysis (Table 2).

Discrimination

Both the models significantly predicted PCa on ROC analysis. The Rotterdam app out-performed the Coral app in the prediction of prostate cancer (AUC: 0.70 versus 0.631, p = 0.001) and high-grade PCa (0.75 versus 0.69, p = 0.001) (Fig. 1).

Calibration

The calibration of the two models was assessed graphically and with the Hosmer–Lemeshow test. Both apps showed good calibration (p > 0.05) for the prediction of PCa according to the Hosmer–Lemeshow test. In terms of prediction of high-grade disease, only the Rotterdam app showed a good calibration when compared to the Coral app. (See Figs. 2 and 3).

Performance of the models

At the decision curve analysis (DCA), the net benefit for the Rotterdam app was greater when compared to the Coral app for the prediction of both PCa and high-grade PCa. More specifically, the Rotterdam app showed a net benefit when the threshold probability was between 30% and 90% for PCa detection and between 15% and 60% for high-grade PCa detection. The Coral app showed a net benefit when the threshold probability was between 20% and 60%

Table 1
Patient characteristics.

	Overall	No cancer	Cancer	p value	Low-grade (GS 6)	High-grade (GS > 7)	p value
Patients	1682	1046/1682 (62%)	636/1693 (38%)		270/636 (43%)	366/636 (57%)	
Age (years)	67.3 ± 8.0 (68; 62/73)	66.3 ± 7.9 (66; 61/72)	69.1 ± 7.9 (70; 64/75)	.001	67.3 ± 8.0 (68; 61/74)	70.5 ± 7.7 (71; 65/76)	0.001
PSA (ng/mL)	8.3 ± 4.9 (6.7; 4.8/9.9)	7.7 ± 5.2 (6.4; 4.6/9.1)	9.4 ± 7.2 (7.0; 5.0/11.2)	.001	7.8 ± 5.0 (6.9; 4.9/9.7)	10.4 ± 8.2 (7.8;5.1/12.2)	0.008
BMI (kg/m^2)	27.1 ± 4.9; (27;25/29)	27.0 ± 3.6 (27; 25/29)	27.3 ± 6.4 (27; 25/29)	.475	26.2 ± 3.6 (26;25/29)	27.3 ± 3.6 (27;25/29)	0.257
TRUS volume (mL)	54.9 ± 28.8 (48; 35/68)	59.3 ± 29.1 (53; 40/72)	47.2 ± 26.6 (40; 30/55)	.001	50.4 ± 31.6 (40;30/58)	44.7 ± 21.7 (40; 30/54)	0.867
DRE	374/1682 (21.3%)	158/1046 (15%)	216/636 (34%)	.001	60/270 (22%)	156/366 (42%)	0.001
Family history	151/1682 (9%)	62/1046 (6%)	89/636 (14%)	.001	30/270 (11%)	20/366 (22%)	0.004
Rotterdam cancer risk output	25.5 ± 19.2 (21; 11/34)	20.0 ± 14.6 (27; 15/27)	34.4 ± 22.2 (29; 17/50)	.001	27.4 ± 18.2 (24; 14/37)	39.7 ± 23.3 (36; 20/57)	0.001
Rotterdam high-grade cancer risk output	10.9 ± 14.42 (5; 2/14)	12.5 ± 8.6 (10; 7/16)	12.5 ± 8.6 (10; 7/16)	.001	11.2 ± 13.1 (6; 2/15)	21.8 ± 20.5 (15; 6/33)	0.001
Coral cancer risk output	32.5 ± 10.2 (31; 26/37)	30.58 ± 9 (30; 25/35)	35.54 ± 11.2 (33; 28/42)	.001	32.10 ± 8.9 (31; 26/37)	38.12 ± 12.1 (35; 30/45)	0.001
Coral high-grade cancer risk output	12.5 ± 8.6 (10; 7/16)	10.8 ± 7 (9; 6/13)	15.1 ± 10.2 (12; 8/20)	.001	12.02 ± 7.3 (16; 10/16)	17.4 ± 11.3 (14; 9/23)	0.001

Data are presented as means ± DS (median; IQR).
BMI, body mass index; IPSS, International Prostate Symptom Score; GS, Gleason score; PSA, prostate-specific antigen; TRUS, transrectal ultrasound; DRE, digital rectal examination.

Table 2
Multivariable analysis for predicting prostate cancer and high-grade cancer.

	Patients	Prostate cancer	p	High Grade Cancer	p
Age (years)	1682	1.033 (1.017–1.049)	0.001	1.033 (1.008–1.058)	0.009
PSA (ng/mL)	1682	1.052 (1.030–1.075)	0.001	1.062 (1.026–1.100)	0.001
TRUS volume (mL)	1682	0.980 (0.975–0.985)	0.001	0.991 (0.984–0.998)	0.013
DRE	1682	2.798 (2.148–3.645)	0.001	2.853 (1.912–4.258)	0.010

Data are presented as odds ratios (confidence intervals).
PSA, prostate-specific antigen; TRUS, transrectal ultrasound; DRE, digital rectal examination.

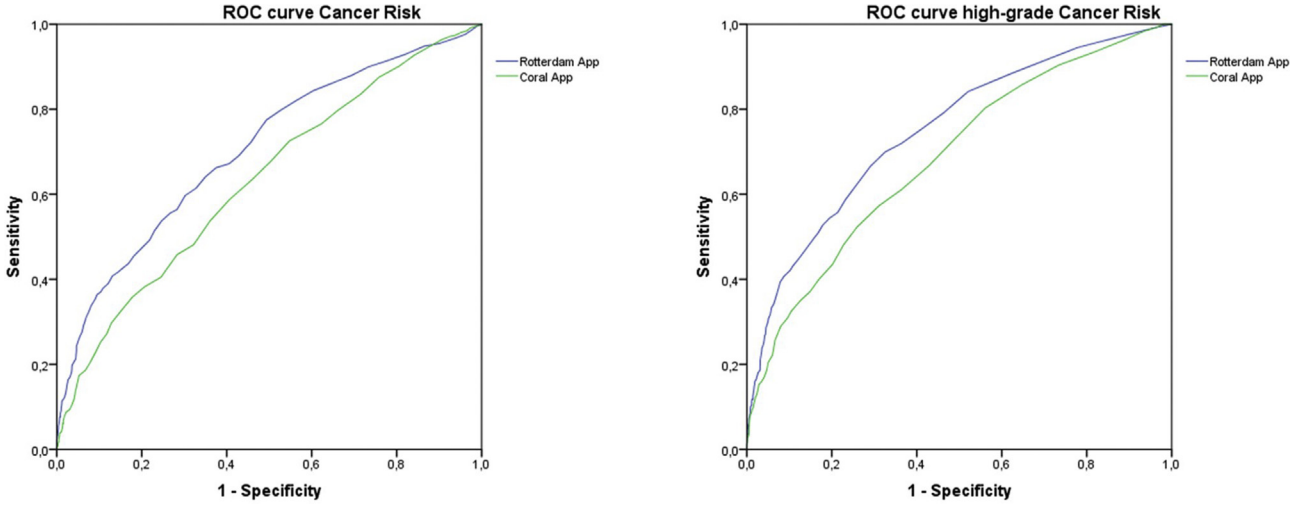

Fig. 1. Receiver operator characteristics for the mobile phone apps.

for PCa detection and between 15% and 60% for high-grade PCa detection Fig. 4.

Usability

PSSUQ data revealed that both Rotterdam and Coral applications were comparable in terms of usefulness (87% versus 83%, p = 0.708), information quality (74% versus 72%, p = 0.349), interface quality (79% versus 74%, p = 0.216) and satisfaction (76% versus 76%, p = 0.935), respectively. In terms of preferences, 26/50 (54%) preferred the Rotterdam app while 24/50 (46%) preferred the Coral app.

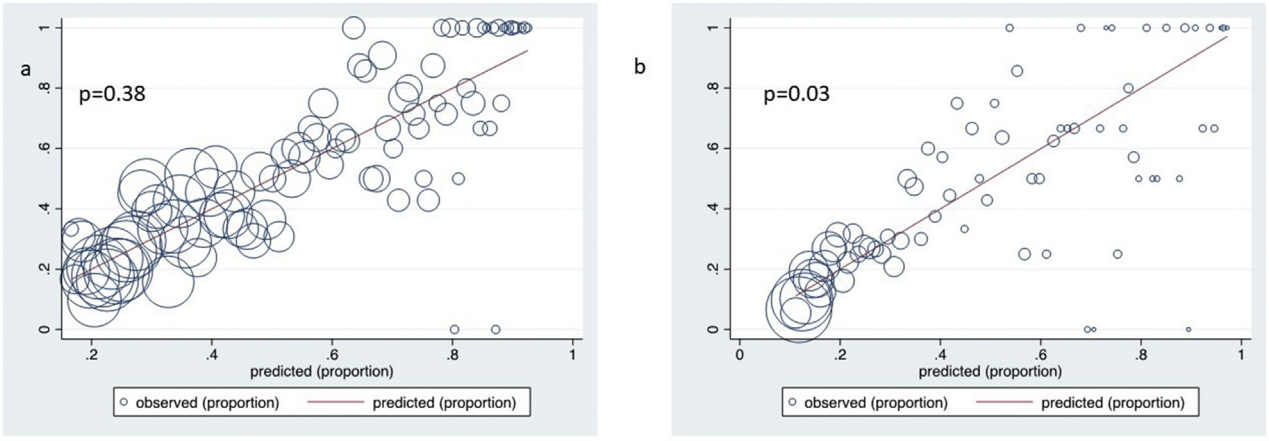

Fig. 2. Hosmer–Lemeshow goodness-of-fit test of observed proportion versus predicted probability of prostate cancer (a) and clinically significant prostate cancer (b) for the Rotterdam app.

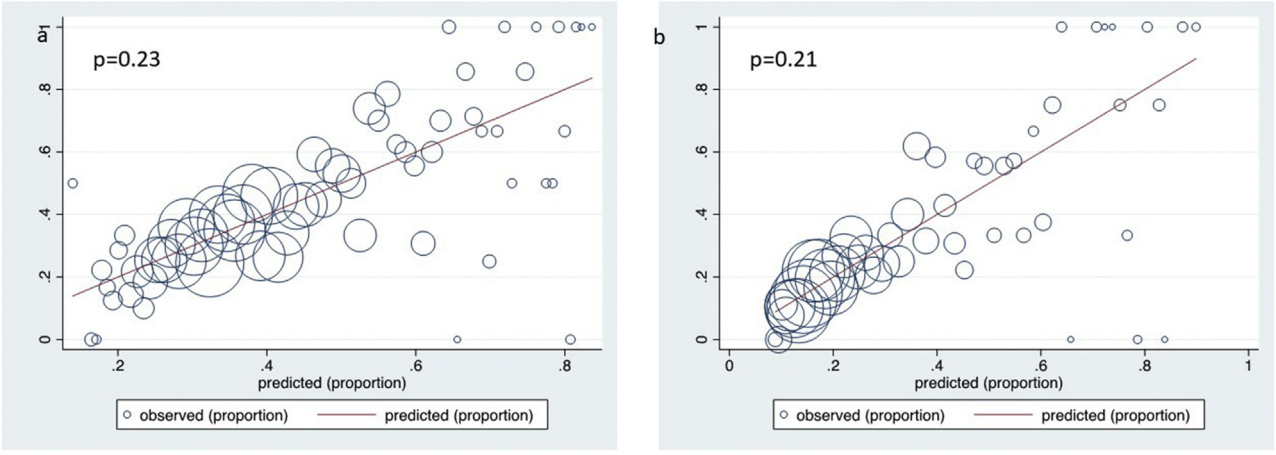

Fig. 3. Hosmer–Lemeshow goodness-of-fit test of observed proportion versus predicted probability of prostate cancer (a) and clinically significant prostate cancer (b) for the Coral app.

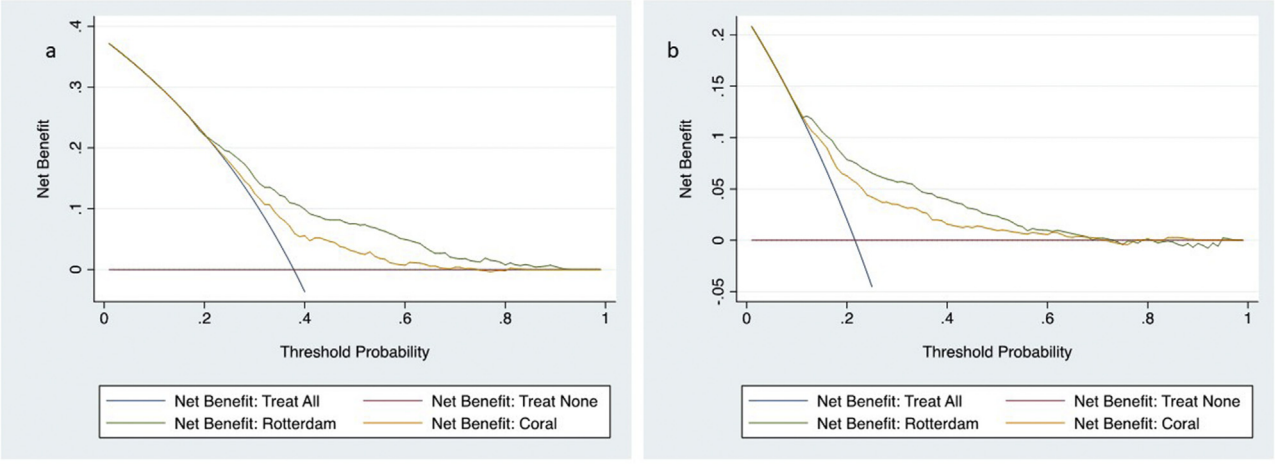

Fig. 4. Decision curve analyses demonstrating the net benefit associated with the use of the novel nomogram on the detection of overall prostate cancer (a) and clinically significant prostate cancer (b). Decision curve analysis is a method for evaluating and comparing prediction models that incorporates clinical consequences.

Discussion

The present study successfully validated the Rotterdam and Coral mobile phone apps in patients at risk of PCa undergoing prostate biopsies. According to our results both apps showed fair predictive accuracies for PCa and high-grade PCa detection. Moreover, both apps showed very good usability among medical students and physicians.

The two mobile phone applications represent mobile versions of the web-based risk calculators. The Coral app is based on the results of the study by Ankerst et al. who modified the first version of the PCPTRC to predict low-versus high-grade (Gleason grade $\geq$7) prostate cancer [10]. Although the PCPT trial was based on six-core biopsy, further studies have shown that the accuracy of PCPTRC 2.0—built on an expanded cohort from that used for the original PCPTRC—is maintained for contemporary extended biopsy populations [10,11]. In our experience, the Coral mobile phone application showed a fair performance and good usability. The Rotterdam app is based on the results of the ERSPC trial and is available as a mobile phone app and also as an online calculator. In our cohorts the Rotterdam app proved to have fair abilities for the prediction of PCa and high-grade PCa and was slightly better than the Coral app. The discriminating abilities of the Rotterdam app are in line with the available studies using the web-based Rotterdam risk calculator. A recent systematic review by Adam et al. searched for and rated all the available applications for prostate cancer [8]. They found 83 apps; however, most of them were excluded, and only seven apps were left for analysis. According to their experience the Coral and Rotterdam apps were rated the best according to the Mobile Application Rating Scale. In line with the experience of Adam et al., we confirm that both apps have optimal usefulness, information quality, interface quality and satisfaction [8].

Nowadays, advances in technology have promoted the use of smartphones for health promotion and clinical practice. Patients and clinicians should be warned to use these tools with caution, especially because apps may not be keeping in touch with the latest evidence-based guidelines. Most of the available studies on mobile phone apps concentrate on usefulness and not on the accuracy of the information given by the app [12]. With this in mind, in our study two physicians calculated the risk of PCa and high-grade PCa according to both mobile apps to test their performance; for the first time we have confirmed the accuracy and clinical benefit of both apps for the prediction of PCa and high-grade PCa.

It is important to underline the advantages and limitations of mobile phone apps for the prediction of PCa. Mobile phone apps, once installed, are widely available and will calculate PCa risk within seconds. Moreover, the real improvement when compared to nomograms relies on the possibility of inputting just the available clinical parameters. More specifically, the app may calculate the risk for a patient only on the basis of clinical history and PSA, or on the basis of additional variables such as DRE, TRUS volume or Phi score when applying the most accurate model. Lastly, apps can be easily downloaded by the patient who can calculate their own risk; however, the patient should always seek clinical/urological advice after the calculation in order to avoid erroneous assumptions.

A possible limitation of the available models is the lack of MRI data or genomic testing in the models; these techniques are slowly becoming widely available, especially in USA [13]. However, in Italy and Spain MRI/genomic testing are not widely available, particularly in the first-biopsy setting, and these models may represent a useful alternative to discuss PCa risk with the patient, as stated in the latest EAU guidelines [14]. Another important limitation of the actual models is the definition of high-grade disease (Gleeson score $\geq$7) which is outdated since the introduction of the new Epstein prognostic grading group (PGG). However, this is a problem common to all the available tools in PCa considering that the new PGG was introduced in 2014. The possible positive impact on patient decision-making of the current mobile phone apps has not been yet demonstrated, and so far in our institution the Rotterdam app has been implemented in everyday clinical practice to evaluate the possible effect on patient decisions [15].

We have to consider some limitations to our study. This is a European two-center experience, so the results clearly depend on the enrolled population. We certainly acknowledge that it takes more than one study and one cohort of patients to prove a hypothesis. PCa epidemiology presents large differences due to racial and geographical issues that need to be explored [16,17]. We have performed the study in a southern European cohort of patients that may be different from northern European, North American, South American and Asian populations. Another limitation, common to most studies in this area, derives from the use of biopsy cohorts without confirmation by radical prostatectomy specimens. We also have not compared the two apps with the available online calculators. However, as observed in other medical and non-medical applications, apps are outperforming website applications in relation to their better immediacy, compatibility, shareability and upgradeability. To the best of our knowledge, our study is the first available study comparing the accuracy of the two mobile phone apps for the prediction of PCa in a cohort of patients undergoing prostate biopsy using the same biopsy template for the entire population and confirming the accuracy and clinical applicability of these apps.

Another possible limitation is that prostate volume measured with TRUS is not as accurate as that measured with MRI. Although EAU guidelines and the most updated risk calculators still recommend TRUS as the standard method to evaluate prostate volume [18–20]. Moreover, to validate a model it is important to stay as close as possible to the development cohort which used TRUS volume. Furthermore, in our study we did not test other innovative serum/urine-based tests—prostate health index, 4 K score, prostate cancer gene 3—or MRI imaging in the diagnostic pathway of patients at increased risk of PCa. However, all these tests are expensive, time-consuming and available only in referral centers, which may limit their use in everyday clinical practice. However, at this stage there are no validated MRI-based risk calculators, and the most recent ones still do not include MRI data [18].

Conclusions

In our cohort study, PCa risk apps presented a fair accuracy in the prediction of PCa, and they are better than PSA/DRE alone. The Rotterdam app outperformed the Coral app, although its implementation in clinical practice is needed for a definitive conclusion. Future studies should also integrate these apps with patients' metabolic status, genetic testing, and MRI results, but these are not widely used to evaluate the risk of PCa in the general population. The advantage of a mobile app versus a web-based prostate cancer risk calculator should also be evaluated and balanced in the near future.

Conflict of interest

The authors declare no conflict of interest.

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None.

Author contributions

The authors listed contributed substantially to:

Cosimo De Nunzio: research design, acquisition, analysis and interpretation of data; drafting of the paper, approval of the submitted and final versions.

Riccardo Lombardo: research design, acquisition, analysis and interpretation of data; drafting of the paper, approval of the submitted and final versions.

Giorgia Tema: research design, acquisition, analysis and interpretation of data; drafting of the paper, approval of the submitted and final versions.

Fabiana Cancrini: research design, acquisition and interpretation of data; drafting of the paper, approval of the submitted and final versions.

Giorgio Ivan Russo: research design, analysis and interpretation of data; drafting of the paper, approval of the submitted and final versions.

Rodrigo Chacon: research design, analysis of data; critical revision of the paper; approval of the submitted and final versions.

Eduard Garcia Cruz: research design, analysis of data; critical revision of the paper; approval of the submitted and final versions.

Maria Jose Ribal: research design, interpretation of data; critical revision of the paper; approval of the submitted and final versions.

Giuseppe Morgia: research design, interpretation of data; revised the paper critically; approval of the submitted and final versions.

Antonio Alcaraz: research design, acquisition, analysis and interpretation of data; drafting of the paper, approval of the submitted and final versions.

Andrea Tubaro: research design, acquisition, analysis and interpretation of data; drafting of the paper, approval of the submitted and final versions.

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