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ORIGINAL ARTICLE

External validation of Cormio nomogram for predicting all prostate cancers and clinically significant prostate cancers

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Abstract

Purpose Recently, the Cormio et al. nomogram has been developed to predict prostate cancer (PCa) and clinically significant PCa using benign prostatic obstruction parameters. The aim of the present study was to externally validate the nomogram in a multicentric cohort.

Methods Between 2013 and 2019, patients scheduled for ultrasound-guided prostate biopsy were prospectively enrolled at 11 Italian institutions. Demographic, clinical and histological data were collected and analysed. Discrimination and calibration of Cormio nomogram were assessed with the receiver operator characteristics (ROC) curve and calibration plots. The clinical net benefit of the nomogram was assessed with decision curve analysis. Clinically significant PCa was defined as ISUP grade group > 1.

Results After accounting for inclusion criteria, 1377 patients were analysed. 816/1377 (59%) had cancer at final pathology (574/816, 70%, clinically significant PCa). Multivariable analysis showed age, prostate volume, DRE and post-voided residual volume as independent predictors of any PCa. Discrimination of the nomogram for cancer was 0.70 on ROC analysis. Calibration of the nomogram was excellent ($p = 0.94$) and the nomogram presented a net benefit in the 40–80% range of probabilities. Multivariable analysis for predictors of clinically significant PCa found age, PSA, prostate volume and DRE as independent variables. Discrimination of the nomogram was 0.73. Calibration was poor ($p = 0.001$) and the nomogram presented a net benefit in the 25–75% range of probabilities.

Conclusion We confirmed that the Cormio nomogram can be used to predict the risk of PCa in patients at increased risk. Implementation of the nomogram in clinical practice will better define its role in the patient's counselling before prostate biopsy.

Keywords Prostatic neoplasms · Nomograms · Validation · Prostate biopsy · Prostatic hyperplasia

Introduction

Prostate biopsy (PBx) is the gold standard for diagnosing prostate cancer (PCa) [1]. Nevertheless, the diagnostic yield of this procedure remains low. As such, the rate of PCa detection in the setting of the first PBx performed due to elevated serum prostate-specific antigen (PSA) and/or abnormal digital rectal examination (DRE) is around 40% and even lower in the setting of screening programmes [2, 3]. In the last decades, many efforts have attempted to improve the diagnostic accuracy of PBx, mostly represented by predictive models combining PSA and DRE findings with other patient-related factors such as age and prostate volume (PVol). On the other hand, it has been reported that more complex risk prediction models built up by combining different factors were often unable to outperform PSA alone in predicting PCa [4]. New tools

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are nowadays available in helping to determine the need for a PBx in patients with suspected PCa, namely prostate multiparametric magnetic resonance imaging (mpMRI), and biomarkers such as TMPRSS2-ERG fusion, PCA3 or kallikreins as incorporated in the Prostate Health Index or 4 K score tests [5–9]. They improved sensitivity and specificity versus the ones of PSA alone, but (1) there is limited evidence to implement these biomarkers into the daily practice; (2) prostate mpMRI is not always available [1]. Trying to contribute in this field, Cormio and colleagues recently developed a cheap, non-invasive nomogram based on readily available clinical parameters that could help in assessing the patient's risk of harbouring PCa and clinically significant PCA at PBx [10]. Specifically, the authors found an increased accuracy in predicting both PCa and clinically significant PCa when adding benign prostatic obstruction (BPO) key parameters such as PVol and post-void residual urinary volume (PVR) to a "standard" model based on age, PSA and DRE. The aim of the present study was to externally validate the nomogram in a multi-institutional cohort of patients with suspected PCa who underwent PBx.

Materials and methods

Between 2013 and 2019, the data of patients scheduled for ultrasound-guided PBx (either transrectal or transperineal) because of increased levels of serum PSA (≥ 4 ng/mL) and/or abnormal findings at DRE were prospectively collected in a multi-institutional dataset. Eleven tertiary care Italian institutions contributed to the data collection.

The study was approved by the institutional research ethics committee and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from all individual participants included in the study.

Patient demographics (age), clinical parameters (PSA at biopsy, DRE, PVol, peak flow rate, PVR, eventual mpMRI, ongoing intake of 5-alpha reductase inhibitors (5ARI), indwelling catheter, previous prostate surgery or biopsy) and histological characteristics (number of cores, presence of PCa with Gleason score) were collected and analysed. The International Society of Urological Pathology (ISUP) grade group was assigned accordingly, and the rate of clinically significant prostate cancers was calculated, defined as PCa with an ISUP grade group > 1 [11, 12]. Specifically, for the purpose of the study according to the inclusion criteria of the original nomogram, patients with serum PSA levels > 20 ng/ml at PBx were not considered. Patients taking 5ARI or androgen deprivation therapy at the time of PBx and who had undergone previous PBx were excluded.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS v.24, IBM Corp., Armonk, NY, USA) and STATA (STATA v14.1, College Station, TX, USA). Evaluation of data distribution using the Kolmogorov–Smirnov test showed a non-normal distribution of the study data set. Differences between groups of patients in medians for quantitative variables and differences in distributions for categorical variables were tested with the Kruskal Wallis one-way analysis of variance and Chi-square test, respectively. All variables were assessed using univariate binary logistic regression for the prediction of cancer and high-grade disease. The Cormio nomogram probabilities were calculated for each patient. Receiver operator characteristic (ROC) curves were produced to evaluate the discrimination of the Cormio nomogram for the prediction of PCa and clinically significant PCa. Calibration was assessed using the Hosmer–Lemeshow test (for this test, a p value < 0.05 indicates a poor agreement between the predicted probabilities and observed outcome). Calibration plots were assessed as well, where the x-axis represents the predicted probability and the y-axis represents the actual observed accuracy of the model. Decision curves were generated to evaluate the net benefit of the Cormio nomogram. An alpha value of 5% was considered as the threshold for significance. Data were presented as median with interquartile range (IQR). An α value of 5% was considered as the threshold for significance.

Results

Data of 2003 patients were collected. After accounting for exclusion criteria, 1377 patients were considered. Frequencies and proportions of the contribution per centre are reported in the Supplementary Table 1.

Median age (IQR) was 66 (61–72) years. Median (IQR) PSA at PBx was 6.0 (5.0–9.0) ng/ml. Median (IQR) PVol was 45 (37–64) ml, and median (IQR) PVR 30 (0–52) ml. Four hundred seventy-six out of 1377 patients (35%) had positive DRE. The final pathology reported PCa in 816 out of 1377 patients (59%), with 574 out of 816 patients (70%) showing clinicallybsignificant PCa. Complete data are reported in Table 1.

Multivariable analysis for overall detection of any PCa showed age (odd ratio, OR, 1.035, 95% confidence interval, CI 1.020–1.051, $p = 0.001$), DRE (OR 2.036, 95% CI 1.581–2.621, $p = 0.001$), PSA (OR 1.080, 95% CI 1.047–1.113, $p = 0.001$), PVol (OR 0.981, 95% CI

0.977–0.986, $p = 0.001$), and PVR (OR 0.996, 95% CI 0.993–0.998, $p = 0.001$) as independent predictors of PCa (Table 2).

The discrimination of the nomogram for PCa was 0.70 based on ROC curve analysis (Fig. 1a). The calibration of the nomogram was excellent ($p = 0.94$) and the nomogram presented a net benefit in the 40–80% range of probabilities (Fig. 2a). In a second multivariable model, age (OR 1.058, 95% CI 1.036–1.080, $p = 0.001$), PSA (OR 1.112, 95% CI 1.064–1.162, $p = 0.001$), PVol (OR 0.993, 95%

Table 1 Patient characteristics

	Overall	No cancer	Cancer	*p* value	Low grade (GS 6)	High grade (GS > 7)	*p* value
Patients	1377	560/1377 (41%)	816/1377 (59%)		242/814 (30%)	574/816 (70%)	
Age (years)	66 (61/72)	65 (59/70)	67 (62/72)	0.001	65 (60/69)	68 (63/73)	0.001
PSA (ng/ml)	6.0 (5.0/9.0)	6.0 (4.0/8.0)	6.0 (5.0/9.0)	0.001	6 (4/8)	7 (5/10)	0.001
TRUS volume (ml)	45 (37/64)	52 (40/74)	44 (35/56)	0.001	45 (39/56)	42 (33/56)	0.001
Qmax	13.1 (10/16.3)	13.2 (9.8/16.2)	13 (10/16.3)	0.402	13.2 (10.1/16)	13.3 (10.4/16.4)	0.324
PVR	30 (0/52)	30 (0/58)	25 (0/50)	0.005	30 (0/58)	30 (0/50)	0.001
DRE	476/1377 (35%)	123/560 (23%)	346/816 (42%)	0.001	74/242 (30%)	346/816 (42%)	0.001

Data are presented as mean ± 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 clinically significant prostate cancer

	Prostate cancer prediction				Clinically significant prostate cancer prediction			
	Univariate OR	*p*	Multivariate OR	*p*	Univariate OR	*p*	Multivariate OR	*p*
Age (years)	1.033 (1.019–1.048)	0.001	1.033 (1.008–1.058)	0.001	1.058 (1.036–1.080)	0.001	1.051 (1.034–1.067)	0.001
PSA (ng/ml)	1.053 (1.026–1.080)	0.001	1.080 (1.047–1.113)	0.001	1.112 (1.064–1.162)	0.001	1.113 (1.080–1.148)	0.001
TRUS volume (ml)	0.980 (0.979–0.988)	0.001	0.981 (0.977–0.986)	0.001	0.993 (0.987–0.999)	0.032	0.980 (0.975–0.985)	0.001
Qmax	1.009 (0.992–1.027)	0.306			1.120 (0,990–1.045	0.407		
PVR	0.996 (0.994–0.998)	0.001	0.996 (0.993–0.998)	0.001	0.998 (0.996–1.000)	0.073	0.998 (0.995–1.00)	0.079
DRE	2.435 (1.915–3.097)	0.001	2.036 (1.581–2.621	0.001	2.645 (2.105–3.323)	0.001	2.156 (1.690–2.752	0.001

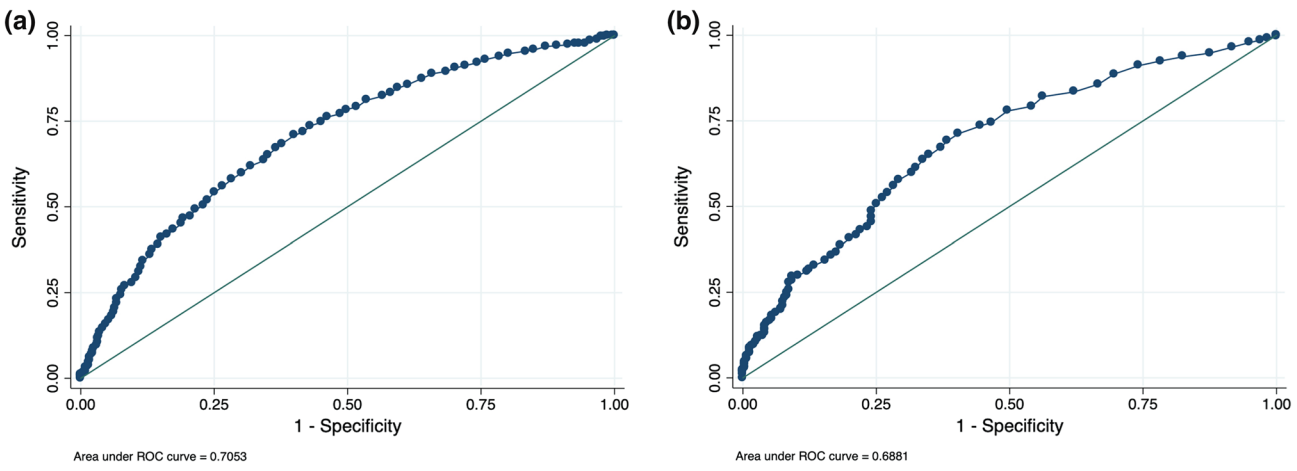

Fig. 1 Receiver operator characteristics (ROC) curves and calibration plots for the Cormio nomogram in the prediction of cancer and clinically significant cancer

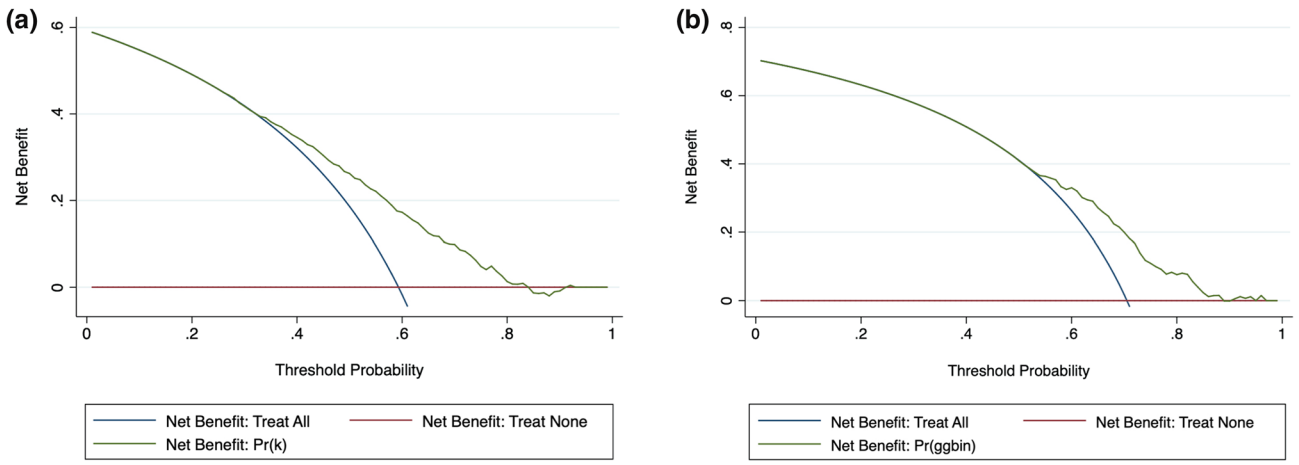

Fig. 2 Decision curve analyses demonstrating the net benefit associated with the use of the Cormio nomogram for the detection of cancer and clinically significant cancer. Decision curve analysis is a method for evaluating and comparing prediction models that incorporate clinical consequences

CI 0.987–0.999, $p = 0.03$), and DRE (OR 2.645, 95% CI 2.105–3.323, $p = 0.001$) were independent predictors of clinically significant PCa (defined as ISUP grade group > 1, versus either no PCa or ISUP grade group = 1). Discrimination of the nomogram for clinically significant PCa was 0.73 according to the ROC curve analysis (Fig. 1b). Calibration of the nomogram was poor ($p = 0.001$) and the nomogram presented a net benefit in the 25–75% range of probabilities (Table 2, Fig. 2b).

Discussion

The 2019 update of the European Association of Urology guidelines for PCa underlines the importance of offering an individualized risk-adapted strategy for the early diagnosis of PCa. Moreover, it stresses the importance of patient participation into the decision-making process when a PBx is suggested [1, 13]. As such, the indication to PBx based on PSA cutoff values can be modified using clinical variables such as the PSA at PBx, the PSA velocity, the PSA ratio, other serum kallikreins, the PVol, and other predictors such as age, family history of PCa, and race alone or in combination within multivariate risk prediction tools, as previously described [14–18]. Cormio et al. recently found that the inclusion of the BPO-related variables (such as PVol and PVR) into a "standard" nomogram based on age, PSA and DRE increases the predictability of PCa in the setting of the first PBx (+ 16% for all prostate cancers versus + 9% for clinically significant PCa) [10]. Their effort ideally aimed to avoid the use of other more expensive, complex, not widely available examinations. As such, the authors underlined that the proposed nomogram was built on reliable clinical parameters that are routinely included in the first-line evaluation of the aging male with lower urinary tract symptoms and/or increased PSA levels.

Actually, a validated predictive tool where a lot of prospective work has been done already suggested the inclusion of BPO-related variables into models for predicting the likelihood of diagnosing PCa at PBx. Namely, the European Randomized Study for Screening of Prostate Cancer (ERSPC) is a well-known PCa risk calculator [19–22]. The ERSPC is based on three variables (PSA, PVol, and DRE): the importance of PVol as a predictor for the biopsy outcome is stressed in the ERSPC model. As such, in one of the original papers about the topic, an interesting example is reported [19]: a PSA of 6 ng/ml that would be undoubtedly considered elevated, especially if paired with an additional suspicious finding at trans-rectal prostate ultrasonography, is compensated by a large PVol (100 cm^3). The probability of diagnosing PCa at PBx would be lowered to roughly 10%. Had the prostate been average around 40 cm^3, the estimated probability of having PCa detected would be equal to 40% instead.

In the present study, we confirmed the reliability of the Cormio nomogram through an external validation based on a multi-institutional cohort of patients with suspected PCa who underwent PBx. The inverse relationship between two proxies of intra-prostatic inflammation, such as increased PVol and PVR, and the risk of being diagnosed with PCa was corroborated as well, in agreement with previous reports [23, 24]. Indeed, prostatic inflammation seems to be associated with benign prostatic hyperplasia rather than PCa [25].

The reader could argue against the high PCa detection rate reported herein. It could potentially affect the calibration of the model from a statistical point of view (the model would overestimate the probability of being diagnosed with PCa, thus requiring the intercept to be modified). However,

the model showed an excellent calibration for PCa in the subset of patients analyzed herein. We therefore believed it would have been useless to recalibrate it. Moreover, in the recent Cochrane review by Drost et al. out of 5219 PBx naïve men pooled from 20 available studies, 53% (95% CI 49–58%) were diagnosed with any PCa that was not significantly different compared to the 59% detected within the present study [26].

Nevertheless, it might be useful to rule out all patients who had positive MRI and perform a re-validation analysis on the subgroup of patients who had negative MRI or remained unexamined. As such, the calibration was poor when considering patient prediction of clinically significant PCa. Notwithstanding these considerations, a recent prospective, multicenter, comparative effectiveness study including 626 patients showed that in biopsy-naïve men, the MRI pathway compared with the standard pathway resulted in an identical detection rate of clinically significant PCa (as defined in the present study), with significantly lower rate of indolent PCa cases [27]. Conversely, there is high-quality evidence showing that MRI in biopsy-naïve men could lower the number of PBx and reduce the overdiagnoses of clinically non-significant PCa [28].

We acknowledge the limitations of the study. (1) The data were collected from multi-institutional experiences, and we were unable to control for different nuances in the setting of PBx. Of course, the multi-institutional nature of the cohort could be seen as a major limitation; however, to evaluate the accuracy and generalizability of prognostic models, the heterogeneity of baseline characteristics, rather than homogeneity, is advisable and desirable. In other terms, the presence of differences among the centres increase the value of the study findings including generalizability. (2) The lack of central pathology review might represent another weakness. However, even if the central pathology review ideally increases validity by minimizing the interobserver variability, it is useless, from a clinical viewpoint, since variability is common in clinical practice. (3) The AUC was not impressively high, but still acceptable. Instead, the decision curve analysis demonstrated the net benefit associated with the use of the model-derived probability for predicting PCa. (4) The Cormio nomogram was not compared with other well-known and widely used predictive models [19, 29]. It will be the goal of future study to compare the performance in predicting PCa among the mentioned models.

Notwithstanding these limitations, the present report confirmed the reliability of the cheap, user-friendly Cormio nomogram, in assessing the risk of PCa in a biopsy-naïve man undergoing the first PBx. In the near future, the adoption of such nomogram could be included in the diagnostic flowchart of men with elevated PSA and/or abnormal DRE: as we definitely enter the prostate MRI era, ideally, when PBx is indicated, a prostate MRI could be subsequently performed in higher risk patients to indicate an eventual targeted PBx to be combined.

Conclusions

The present study better defines the general applicability of Cormio's nomogram for the risk of diagnosing PCa and clinically significant PCa in patients suspected of PCa undergoing the first PBx. Our data suggested that the Cormio nomogram could be a reliable and cheap tool helping the clinicians in the patient's counseling before PBx. Only the implementation of this nomogram in daily practice would better define its true role.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Research involving human participants The study was approved by the institutional research ethics committee and performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all individual participants included in the study.

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