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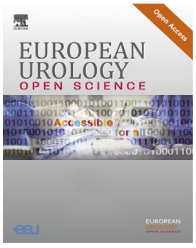

European Association of Urology

Prostate Cancer

A Novel Risk Calculator Incorporating Clinical Parameters, Multiparametric Magnetic Resonance Imaging, and Prostate-Specific Membrane Antigen Positron Emission Tomography for Prostate Cancer Risk Stratification Before Transperineal Prostate Biopsy

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Abstract

Background: Prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) can detect multiparametric magnetic resonance imaging (mpMRI)-invisible prostate tumours and improve the sensitivity of detection of prostate cancer (PCa) in comparison to mpMRI alone. Numerous risk calculators have been validated as tools for stratification of men at risk of being diagnosed with clinically significant (cs)PCa.
Objective: To develop a novel risk calculator using clinical parameters and imaging parameters from mpMRI and PSMA PET/CT in a cohort of patients undergoing mpMRI and PSMA PET/CT before biopsy.
Design, setting, and participants: A total of 291 men from the PRIMARY prospective trial underwent mpMRI and PSMA PET/CT before transperineal prostate biopsy with sampling of systematic and targeted cores.
Outcome measurements and statistical analysis: Novel risk calculators were developed using multivariable logistic regression analysis to predict detection of overall PCa (International Society of Urological Pathology grade group [GG] $\geq$1) and csPCa (GG $\geq$2). The risk calculators were then compared with the European Randomised Study of Screening for Prostate Cancer risk calculator incorporating

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mpMRI (ERSPC-MRI). Resampling methods were used to evaluate the discrimination and calibration of the risk calculators and to perform decision curve analysis.
Results and limitations: Age, prostate-specific antigen, prostate volume, and mpMRI Prostate Imaging-Reporting and Data System scores were included in the MRI risk calculator, resulting in area under the receiver operating characteristic curve (AUC) values of 0.791 for overall PCa (GG $\geq$1) and 0.812 for csPCa (GG $\geq$2). Addition of the maximum standardised uptake value (SUVmax) on PSMA PET/CT for the prostate lesion, and of SUVmax for the mpMRI lesions for the MRI-PSMA risk calculator resulted in AUCs of 0.831 for overall PCa and 0.876 for csPCa ($\geq$ISUP2).The ERSPC-MRI risk calculator had AUCs of 0.758 (p = 0.02) for overall PCa and 0.805 (p = 0.001) for csPCa. Both the MRI and MRI-PSMA risk calculators were superior to the ERSPC-MRI for both overall PCa and csPCa.
Conclusions: These novel risk calculators incorporate clinical and radiological parameters for stratification of men at risk of csPCa. The risk calculator including PSMA PET/CT data is superior to a calculator incorporating mpMRI data alone.
Patient summary: We evaluated a new risk calculator that uses clinical information and results from two types of scan to predict the risk of clinically significant prostate cancer on prostate biopsy. This risk model can guide patients and clinicians in shared decision-making and may help in avoiding unnecessary prostate biopsies.

1. Introduction

In the past, men at risk of prostate cancer (PCa) on the basis of elevated prostate-specific antigen (PSA) and/or an abnormal digital rectal examination (DRE) underwent transrectal ultrasound (TRUS)-guided systematic biopsy, mostly conducted in a blind or nontargeted manner. However, standard practice has now evolved to include multiparametric magnetic resonance imaging (mpMRI), followed by avoidance of biopsy in cases with negative findings or systematic and/or targeted transperineal prostate biopsy in cases with positive findings, with sufficient evidence to support this strategy [1,2]. A variety of tools and risk calculators have also been developed and validated to aid in improved prebiopsy risk stratification and shared decision-making. These risk calculators have expanded from the use of clinical parameters alone to incorporation of mpMRI findings [3–8].

Use of prostate-specific membrane antigen (PSMA) positron emission topography/computed tomography (PET/CT) in clinical practice is increasing for staging of high-risk PCa because of encouraging evidence supporting its utility for PCa imaging [9–13]. The proPSMA trial identified the superior accuracy and cost-effectiveness of PSMA PET/CT relative to conventional imaging for staging purposes [14,15]. Prospective trials have led to approval of PSMA PET/CT for initial staging and detection of biochemical recurrence in the USA and in other health care systems [16–19]. Retrospective analyses in Australia of the value of PSMA PET/CT for localisation of PCa within the prostate revealed that in comparison to mpMRI and final histopathology, PSMA PET/CT further increases the accuracy of MRI for csPCa detection in the prostate [9,20].

One limitation of MRI is its inability to detect all clinically significant lesions, and the PRIMARY trial demonstrated that addition of PSMA PET/CT to MRI significantly improved the negative predictive value for csPCa [21]. The aim of the present investigation was to develop a novel risk calculator using the data set from the PRIMARY trial.

2. Patients and methods

2.1. Patient data

The data used to formulate the nomogram were from the prospective, multicentre, phase 2 PRIMARY imaging trial [21,22]. The 291 men selected in the trial were biopsy-naïve with a degree of clinical suspicion for malignancy sufficient to recommend transperineal prostate biopsy. Results from this trial have been published. For these patients, full data on age, PSA, DRE, prostate volume, MRI Prostate Imaging-Reporting and Data System (PI-RADS) score, PSMA PET/CT maximum standardised uptake value (SUVmax), and transperineal prostate biopsy histology were available.

2.2. Imaging

All mpMRI scans were performed using a 3-T or 1.5-T scanner. All image analyses were performed according to PI-RADS version 2.0 under the supervision of a dedicated uroradiologist. PI-RADS scores were assigned on the basis of data from T2-weighted, diffusion-weighted, and dynamic contrast-enhanced imaging sequences. Prostate volume was calculated from T2-weighted images.

Pelvis-only PSMA PET/CT imaging was performed at a minimum of 60 min after administration of 1.8–2.2 MBq/kg ^{68}Ga-PSMA-11 using a low-dose noncontrast CT image acquisition protocol. Using a four-segment prostate model, the SUVmax was recorded in each prostate quadrant. All PSMA PET/CT scans were centrally read by two experienced nuclear medicine specialists, blinded to previous imaging and clinical outcomes, with a third read to adjudicate on any discordance.

2.3. Biopsy protocol

Systematic transperineal prostate biopsies with a recommended minimum of 18 cores were performed. Additional targeted biopsies of lesions identified on mpMRI and/or PSMA PET/CT were obtained, when possible, with all urology investigators provided with key images to demonstrate sites of both MRI and/ or PSMA PET/CT abnormalities before biopsy.

2.4. Histopathology

Histological analyses were performed according to International Society of Urological Pathology (ISUP) standards. csPCa was defined as ISUP grade group (GG) ≥2 (Gleason score ≥ 3 + 4).

2.5. Model creation

Multivariable logistic regression models were created to predict the presence of overall PCa overall (GG ≥1) and csPCa (GG ≥2). The whole cohort was used to construct each model, and a bootstrapped sample with replacement (10 000×) was used to assess the performance of each model for detection of overall PCa and csPCa.

Variables included clinical parameters and MRI and PSMA PET/CT data available before prostate biopsy. An ensemble feature-selection algorithm was used to choose the most relevant features from the training data set. This method reduces the dispersion of prediction and model performance and is suitable for regression of high-dimensional data; it includes estimates of feature significance based on individual discriminative ability [23,24].

2.6. Statistical analysis

All analyses were performed using R statistical software (R Foundation for Statistical Analysis, Vienna, Austria) [25]. Continuous data are reported as the median and interquartile range (IQR); comparisons between groups used independent-group t tests for normally distributed data, or the Mann-Whitney *U* test for non–normally distributed data. Categorical data are reported as the frequency and percentage. Analysis was in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guideline specifications for predictive models used in disease diagnosis or prognosis [26].

We assessed the discriminative ability of the models in terms of the area under the receiver operating characteristic curve (AUC) with 95% confidence interval (CI). AUC values for the various models were compared using U statistics [27]. The maximum AUC value possible is 1.0, indicating perfect discrimination, whereas 0.5 indicates a random chance of correctly discriminating the outcome with the model. Calibration plots were generated using 10 000 bootstrapped samples to analyse the consistency between the predicted probability and the actual outcome. Calibration curves were used to assess the calibration of the models and were computed by comparing observed proportions for a PCa diagnosis to the mean risks calculated by the model in the hold-out cohort [28].

Decision curve analysis was performed to assess for the gain derived from using this model in the holdout cohort over the corresponding net benefit curves of performing a prostate biopsy on all of these patients, or none of these patients [29]. Evaluation of discrimination and calibration and decision curve analysis for the European Randomised Study of Screening for Prostate Cancer (ERSPC-MRI) risk calculator and our MRI and MRI-PSMA risk calculators were as previously described [4]. Nomograms were developed using these multivariable logistic regression models and the *rms* package in R (R Foundation for Statistical Computing).

3. Results

Of 291 patients; 77 (26%) had a benign histological finding, 52 (18%) had GG 1 PCa, and 162 (56%) had csPCa (GG ≥2). The median age at biopsy was 64 yr (IQR 58.7–69.9) and median PSA was 5.6 ng/ml (IQR 4.2–7.5). The median mpMRI estimate of prostate volume was 40 cm^3 (IQR 29–55). There were 53 (18%) PI-RADS 3, 90 (31%) PI-RADS 4, and 53 (18%) PI-RADS 5 lesions. The median SUVmax on PSMA PET/CT was 5.4 (IQR 4.1–8.1); 80 patients (27%) had negative PSMA PET/CT findings (Table 1).

Models were constructed using features available from clinical data and mpMRI and PSMA PET/CT imaging for prediction of diagnosis of overall PCa (GG ≥1) and csPCa (GG ≥2). The first model (MRI risk calculator) included age, PSA, prostate volume, and PI-RADS score on mpMRI. The second model (MRI-PSMA) included the same clinical parameters, SUVmax for the lesion with the highest PI-RADS score on mpMRI, and the highest SUVmax result (from PSMA PET/CT) within the prostate. The MRI risk calculator had AUC values of 0.791 (95% CI 0.726–0.856) for overall PCa and 0.812 (95% CI 0.755–0.869) for csPCa. The MRI-PSMA risk calculator had AUC values of 0.831 (95% CI 0.773–0.890) for overall PCa and 0.876 (95% CI 0.755–0.869) for csPCa in the independent hold-out data set, suggesting good discriminative ability.

Calibration plots provide a visual representation of the reliability of a predicted risk estimate as the accuracy of risk estimates in terms of the agreement between estimated and observed events [6]. A curve close to the diagonal indicates that predicted risks correspond well to observed propor-

Table 1 – Patient characteristics of the PRIMARY trial cohort (*n* = 291)

Parameter	Result[a]
Age at biopsy (yr)	64.0 (58.7–69.9)
Latest PSA (ng/ml)	5.6 (4.2–7.5)
Prostate volume on MRI (cm^3)	40 (29–55)
PI-RADS score, *n* (%)	
2	95 (33)
3	53 (18)
4	90 (31)
5	53 (18)
SUV max (local PSMA read)	5.4 (4.1–8.3)
PSMA PET findings, *n* (%)	
Negative	80 (27)
Positive	211 (73)
ISUP grade group, *n* (%)	
No cancer/benign	77 (26)
Grade group 1	52 (18)
Grade group 2	102 (35)
Grade group 3	39 (13)
Grade group 4	7 (2.4)
Grade group 5	14 (4.8)

IQR = interquartile range (IQR); ISUP = International Society of Urological Pathology; PI-RADS = Prostate Imaging-Reporting and Data System; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; PET = positron emission tomography; SUVmax = maximum standardised uptake value.

[a] Results for continuous variables are presented as median (interquartile range).

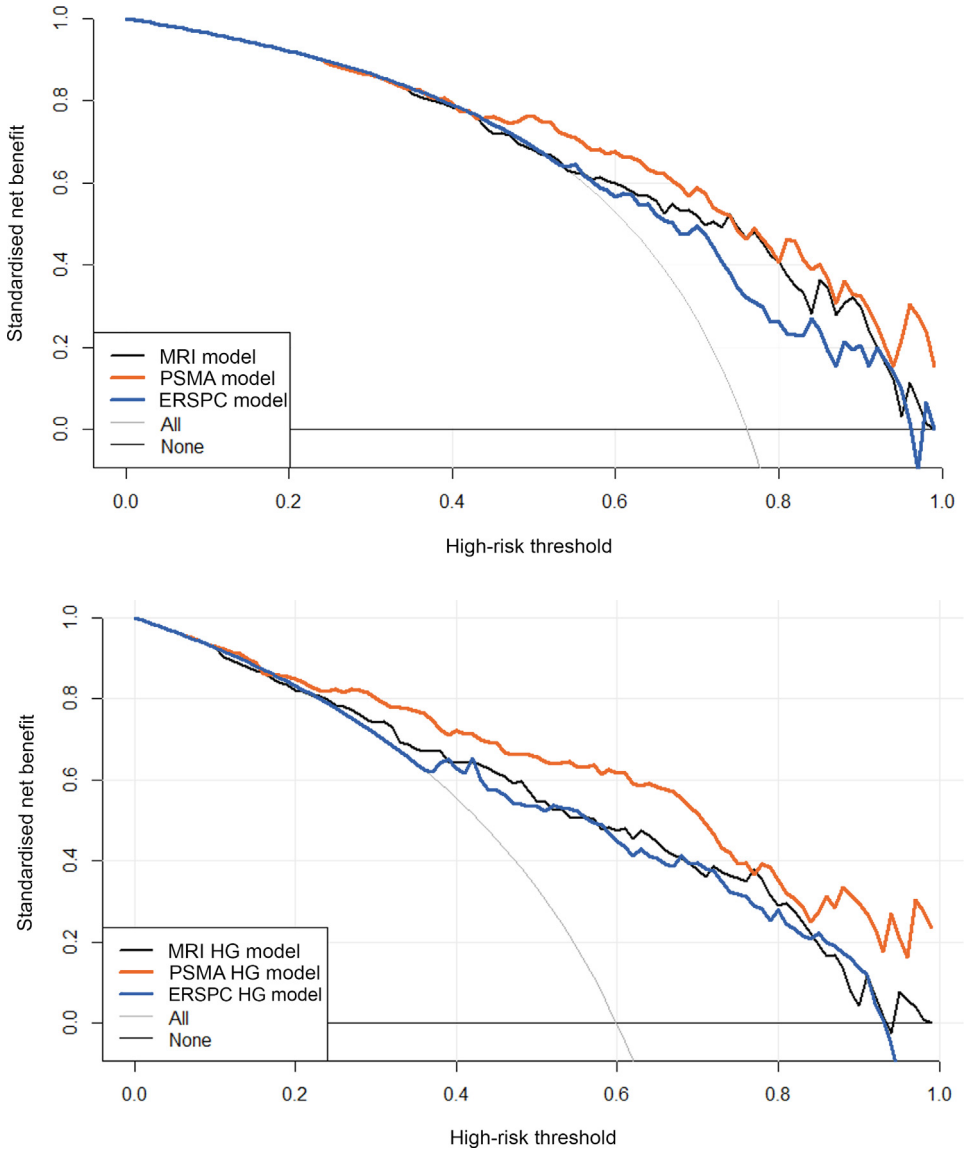

Fig. 1 – Decision curve analysis for (A) overall prostate cancer and (B) clinically significant prostate cancer. MRI = magnetic resonance imaging; PSMA = prostate-specific membrane antigen; ERSPC = European Randomised Study of Screening for Prostate Cancer; HG = high grade.

tions, that is, there is very good agreement between observed risk and risk predicted by the model.

Decision curve analysis was performed to evaluate the clinical relevance of the models (Fig. 1). This is based on the principle that the probability at which a physician would advise treatment is informative regarding how the physician and patient weigh the harms of false-positive results in comparison to the harms of false-negative results [28]. This probability is referred to as the threshold probability and can then be used to derive the net benefit of the model across different thresholds. The straight black line at $y = 0$ represents the net benefit of a test-nobody strategy, while the grey line represents the net benefit of a test-everybody strategy. Each model was superior to both of these strategies across the entire range of clinically useful risk thresholds.

The ERSPC-MRI risk calculator that includes MRI was also externally validated in this group for comparison with our novel MRI-PSMA risk calculator [4]. The AUC for prediction of overall PCa (GG $\geq$1) was 0.831 (95% CI 0.773–0.890) for the MRI-PMSA risk calculator and 0.758 (95% CI 0.613–0.993) for the ERSPC-MRI risk calculator ($p = 0.02$, DeLong's test). The AUC for prediction of csPCa was 0.876 (95% CI 0.755–0.869) for the MRI-PSMA risk calculator and 0.805 (95% CI 0.746–0.863) for the ERSPC-MRI risk calculator ($p = 0.001$). This external validation of the ERSPC-MRI risk calculator demonstrates moderate to reasonable calibration (Fig. 2). Figure 3 provides visual nomograms for the risk calculators for detection of overall PCa and csPCa.

4. Discussion

We developed the first novel risk calculator that includes prebiopsy PSMA PET/CT data for prediction of csPCa in clinical practice. Our MRI-PSMA risk calculator demonstrated superior discriminative ability (high sensitivity and speci-

ficity) in identifying PCa and csPCa in comparison to other risk tools without PSMA PET/CT variables.

This risk calculator was developed using data from PRIMARY, the first prospective multicentre trial to evaluate the potential of PSMA PET/CT for the diagnosis of localised or locally advanced PCa in men who underwent prebiopsy mpMRI [21]. The trial found that use of both mpMRI and PSMA PET/CT improved the sensitivity and negative predictive value (NPV) for csPCa in comparison to MRI alone. The subsequent risk calculator developed that includes clinical, mpMRI, and PSMA PET/CT parameters had an AUC of 0.876 for csPCa detection. This MRI-PSMA risk calculator includes SUVmax for the lesion with the highest PI-RADS score on mpMRI, as well as the highest SUVmax anywhere else within the prostate to account for PSMA-only detected lesions or lesions that appeared indolent or were invisible on MRI. As previously reported, 67% of patients in PRIMARY had a PI-RADS ≥3 lesions and 73% of patients had positive PSMA findings; the NPV for csPCa was better with PSMA and MRI combined (91%) than with MRI alone (72%). The PROMIS trial reported NPV of 92% with MRI alone for detection of csPCa (defined as Gleason score 7–10 with >5% Gleason grade 4, ≥20% positive cores, or tumour ≥7 mm) [30]. For men with PI-RADS 2 and PI-RADS 3 lesions, our MRI-PSMA risk calculator was significantly superior to the ERSPC-MRI risk calculator (p = 0.005) for detection of csPCa.

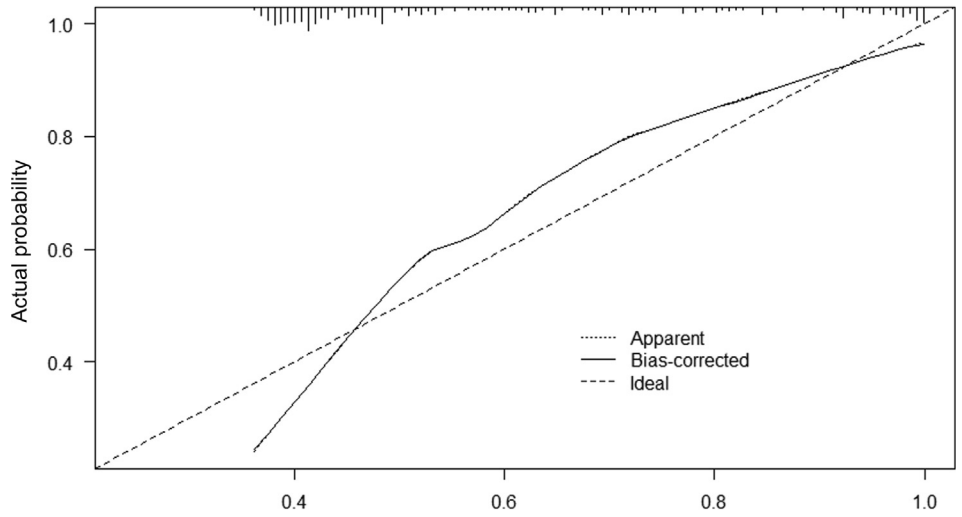

Fig. 2 – Calibration of the European Randomised Study of Screening for Prostate Cancer model for clinically significant prostate cancer.

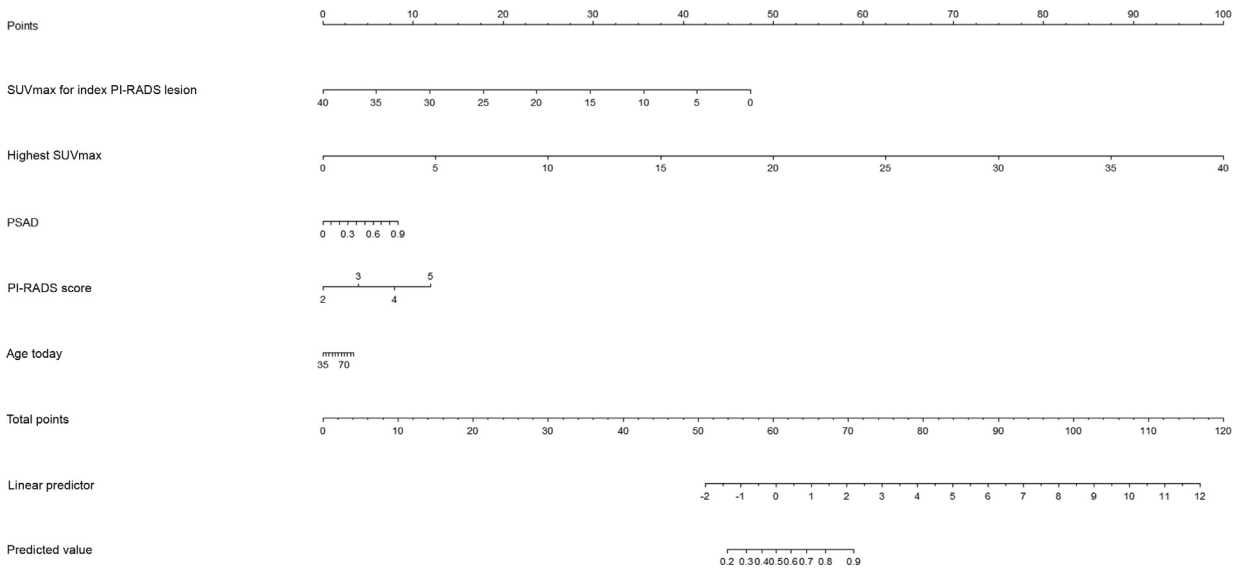

Fig. 3 – Magnetic resonance imaging/prostate-specific membrane antigen imaging nomograms to predict (A) overall prostate cancer and (B) clinically significant prostate cancer. SUVmax = standardised uptake value; PSAD = prostate-specific antigen density; PI-RADS = Prostate Imaging-Reporting and Data System.

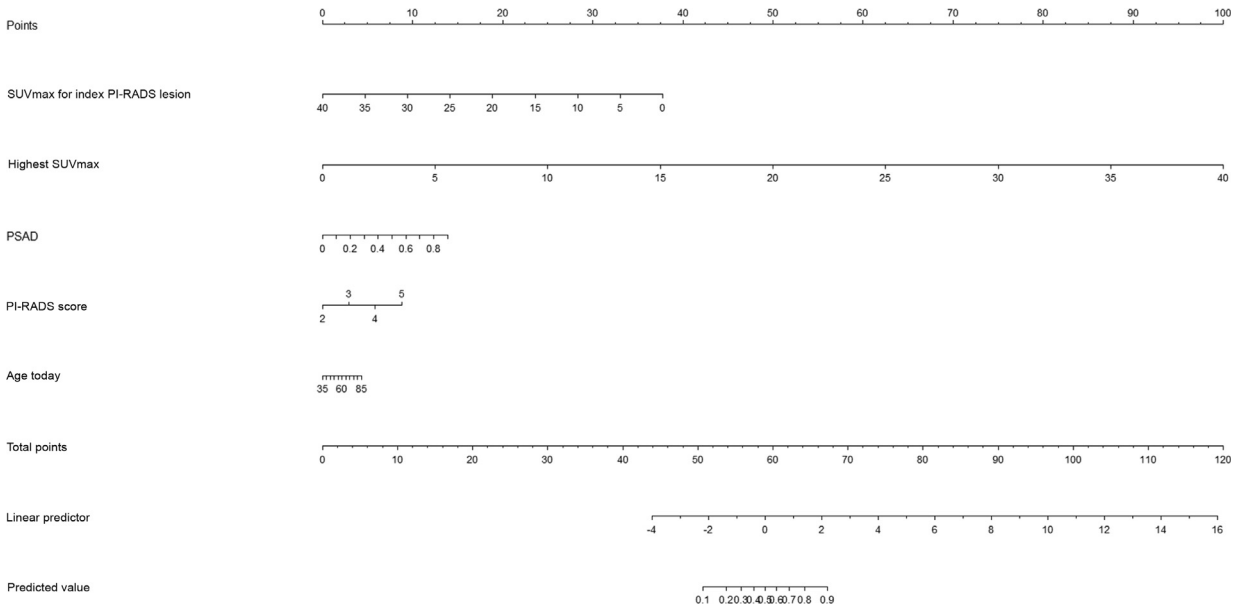

Fig. 3 (*continued*)

This highlights the importance not only of a multivariable risk calculator to improve stratification of men at risk of PCa but also of multimodal risk estimation using PSMA PET/CT, mpMRI, clinical, and other assessments to help in patient decision-making and reduce unnecessary prostate biopsies.

Individual risk stratification for PCa continues to evolve. The initial risk calculators have limitation that include the use of data from predominantly healthy individuals in some, and relatively homogeneous populations in others [3,31]. Objective clinical parameters such as age, PSA, and prostate volume were combined with clinical variables prone to subjective reporting, such a; family history, DRE findings, and suspicious TRUS findings [32,33].

Our PSMA-MRI risk calculator incorporates variables that can be standardised: age, serum PSA, prostate volume, PI-RADS score on mpMRI, SUVmax for the lesion with the highest PI-RADS score on mpMRI, and the highest SUVmax result within the prostate. Although there is interobserver and intraobserver variability in the reporting of PI-RADS scores for prostate MRI, it has been demonstrated that this is minimal in the hands of specialist radiologists. Similar concerns regarding PSMA PET/CT may also be mitigated by standardising both the performance and reporting of this imaging, as addressed in the PRIMARY trial [21]. The impact of such subjective reporting of clinical features is also highlighted by the Prostate Biopsy Collaborative Group (PBCG), which noted that the coefficient or relative importance of DRE findings differed between the PBCG and Prostate Cancer Prevention Trial (PCPT) models [34]. There was a higher association between positive DRE and high-grade PCa in the study used to develop the PBCG risk tool in comparison to the PCPT risk calculator, which was attributed to patients in the PBCG study being more likely to have been examined by academic urologists specialising in PCa rather than general urologists, again highlighting the importance of standardised reporting and specialist-driven care [34].

Our study has several strengths and limitations. The patient cohort used to develop the risk calculator were all biopsy-naïve and did not have a history of PCa. Given that MRI can miss ~13% of csPCa cases, addition of PSMA PET/CT to a risk calculator could reduce this percentage, with improved detection of csPCa because of identification of other lesions that could be targeted during transperineal prostate biopsy [30,35,36]. The limited number of cases for development of our risk calculator is because of the sample size in PRIMARY, which is the first trial to use PSMA PET/CT in the diagnostic setting for PCa. Although the only PSMA PET/CT feature included in our risk calculator is SUVmax, other features from PSMA-PET/CT, albeit yet to be validated, could be incorporated in future risk calculators and improve on the use of PSMA-PET/CT in diagnosis, such as intraprostatic patterns and intensities, as suggested by the recently published PRIMARY score system [37]. Another limitation is the use of PI-RADS version 2.0 rather than version 2.1; the earlier version was the one used for mpMRI reporting as prespecified in the trial protocol. It should also be noted that patients used to develop the ERSPC risk calculator all underwent transrectal biopsy.

It was not possible to externally validate our MRI-PSMA risk calculator, as the novel nature of the PRIMARY trial means that there is no suitable external database for validation. PRIMARY2 (NCT05154162) is under way and will provide definitive data on the subgroup with PI-RADS 3/2 lesions on mpMRI. Negative mpMRI and PSMA PET/CT findings have the potential to obviate the need for prostate biopsy, but future trials, including randomised controlled trials, are required before implementation of this strategy. Further external validation and calibration of our risk calculator are warranted in disparate populations before imple-

mentation in clinical practice. The patients in PRIMARY underwent pelvis-only PSMA PET/CT with a radiation dose of only 4 mSv, which is appropriate for screening [21]. PSMA PET/CT adds costs to health care systems. We are not advocating for this imaging modality for all men; rather, given its potential to aid in risk stratification, it should be further evaluated in prospective trials.

The European Association of Urology guidelines recommend the use of risk calculators or risk tools to aid in risk stratification and counselling of men before prostate biopsy [38]. As these risk calculators and guidelines have evolved over the past number of years, the recommendations have progressed from TRUS-guided biopsy to prebiopsy mpMRI followed by targeted and/or systematic transperineal biopsies. A risk calculator that includes PSMA PET/CT data has the ability to improve on the limitations of previous calculators and help in avoiding unnecessary biopsies and in targeting high-risk lesions when biopsy is performed.

5. Conclusions

This study demonstrates that patient risk stratification for PCa and csPCa can be improved via the use of a multivariable risk tool incorporating PSMA PET/CT data. Such a risk tool could help in reducing the number of men undergoing prostate biopsy and overdiagnosis and overtreatment of men with PCa, while identifying those with clinically significant disease.

Author contributions: Brian D. Kelly had full access to all of 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: Kelly, Thompson, Emmett, Murphy, Moon.
Acquisition of data: Alghazo, Emmett, Moon.
Analysis and interpretation of data: Kelly, Lundon.
Drafting of the manuscript: Kelly, Ptasznik.
Critical revision of the manuscript for important intellectual content: Roberts, Doan, Stricker, Thompson, Buteau, Chen, Alghazo, O'Brien, Hofman, Frydenberg, Lawrentschuk, Emmett, Murphy, Moon.
Statistical analysis: Kelly, Lundon.
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