Optimizing Detection of Clinically Significant Prostate Cancer through Nomograms incorporating MRI, Clinical Features, and Advanced Serum Biomarkers

Mohammad Siddiqui (mohammad.siddiqui2@northwestern.edu)
Feinberg School of Medicine, Northwestern University https://orcid.org/0000-0001-8196-5864

Mohammad Siddiqui
Feinberg School of Medicine, Northwestern University

Eric Li
Northwestern University

Sai Kumar
Feinberg School of Medicine, Northwestern University

Anna Busza
Feinberg School of Medicine, Northwestern University

Jasmine Lin
Feinberg School of Medicine, Northwestern University

Ashorne Mahenthiran
Northwestern University https://orcid.org/0000-0003-3409-2460

Jonathan Aguiar
Feinberg School of Medicine, Northwestern University

Parth Shah

Brandon Ansbro
Northwestern University

Jordan Rich
Northwestern University

Moataz Solima
Department of Radiology, Feinberg School of Medicine, Northwestern University

Mary-Kate Keeter
Feinberg School of Medicine, Northwestern University

Quan Mai
Northwestern University

Xinlei Mi
Department of Preventative Medicine, Feinberg School of Medicine, Northwestern University

Jeffrey Tosoian

University of Michigan
Edward Schaeffer
Northwestern University https://orcid.org/0000-0003-0699-1899
Hiten Patel
Feinberg School of Medicine, Northwestern University
Ashley Ross
Northwestern University Feinberg School of Medicine https://orcid.org/0000-0001-7044-9688

Article

Keywords:

Posted Date: December 16th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2363224/v1

Version of Record: A version of this preprint was published at Prostate Cancer and Prostatic Diseases on March 27th, 2023. See the published version at https://doi.org/10.1038/s41391-023-00660-8.

Abstract

Purpose

To develop nomograms that predict the detection of clinically significant prostate cancer at diagnostic biopsy based on multiparametric prostate MRI (mpMRI), serum biomarkers, and patient clinicodemographic features.

Materials and Methods

Nomograms were developed from a cohort of biopsy-naïve men presenting to our 11-hospital system with a PSA of 2-20ng/mL who underwent pre-biopsy mpMRI from March 2018-June 2021 (n = 1494). The outcomes were the presence of clinically significant and high-grade prostate cancer (defined as ≥ GG2 [Grade Group 2] and ≥ GG3 prostate cancer, respectively). Using significant variables on multivariable logistic regression, individual nomograms were developed for men with PSA, % free PSA, or prostate health index (PHI) when available. The nomograms were both internally validated and evaluated in an independent cohort of 366 men presenting to our hospital system from July 2021-February 2022.

Results

1031 of 1494 men (69%) underwent biopsy after initial evaluation with mpMRI, 493 (47.8%) of whom were found to have ≥ GG2 PCa, and 271 (26.3%) were found to have ≥ GG3 PCa. Age, race, highest PIRADS score, prostate health index (PHI) when available, % free PSA when available, and PSA density were significant predictors of ≥ GG2 and ≥ GG3 PCa on multivariable analysis and were used for nomogram generation. Accuracy of nomograms in both the training cohort and independent cohort were high, with areas under the curves (AUC) of ≥ 0.885 in the training cohort and ≥ 0.896 in the independent validation cohort. In our independent validation cohort, our model for ≥ GG2 prostate cancer with PHI saved 39.1% of biopsies (143/366) while only missing 0.8% of csPCa (1/124) with a biopsy threshold of 20% probability of csPCa.

Conclusions

Here we developed nomograms combining serum testing and mpMRI to help clinicians risk stratify patients with elevated PSA of 2-20ng/mL who are being considered for biopsy. Our nomograms are available at https://rossnm1.shinyapps.io/MynMRIskCalculator/ to aid with biopsy decisions.

Introduction

Prostate cancer is the most commonly diagnosed malignancy, with an estimated 268,500 new diagnoses in the US in 2022, and the second leading cause of cancer-related death, with 34,500 estimated deaths in

the US in 2022.(1) Prostate specific antigen (PSA) screening is effective, but leads to overdiagnosis and overtreatment.(2) Other screening methods, such as serum and urine biomarkers and multiparametric prostate MRI (mpMRI), can augment evaluation for risk of clinically significant prostate cancer (csPCa, Gleason Grade Group ≥ 2). Percentage free PSA and the prostate health index (PHI), which combines total PSA, percentage free PSA, and − 2proPSA, are among serum-based biomarkers that improve risk stratification for detection of any prostate cancer and csPCa.(3) Similarly, mpMRI has been shown in clinical trials to improve detection of csPCa while identifying men at lower risk of harboring csPCa who may be candidates to avoid prostate biopsy.(4–6)

The National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) guidelines recommend MRI prior to biopsy (NCCN v1.2023, EAU 2022). However, Prostate Imaging-Reporting and Data System (PIRADS) lesions graded as PIRADS 3 and 4 have csPCa concordance rates of 17–20% and 46–52%, respectively, which requires further consideration of clinical variables such as age, race, PSA density, and advanced serum biomarkers when making biopsy decisions.(7, 8) Recently, the European Randomized Study of Prostate Cancer nomograms have been updated to include mpMRI factors (MRI-ERSPC), and nomograms in North American populations incorporating mpMRI have emerged (PCRC-MRI, PLUM).(9–11)

However, prostate cancer screening nomograms incorporating mpMRI and advanced serum biomarkers such as PHI to guide biopsy decisions are lacking. Additionally, model performance and estimates of biopsies avoided from these models are often inflated by inclusion of patients with prior negative TRUS biopsies which comprise majority of potentially avoidable biopsies; applicability of prior models in the purely biopsy naïve population where upfront mpMRI is being increasingly utilized is limited.(10, 12) Lastly, men who do not receive biopsy after mpMRI or with negative mpMRI are often excluded from cohorts of prior studies which skews risk estimates compared to the broader intended population for subsequent use. To that end, we sought to utilize our contemporary institutional experience with serum biomarkers and mpMRI to create nomograms to optimize risk stratification of patients with suspected csPCa. Furthermore, as patient and provider preferences for biopsy depend on the risk of disease diagnosed, we additionally developed nomograms providing point estimates for the identification of higher-grade prostate cancer (≥ GG3).

Methods

Study Population and Clinicodemographic Characteristics

We retrospectively reviewed the Northwestern Medical Group's Electronic Data Warehouse, which passively collects information in our EMR across our 11-hospital system, for all biopsy-naïve men presenting with PSA 2-20ng/mL who underwent initial mpMRI prior to biopsy decision. Our nomogram development cohort consisted of 1494 men considering prostate biopsy between March 2018 to June 2021, and our validation cohort included 366 men considering prostate biopsy between July 2021 and February 2022. Baseline clinicodemographic information were obtained, including PIRADS score and

Prostate Needle Biopsy (PNB) pathology reports. In regards to categorization, BMI was categorized as < 25, 25–30, or > 30 kg/m^2. CCI was categorized as ≤ 2 or > 2. PSA was stratified into three groups: 2–4, > 4–10, and > 10–20 ng/mL. PHI was similarly grouped by quartile with ranges of 0-26.9, 27-35.9, 36-54.9, and ≥ 55. Additionally, PSA density (PSAD) was stratified into four groups: ≤0.10, > 0.10-≤0.15, > 0.15-≤0.2, and > 0.20 ng/mL/cm^3. Digital rectal exam (DRE) was not consistently recorded and subsequently excluded from our analysis.

Patients undergoing mpMRI were given an assessment category using PI-RADSv2.0 (before 2019) or v2.1 (2019 or later). Only the highest PIRADS score was included in our analysis. mpMRI was initially interpreted by specialized genitourinary (GU) radiologists. Biopsy is offered primarily to men with PIRADS ≥ 3 lesion. However, the decision to biopsy was ultimately at provider's discretion after considering other clinical variables. Furthermore, we retrospectively reviewed the records of those who underwent initial mpMRI but not biopsied for subsequent detection of csPCa. Ultimately, men with PIRADS 1–3 lesions who were not biopsied were assumed to be negative for csPCa in the primary analysis, as the subsequent detection rate of csPCa over the median follow-up of 1.8 years was 2% (Li et al, manuscript in preparation). Inclusion of these patients maintained a representative population of biopsy-naïve men screened via a mpMRI-based approach often incorporating advanced biomarkers such as PHI.

MRI-Guided Biopsy Protocol and Pathology Review

1031 (69%) underwent systematic and MRI-fusion targeted transrectal or transperineal prostate biopsy. Targeted biopsy was completed with either cognitive or software fusion per provider preference. Prostate biopsy results were reported as ISUP Gleason Grade Group (GG) based on histological Gleason Grading by specialized GU pathologists. The highest histologic grade was recorded for each patient's biopsy results irrespective of whether the highest GG was detected in targeted or systematic biopsy.

Outcomes

Outcomes included clinically significant prostate cancer defined as ≥ GG2 (Gleason Grade Group 2 or higher) and higher-grade prostate cancer defined as ≥ GG3 prostate cancer.

Statistical Analysis

Statistical analyses were performed using R (Version 4.2.0). Pearson's Chi-squared test, Fisher's exact test, and Wilcoxon rank sum test were performed for baseline demographics. Statistical significance was considered $p < 0.05$.

Univariable and multivariable logistic regression models were used to identify independent predictors of csPCa and higher grade PCa. Total PSA was not included in the multivariate analysis due to co-linearity with PSA density. The nomogram input was determined by statistically significant variables on multivariable logistic regression. Receiver Operating Characteristics (ROC) curves and the Area under the Curve (AUC) were generated. Decision curve analysis (DCA) was conducted to compare net benefit at various biopsy thresholds relative to biopsy for all or no patients. Other performance metrics, including

accuracy, sensitivity, specificity, PPV and NPV were also calculated at various biopsy thresholds to biopsy.

Internal Validation

For performance evaluation, internal validation with bootstrapping repeated 1,000 times and leave one out cross-validation were completed. The internal validation will further evaluate for discordance for the patients who were assumed to be negative with initial mpMRI and found to have PIRADS 1–3 but did not undergo biopsy.

Validation on an Independent Cohort

We applied the nomograms to an independent cohort of biopsy naïve patients who subsequently presented to Northwestern from July 2021-February 2022 (n = 366) for evaluation of elevated PSA 2–20 ng/mL. AUC estimates and DCA with modeling of biopsies saved at various biopsy thresholds were generated to evaluate performance of the nomograms in our independent validation set.

Results

Study Cohort Characteristics

Of the 1494 men in our development cohort, the median age was 63 years (IQR 57–69), and 167 (11.1%) men were Black. 1204 (80.6%) men underwent PHI testing (**Table 1**). Ultimately, 1031 (69%) men underwent biopsy. The highest PIRADS lesion score was associated with higher rates of biopsy with most men with PIRADS 3 (n = 248, 77%), PIRADS 4 (n = 504, 97.1%), and PIRADS 5 (n = 172, 100%) lesions undergoing biopsy, respectively (**Supplemental Fig. 1a**). The csPCa detection rate stratified by highest PIRADS was 16.8%, 54.0%, and 85.5% for PIRADS 3, 4, and 5, respectively (**Supplemental Fig. 1b**).

Compared to our development cohort, the 366 men in the validation cohort had a higher incidence of PIRADS 3–5 lesions 77% vs. 68% ($p < 0.001$), Medicaid insurance 2.6% vs. 5.2% ($p = 0.024$), % Free PSA category ≥0.25 17% vs. 27% ($p = 0.001$), and higher PSAD ($p = 0.002$) (**Table 1**). There was no significant difference in age, race, PHI, CCI, BMI, or percentage of patients proceeding to prostate biopsy.

Of the 1031 patients in the development cohort who underwent prostate biopsy, 493 (47.8%) had ≥ GG2 prostate cancer, and 271 (26.3%) had ≥ GG3 prostate cancer. Univariable and multivariable logistic regressions for the prediction of csPCa in men with available PHI is presented in **Table 2**. Multivariable logistic regressions predicting csPCa and higher grade PCa in men with available PHI, % free PSA, and total PSA only are presented in **Supplemental Tables 1–5**. On multivariable logistic regression, African American race, PSAD, and presence of PIRADS 3–5 lesions were significant independent predictors of both ≥ GG2 and ≥ GG3 PCa. PHI and % free PSA if available were additional independent predictors of csPCa and higher-grade cancer. Age was a significant predictor for all ≥ GG3 PCa models and in ≥ GG2 PCa with PHI, but it was subsequently included in all nomograms as age is an established risk factor for prostate cancer (**Table 2, Supplemental Tables 1–5**).

Nomograms to Estimate Risk of Prostate Cancer

Using the significant variables on multivariable logistic regression, nomograms predicting ≥ GG2 and ≥ GG3 prostate cancer were developed (Fig. 1, **Supplemental Fig. 2**). In the training cohort, the AUC ranged from 0.885–0.901 for the various nomograms (**Table 3**). Highest PIRADS score, PHI (if available), % free PSA (if available) and PSAD were the strongest predictors of csPCa and higher-grade cancer (**Supplemental Figs. 2–3**). Notably, the AUC of the model for ≥ GG2 with PHI and ≥ GG3 with PHI were 0.895 and 0.905, respectively. Figure 2 and **Supplemental Fig. 4** graphically represent biopsies potentially saved at different thresholds of PCa detection. With a biopsy threshold of 20% probability of detecting ≥ GG2 and ≥ GG3 in patients with PHI, the respective models avoid 49% (731 of 1479) and 67% (996 of 1479) of biopsies at the risk of missing 9.7% (48 of 493) ≥ GG2 and 14% (38 of 271) ≥ GG3 disease (Fig. 2a and 2c). The AUCs, biopsy saved diagrams, and test characteristics for the nomograms in the development cohort are available in **Supplemental Figs. 3–5**.

Internal Cross-validation

We performed bootstrapping with 1,000 replicates and leave-one-out cross-validation (**Table 3, Supplemental Fig. 6**) which showed similar AUCs and test characteristics. A DCA in the development cohort was performed which showed a strong net benefit across threshold probabilities up to 70% when compared to biopsy for no patients and all patients (**Supplemental Fig. 5**). Results were similar on sensitivity analyses limited to the biopsied subgroup.

Independent Cohort Validation and Decision Curve Analysis

In the independent validation cohort (n = 366), nomograms were highly accurate for the prediction of csPCa and higher-grade prostate cancer with AUCs greater than 0.896 for all nomograms (**Table 3**). With a biopsy threshold of 20% probability of ≥ GG2 PCa, the nomogram utilizing PHI saved 39.1% of biopsies (143 of 366) while only missing 0.8% (1 of 124) of csPCa. DCA of the independent validation cohort showed a similar net benefit to the development cohort up to biopsy threshold probability of 70%. The AUCs, DCAs, and biopsy saved diagrams for the other nomograms had similar discriminating ability to predict ≥ GG2 and ≥ GG3 PCa (Fig. 2, **Supplemental Figs. 6–9**).

Online Versions of my nMRIsk Calculator

We created an online application at https://rossnm1.shinyapps.io/MynMRIskCalculator/ for easy reference and utilization of the nomograms.

Discussion

We used real-world data from our large academic system incorporating serum biomarker data (PHI, % free PSA or total PSA) and mpMRI along with other clinical variables to develop nomograms that can improve detection of csPCa and higher grade PCa while significantly reducing unnecessary biopsies. We created adaptable versions of the nomogram based on available serum biomarkers and openly published the tool

for transparent and wider adoption. Performance of the models was high with accuracies of ≥ 0.885 in the training cohort and ≥ 0.896 in the independent validation cohort.

Traditionally, PSA based screening has been marred by overdiagnosis and overtreatment. Originally, studies evaluated patient factors like age, race, and PSAD for risk stratification. Advanced serum- and urine-based markers such as 4k score, MyProstateScore, and SelectMDx have also been developed to further enhance the detection of csPCa.(13) While these markers offer clinical value when used individually, biopsies avoided are based on a prior paradigm of detection by TRUS biopsy with uncertain utility in conjunction with mpMRI. For example, setting the PHI threshold at 28.6 avoids 30% of TRUS biopsies.(14) Similarly, 4kscore cut-off of 20% risk of cancer reduces the number of biopsies by 36% while delaying diagnosis of csPCa in 4.7%, but performance in a mpMRI-based diagnostic approach is unknown.(15) Moreover, these tools are not able to localize csPCa within the prostate at the time of biopsy if one is performed.

Therefore, there is a strong interest in combining advanced serum biomarkers with mpMRI, as the advent of mpMRI has greatly improved our ability to detect csPCa. In the PRECISION trial, mpMRI avoided 28% of primary biopsy while diagnosing 13% fewer clinically insignificant cancers.(16) Furthermore, targeting mpMRI lesions increased detection of csPCa by 12% compared to standard TRUS biopsy. However, the sensitivity and specificity of mpMRI for csPCa vary across studies, ranging between 58–96% and 23–87% respectively.(17) This variability is significant for commonly biopsied PIRADS 3 and 4 lesions, which is also reflected in our experience (**Supplemental Fig. 1**) with 83% and 46% of PIRADS 3 and 4, respectively, having clinically insignificant (Negative or GG1) outcome. By combining MRI with other biomarkers and clinical variables, we believe that unnecessary biopsies, particularly among men with PIRADS 3 lesions mpMRI, can be largely avoided.

Nomograms offer an avenue to combine various advanced screening tools to improve patient risk stratification, and have been shown to offer higher accuracy for predicting outcomes in comparison to other predictive tools, such as look-up tables or decision trees.(18–20) In fact, a national survey of radiation oncologists and urologists found that 60% of providers were familiar with prostate cancer nomograms, 55% used nomograms routinely in their practice, and 74% found nomograms to be user friendly.(21) Nomograms in urology were pioneered by Kattan and colleagues predicting likelihood of disease recurrence and progression. Since then, various validated nomograms have been created at different stages of the prostate cancer disease stages e.g. UCSF-CAPRA score for post-biopsy risk stratification and MSKCC nomograms for pre- and post- radical prostatectomy or for salvage radiation.

Currently, there is no singular widely adopted and validated nomogram that combines advanced screening biomarkers and mpMRI in a pre-biopsy setting to predict risk of csPCa and higher risk PCa. In a recent randomized control clinical trial of STHLM3, combining the Stockholm 3 test with mpMRI reported AUC of 0.76 for their nomogram for csPCa.(22, 23) A retrospective series by Wagasker et al proposed a nomogram combining 4kscore with mpMRI that had AUCs of 0.84 for any prostate cancer, 0.88 for csPCa, and 0.86 for ≥ GG3 prostate cancer.(24) The PROMOD study combined PSAD with mpMRI and

evaluated its performance in detection of csPCa in a large retrospective multi-institutional cohort, reporting a high sensitivity of 96.7% but low specificity of 30.1% in their biopsy naïve population.(25) Lastly, as an example of models based on PSA and mpMRI parameters, Kinniard et al developed a nomogram with sensitivity of 90% and specificity of 54% at a biopsy threshold of 20% probability of csPCa, with AUC values of 0.843 and 0.888 in discovery and validation cohorts.

In our cohort, we report a similar high sensitivity of 90%, but with higher specificity of 69% for our model utilizing PHI for prediction of ≥ GG2 prostate cancer. Furthermore, the AUCs for our nomograms are generally superior to those published in the literature, with ≥ 0.885 in the development cohort and ≥ 0.896 in the independent validation cohort. While PHI does make our model more robust, the nomograms utilizing % free PSA and total PSA overall have high discriminatory characteristics in both the development and independent validation cohort, demonstrating the overall versatility of our nomograms across practice settings and preferences. This is best demonstrated in our independent validation cohort, where application of our csPCa model with PHI and biopsy threshold of 20% saved biopsy for 143/366 (39.1%) men while only missing 1 case (0.8%) of csPCa. In comparison, the nomogram for prediction of csPCa with total PSA at a biopsy threshold of 20% similarly saved biopsy for 140/366 (38.3%) men while again only missing 1 case (0.8%) of csPCa.

Furthermore, prior nomograms include both biopsy naïve and prior negative biopsy patients, whereas our nomogram focused on biopsy naïve patients. The rate of csPCa is higher in the biopsy naïve setting compared to prior negative biopsy patients, with the latter inflating estimates of overall biopsies avoided in prior analyses; for example, the PLUM cohort showed 45.8% of biopsies could be avoided among prior negative patients but only 18.1% for biopsy naïve patients.(11, 12) Overall, our nomograms predict csPCa and higher grade PCa with high accuracy and greater potential for avoiding biopsies among biopsy naïve patients.

A few limitations of the present study deserve to be noted. First, it is a retrospective series, which may create a selection bias and not perfectly represent the general screening population. However, we included all men evaluated with serum biomarkers and mpMRI to improve generalizability of our cohort compared to prior analyses where many patients with low suspicion on mpMRI have often been excluded or not captured. Our nomograms assume that men with PIRADS 1–3 not undergoing biopsy would have had a clinically insignificant outcome, potentially inflating nomogram's performance (specificity, negative predictive value). However, upon review of patients who did not undergo initial biopsy, only 2% of these patients with follow up were found to have csPCa over the median follow-up of 1.8 years, with the majority of these patients having a repeat mpMRI prior to biopsy showing upgrading of highest PIRADS lesions. Therefore, the impact of this assumption is negligible given the low rate of on follow up, demonstrating that men can be safely monitored with serial serum biomarker screening and for cause mpMRI. While we did perform validation with an independent cohort at our institution, further external validation is required across institutions and community practice to establish generalizability of the nomograms. Furthermore, our academic institution has dedicated genitourinary radiologists and

pathologists, but application in the community may also be affected by interrater variability among radiologists and pathologists.

Conclusion

We created novel nomograms combining patient characteristics, serum biomarkers (total PSA, % free PSA when available, PHI when available) and mpMRI to help clinicians better risk stratify biopsy naïve patients with PSA 2-20ng/mL prior to biopsy consideration. Using the nomograms, clinicians will be able to significantly improve csPCa detection rates, reduce the number of negative biopsies or biopsies with clinically indolent disease, and spare large numbers of men from prostate biopsy.

Abbreviations

GG: Grade Group

csPCa: Clinically Significant Prostate Cancer (GG≥2)

CS: Clinically Significant

PSA: Prostate Specific Antigen

PSAD: PSA density

PHI: Prostate Health Index

mpMRI: multiparametric prostate Magnetic Resonance Imaging

NPV: Negative Predictive Value

PPV: Positive Predictive Value

Declarations

Funding:

Urology Care Foundation: Robert J Krane, MD Resident Research Award

References

1. American Cancer Society. Cancer Facts & Figures 2022 [Internet]. Atlanta: American Cancer Society;2022; 2022. Available from: https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2022/2022-cancer-facts-and-figures.pdf

2. Loeb S, Sanda MG, Broyles DL, Shin SS, Bangma CH, Wei JT, et al. The Prostate Health Index Selectively Identifies Clinically Significant Prostate Cancer. J Urol [Internet]. 2015 Apr 1 [cited 2022 Mar 10];193(4):1163. Available from: /pmc/articles/PMC4404198/
3. Loeb S, Sanda MG, Broyles DL, Shin SS, Bangma CH, Wei JT, et al. The Prostate Health Index Selectively Identifies Clinically Significant Prostate Cancer. J Urol [Internet]. 2015 Apr 1 [cited 2022 Jan 4];193(4):1163. Available from: /pmc/articles/PMC4404198/
4. Padhani AR, Petralia G, Sanguedolce F. Magnetic Resonance Imaging Before Prostate Biopsy: Time to Talk. Eur Urol. 2016 Jan 1;69(1):1–3.
5. Ahmed HU, El-Shater Bosaily A, Brown LC, Gabe R, Kaplan R, Parmar MK, et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. Lancet. 2017 Feb 25;389(10071):815–22.
6. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med. 2018;1767–77.
7. Park KJ, Choi SH, Lee JS, Kim JK, Kim MH, Jeong IG. Risk Stratification of Prostate Cancer According to PI-RADS® Version 2 Categories: Meta-Analysis for Prospective Studies. J Urol. 2020;204(6):1141–9.
8. Oerther B, Engel H, Bamberg F, Sigle A, Gratzke C, Benndorf M. Cancer detection rates of the PI-RADSv2.1 assessment categories: systematic review and meta-analysis on lesion level and patient level. Prostate Cancer Prostatic Dis [Internet]. 2021;(March). Available from: http://dx.doi.org/10.1038/s41391-021-00417-1
9. Kinnaird A, Brisbane W, Kwan L, Priester A, Chuang R, Barsa DE, et al. A prostate cancer risk calculator: Use of clinical and magnetic resonance imaging data to predict biopsy outcome in North American men. Can Urol Assoc J [Internet]. 2022 Mar 1 [cited 2022 Nov 28];16(3):E161. Available from: /pmc/articles/PMC8923894/
10. Alberts AR, Roobol MJ, Verbeek JFM, Schoots IG, Chiu PK, Osses DF, et al. Prediction of High-grade Prostate Cancer Following Multiparametric Magnetic Resonance Imaging: Improving the Rotterdam European Randomized Study of Screening for Prostate Cancer Risk Calculators. Eur Urol. 2019 Feb 1;75(2):310–8.
11. Patel HD, Koehne EL, Shea SM, Fang AM, Gerena M, Gorbonos A, et al. A prostate biopsy risk calculator based on MRI: development and comparison of the Prospective Loyola University multiparametric MRI (PLUM) and Prostate Biopsy Collaborative Group (PBCG) risk calculators. BJU Int [Internet]. 2022 [cited 2022 Dec 7]; Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.galter.northwestern.edu/35733400/
12. Patel HD, Koehne EL, Shea SM, Bhanji Y, Gerena M, Gorbonos A, et al. Risk of prostate cancer for men with prior negative biopsies undergoing magnetic resonance imaging compared with biopsy-naive men: A prospective evaluation of the PLUM cohort. Cancer [Internet]. 2022 Jan 1 [cited 2022 Nov 28];128(1):75–84. Available from: https://onlinelibrary-wiley-com.ezproxy.galter.northwestern.edu/doi/full/10.1002/cncr.33875

13. Eyrich NW, Morgan TM, Tosoian JJ. Biomarkers for detection of clinically significant prostate cancer: contemporary clinical data and future directions. Transl Androl Urol [Internet]. 2021 Jul 1 [cited 2022 May 3];10(7):3091–103. Available from: https://pubmed-ncbi-nlm-nih-gov.ezproxy.galter.northwestern.edu/34430413/
14. Loeb S, Shin SS, Broyles DL, Wei JT, Sanda M, Klee G, et al. Prostate Health Index (phi) Improves Multivariable Risk Prediction of Aggressive Prostate Cancer. BJU Int [Internet]. 2017 Jul 1 [cited 2022 Mar 10];120(1):61. Available from: /pmc/articles/PMC5392379/
15. Konety B, Zappala SM, Parekh DJ, Osterhout D, Schock J, Chudler RM, et al. The 4Kscore® Test Reduces Prostate Biopsy Rates in Community and Academic Urology Practices. Rev Urol [Internet]. 2015 [cited 2022 Apr 18];17(4):231. Available from: /pmc/articles/PMC4735670/
16. Kasivisvanathan V, Rannikko AS, Borghi M, Panebianco V, Mynderse LA, Vaarala MH, et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. N Engl J Med [Internet]. 2018 Mar 18 [cited 2022 Mar 10]; Available from: https://www-nejm-org.ezproxy.galter.northwestern.edu/doi/10.1056/NEJMoa1801993
17. Fütterer JJ, Briganti A, De Visschere P, Emberton M, Giannarini G, Kirkham A, et al. Can Clinically Significant Prostate Cancer Be Detected with Multiparametric Magnetic Resonance Imaging? A Systematic Review of the Literature. Eur Urol. 2015 Dec 1;68(6):1045–53.
18. Shariat SF, Karakiewicz PI, Suardi N, Kattan MW. Comparison of nomograms with other methods for predicting outcomes in prostate cancer: A critical analysis of the literature. Clin Cancer Res. 2008;14(14):4400–7.
19. Chun FK, Karakiewicz PI, Briganti A, Walz J, Kattan MW, Huland hartwig, et al. A critical appraisal of logistic regression-based nomograms, artificial neural networks, classification and regression-tree models, look-up tables and risk-group stratification models for prostate cancer. BJU Int; 2006.
20. Touijer K, Scardino PT. Nomograms for staging, prognosis, and predicting treatment outcomes. Cancer. 2009;115(SUPPL 13):3107–11.
21. Kim SP, Karnes RJ, Nguyen PL, Ziegenfuss JY, Han LC, Thompson RH, et al. Clinical Implementation of Quality of Life Instruments and Prediction Tools for Localized Prostate Cancer: Results from a National Survey of Radiation Oncologists and Urologists. J Urol [Internet]. 2013 [cited 2022 Mar 24];189(6):2092–8. Available from: https://www.auajournals.org/doi/full/10.1016/j.juro.2012.11.174
22. Eklund M, Jäderling F, Discacciati A, Bergman M, Annerstedt M, Aly M, et al. MRI-Targeted or Standard Biopsy in Prostate Cancer Screening. N Engl J Med [Internet]. 2021 Sep 2 [cited 2022 Jan 4];385(10):908–20. Available from: https://www-nejm-org.ezproxy.galter.northwestern.edu/doi/10.1056/NEJMoa2100852
23. Nordström T, Discacciati A, Bergman M, Clements M, Aly M, Annerstedt M, et al. Prostate cancer screening using a combination of risk-prediction, MRI, and targeted prostate biopsies (STHLM3-MRI): a prospective, population-based, randomised, open-label, non-inferiority trial. Lancet Oncol. 2021;22(9):1240–9.

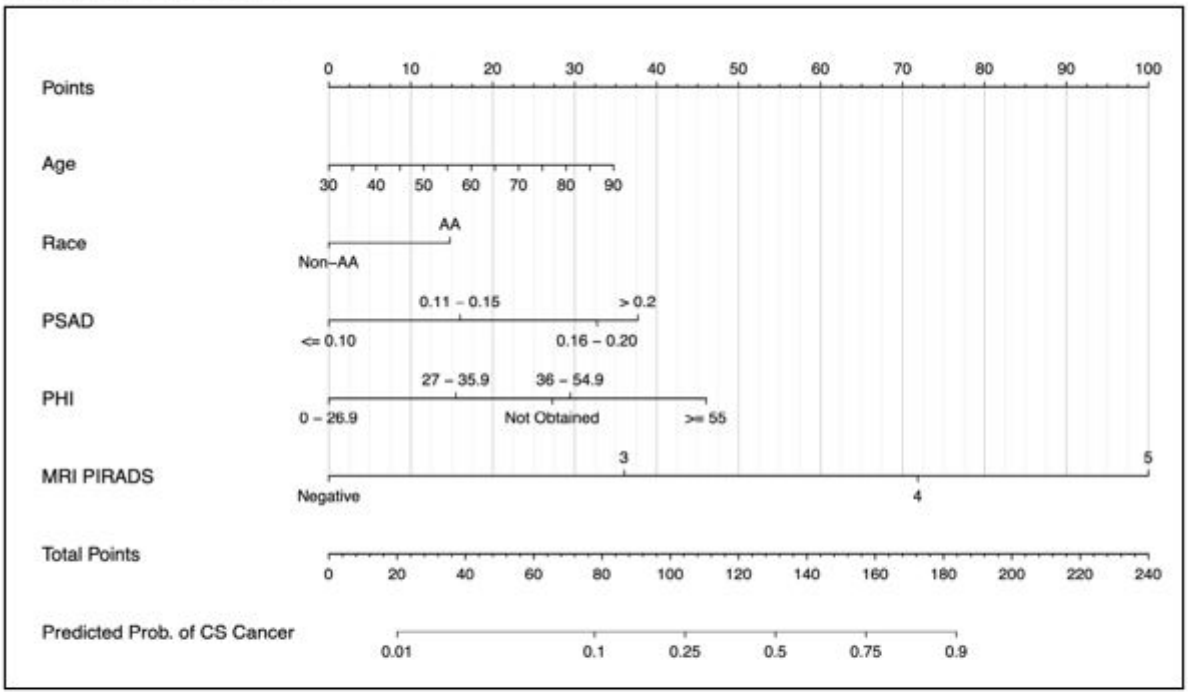
24. Wagaskar VG, Sobotka S, Ratnani P, Young J, Lantz A, Parekh S, et al. A 4K score/MRI-based nomogram for predicting prostate cancer, clinically significant prostate cancer, and unfavorable prostate cancer. Cancer Rep. 2021;4(4):1–9.
25. Falagario UG, Jambor I, Lantz A, Ettala O, Stabile A, Taimen P, et al. Combined Use of Prostate-specific Antigen Density and Magnetic Resonance Imaging for Prostate Biopsy Decision Planning: A Retrospective Multi-institutional Study Using the Prostate Magnetic Resonance Imaging Outcome Database (PROMOD). Eur Urol Oncol. 2021;4(6):971–9.

Tables

Tables 1 to 3 are available in the Supplementary Files section.

Figures

a. PHI for ≥GG2 PCa



b. PHI for ≥GG3 PCa

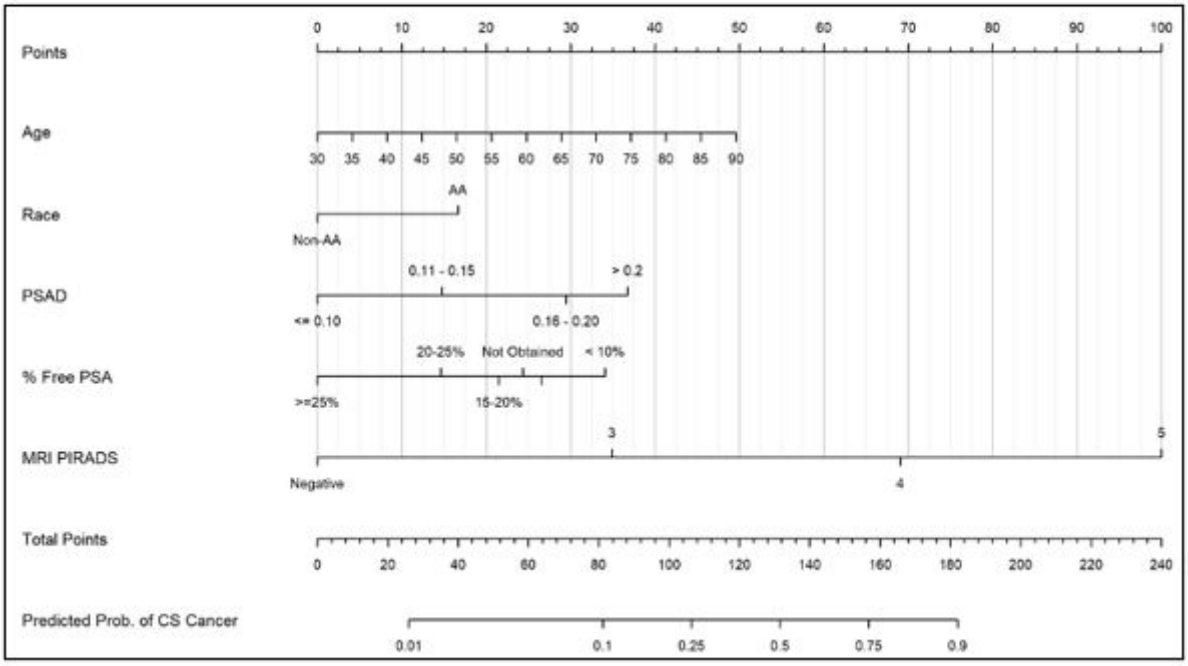


Figure 1

Legend not included with this version

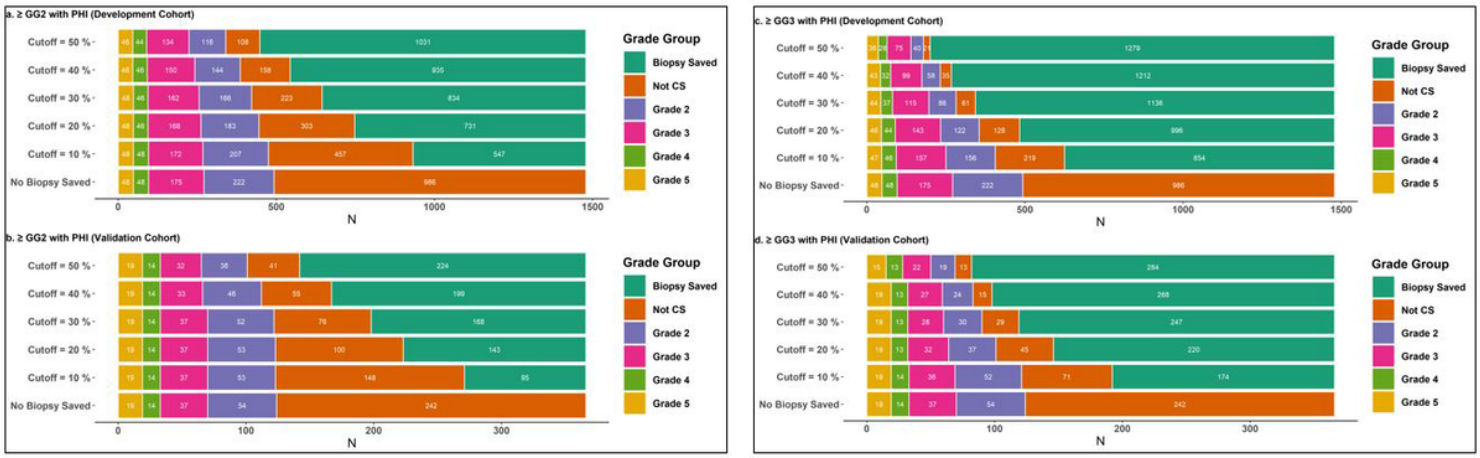


Figure 2

Legend not included with this version

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- SuppFig1.jpg
- SuppFig2.jpg
- SuppFig3.jpg
- SuppFig4.jpg
- SuppFig5.jpg
- SuppFig6.jpg
- SuppFig7.jpg
- SuppFig9.jpg
- SuppTable2.xlsx
- SuppTable4.xlsx
- SuppTable5.xlsx
- SuppTable6.xlsx
- Table1.xlsx
- Table2.xlsx
- Table3.xlsx