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Individual risk prediction of high grade prostate cancer based on the combination between total prostate-specific antigen (PSA) and free to total PSA ratio

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Abstract

Objectives: Clinical practice guidelines endorse the stratification of prostate cancer (PCa) risk according to individual total prostate-specific antigen (tPSA) values and age to enhance the individual risk-benefit ratio. We defined two nomograms to predict the individual risk of high and low grade PCa by combining the assay of tPSA and %free/tPSA (%f/tPSA) in patients with a pre-biopsy tPSA between 2 and 10 µg/L.

Methods: The study cohort consisted of 662 patients that had fPSA, tPSA, and a biopsy performed (41.3% with a final diagnosis of PCa). Logistic regression including age, tPSA and %f/tPSA was used to model the probability of having high or low grade cancer by defining 3 outcome levels: no PCa, low grade (International Society of Urological Pathology grade, ISUP<3) and high grade PCa (ISUP≥3).

Results: The nomogram identifying patients with: (a) high vs. those with low grade PCa and without the disease showed a good discriminating capability (~80%), but the calibration showed a risk of underestimation for predictive probabilities >30% (a considerable critical threshold of risk), (b) ISUP<3 vs. those without the disease showed a discriminating capability of 63% and overestimates predictive probabilities >50%. In ISUP 5 a possible loss of PSA immunoreactivity has been observed.

Conclusions: The estimated risk of high or low grade PCa by the nomograms may be of aid in the decision-making process, in particular in the case of critical comorbidities and when the digital rectal examinations are inconclusive. The improved characterization of the risk of ISUP≥3 might enhance the use for magnetic resonance imaging in this setting.

Keywords: high grade; nomogram; risk; risk-benefit ratio; rule-in.

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Introduction

Current clinical practice guidelines (CPGs) addressing the early detection of prostate cancer (PCa) endorse the stratification of PCa risk according to individual total prostate-specific antigen (tPSA) values and age, with the final aim to offer biopsy to patients at increased risk of high-grade disease, active surveillance to those at risk of low-grade tumors, seeking for a reduction of harms associated with the procedure invasiveness, overdiagnosis and overtreatment of low risk disease [1].

The individual risk-benefit ratio is enhanced when: (a) the capability of PSA testing to rule in high grade PCa is high, (b) there is a considerable decrease of undue biopsies, (c) the estimate of individual risk of PCa is unbiased and precise [2, 3]. Different risk prediction models to improve the diagnostic capability of tPSA for overall PCa have been proposed without resulting in a successful clinical implementation, but very few data are available on the capability of PSA to predict high-grade PCa, fulfilling the requirements of current CPGs [4–6]. Most of CPGs underscore the contribution of the percent free/total PSA ratio (%f/tPSA) which was introduced in clinical practice as reflex testing in the tPSA range of 2–10 µg/L (commonly 4–10 µg/L), to improve the rule-in capability for biopsy referral, although there is no universally accepted cut-off point for %f/tPSA, with values ranging from 8 to 28% [7, 8]. The evaluation of f/tPSA was shown to imply that up to 50% of unnecessary biopsies could be avoided in men with a tPSA falling in the range 4–10 µg/L and 35% in men with a tPSA of 2–4 µg/L, whilst missing 20% of PCa of overall grade [9]. There is a general consensus on optimizing the application of reflex testing to refine the risk for biopsy referral, notwithstanding that the recalibration of tPSA assays to WHO International Standard (IS) has resulted in approximately 20–25% lower tPSA values than Hybritech IS and that 19% of PCa for patients in the tPSA range 2.1–3.0 µg/L are of high grade [2, 9].

Therefore, the main challenge is to define the capability of the combined use of tPSA and %f/tPSA to predict high grade PCa and for identifying patients who most likely will benefit from biopsy referral or expensive second level tests such as magnetic resonance imaging (MRI), with the goal of increasing cost-effectiveness of overall diagnostic pathway [1, 10].

A wide spectrum of pre-biopsy risk nomograms has been proposed to aid in the decision process with the aim to maximize the diagnostic specificity, but the predictive capability resulting from the validation phases has prevented their use [4, 5].

It is important to note that tPSA, fPSA and the f/tPSA ratio are method-dependent, and thus PSA, fPSA and f/tPSA ratio results contributing to modeling the individual risk prediction have to be generated by the same immunoassay system, to avoid miscalibration of the predictive models and consequent misclassification of the individual risk [6]. By considering the above limitations, our objective in this study was to derive a nomogram to predict the individual risk of high grade PCa defined as ISUP≥3 for the combination of tPSA and %f/tPSA using one manufacturer, in patients with a pre-biopsy tPSA between 2 and 10 µg/L. This nomogram might be extended to other assays, by converting tPSA and %f/tPSA Roche into other methods by the use of appropriate conversion factors [11, 12].

Materials and methods

Patients and histological diagnosis

We retrospectively retrieved a continuous case series of 662 patients [274 with PCa (41.5%)], tested for tPSA and fPSA with the Roche immunoassays in two academic hospitals in Milan from 2014 to the first half of 2022.

Serum for testing was obtained before performing a prostate biopsy, or from patients having a dubious or positive digital rectal examination (DRE), and/or to increased transrectal ultrasonography prostate volume, and/or abnormal serial PSA testing.

Patients with tPSA concentrations falling in the range 2–10 µg/L and %f/tPSA were selected. Patients with: (1) a previous biopsy, (2) under active surveillance for previous diagnosis of PCa, (3) PSA testing with a different manufacturer immunoassay were excluded. Disease status (i.e. evidence/no evidence of PCa and evidence of acute glandular inflammation) was determined histologically by prostate biopsy on >12 cores. The International Society of Urological Pathology (ISUP) grade were used for PCa grading, as the ISUP is now recommended to replace total Gleason score by the updated CPGs [13]. Notably, ISUP grading allows to split the Gleason score 7 patterns, including the prognostically different 3 + 4 and 4 + 3 groups, in ISUP grade 2 and 3, the former mostly including well differentiated cancers, whereas the latter mostly including a higher percentage of poorly differentiated cancers associated to a worse prognosis [14]. The Review Board of our institution approved the study, carried out according to the Helsinki Declaration of 1975, as revised in 1996.

Laboratory methods

TPSA and fPSA measurements were carried out by electrochemiluminescence immunoassays on Cobas e601 platform, until 2017 and then on Cobas e801 marketed by Roche Diagnostics. The tPSA and fPSA results obtained by the two analytical platforms have been reported by the manufacturer to be aligned (tPSACobas e801=0.976 tPSACobas e601 − 0.03 µg/L, r=1; fPSACobas e801=0.936Cobas e601 + 0.042; r=1.00).

The main characteristics of the immunoassays have been extensively described in a previous study [15]. The most important performance characteristics are reported as follows: (a) declared limit of detection (LoD) of 0.014 and of 0.018 µg/L for tPSA and fPSA

respectively; (b) declared upper measurement limit of 100 and of 50 µg/L for tPSA and fPSA respectively; (c) one calibrator with a stated traceability to WHO IS 96/670 and WHO IS 96/668 for tPSA and fPSA, respectively.

Statistical analysis

Counts and percentages were reported for categorical variables and mean with standard deviation for continuous variables. The impact of age, tPSA, f/tPSA% for predicting PCa classification in no PCa, low grade (ISUP<3) and high grade PCa (ISUP≥3) were evaluated through logistic regression modeling methods. A continuous ratio logistic model was fitted, with the classification of PCa in the aforementioned categories as response variable, and tPSA, f/tPSA% and age as predictors. The choice of this particular class of logistic regression models allowed us to evaluate the ability for discriminating: (1) "high grade PCa" vs. "low grade PCa"; and, (2) "low grade" vs. "No PCa", conditionally to the knowledge that in (2) grade is not high [16]. For fitting the model, at first non linear effects and an interaction effect between f/tPSA% and age were evaluated by likelihood ratio test, and statistical significance was conventionally deemed when $p<0.05$.

The predictive ability was then reported in terms of calibration and discrimination, the former by calibration plots and the latter by Harrell's C index which is equivalent to the area under the Receiving Operating Curve (AUROC), and the respective 95% confidence intervals (95% CI).

The generalizability of model predictions was assessed through internal validation techniques [17]. To this aim, calibration curves and the AUROC were calculated using Bootstrap resampling technique for a total of 1,000 bootstrap samples.

Finally, nomograms were produced in order to give insights about the relationships among the predictors and the predicted probabilities from the logistic regression model.

All statistical analyses were performed using R software, version 4.1.2, by the VGAM and Rms (https://CRAN.R-project.org/package=rms) packages [17, 18].

Results

Patients with PCa (n=274) were older ($p<0.0001$) and had higher tPSA values ($p<0.0001$) and lower % f/tPSA ($p=0.0039$) than those without the disease (n=389) (Table 1). Patients with ISUP≥3 were older ($p=0.0152$), had similar tPSA values ($p=0.22$) but lower f/tPSA ratio (<0.0001) vs. those with ISUP<3 (Supplementary Figure 1). Acute inflammation (prostatitis) was detected post biopsy in none of ISUP≥3 PCa, in 5.2% of patients with ISUP<3 PCa, and in 39.2% of patients without the disease. Patients with ISUP≥3 were partitioned into the following categories: 38 with ISUP 3 (46.4%), 27 with ISUP 4 (32.9%) and 17 with ISUP 5 (20.7%), with no difference observed for age and tPSA between the groups. However, the f/tPSA ratio was significantly higher in ISUP5 as compared to ISUP3 ($p=0.01$) and ISUP4 ($p=0.06$) (Figure 1).

For the logistic regression modelling, non-linear effects were not observed ($p=0.6964$, $p=0.9849$ and $p=0.9417$, respectively for tPSA, %f/tPSA and age), however, a significant interaction effect between age and %f/tPSA was evident ($p=0.0346$).Yet, the interaction did not add any major clinical information with respect to the three predictors, therefore we considered the simpler additive model. The estimates for such models are reported in Supplementary Table 1. The estimates of Harrell's C index are reported in Supplementary Table 2. First, we considered the ability to discriminate high grade PCa (ISUP≥3) from no PCa and low risk PCa, and the AUC was 0.766 (95% CI: 0.715–0.820) (Figure 2A). Bootstrap methods confirmed this result with minimal shrinkage effect (AUC=0.75), and calibration plot on overall case series using as outcome the diagnosis of PCa ISUP≥3 showed a pattern of overestimation for predicted probabilities between 0.15 and 0.3 and underestimation after 0.3 (possibly due to the low sample size) (Figure 2B). Second, we considered the predictive ability of the model to discriminate low risk PCa from non PCa. The AUC was 0.633 (95% CI: 0.585–0.682) (Figure 3A). Bootstrap methods confirmed this result with minimal shrinkage effect (AUC=0.62), and calibration plot on overall case series using as outcome the diagnosis of PCa ISUP<3 showed a pattern of overestimation after the predicted

Table 1: Main features of the case series.

	Age, years	tPSA, µg/L		f/tPSA, %		Inflammation detected at biopsy
	Mean, SD	Mean, SD	Comparison: t, p-value	Mean, SD	Comparison: t, p-value	n (%)
Overall (n=662)	67.1, 8.4	5.7, 1.9		18.2, 7.5		162 (24.4%)
No PCa (n=388; 58.5%)	65.5, 8.4	5.6, 1.8	PCa vs. non-PCa	19.2, 7.7	PCa vs. non-PCa	152 (39.2%)
PCa (n=274; 41.5%)	69.3, 8.0	5.8, 1.9	−4.22, <0.0001[a]	16.9, 6.8	2.90, 0.0039[a]	10 (3.6%)
PCa with ISUP<3 (n=192; 29.0%[b])	68.5, 8.0	5.5, 1.9	ISUP<3 vs. ISUP≥3	17.7, 6.9	ISUP<3 vs. ISUP≥3	10 (5.2%)
PCa with ISUP≥3 (n= 82; 12.4%[b])	71.2, 7.6	6.6, 1.9	1.18, 0.2243	14.9, 6.1	4.05, <0.0001[a]	0 (0.0%)

tPSA, total PSA; f/tPSA, ratio free/total PSA. [a]$p<0.05$, [b]% reported vs. overall PCa.

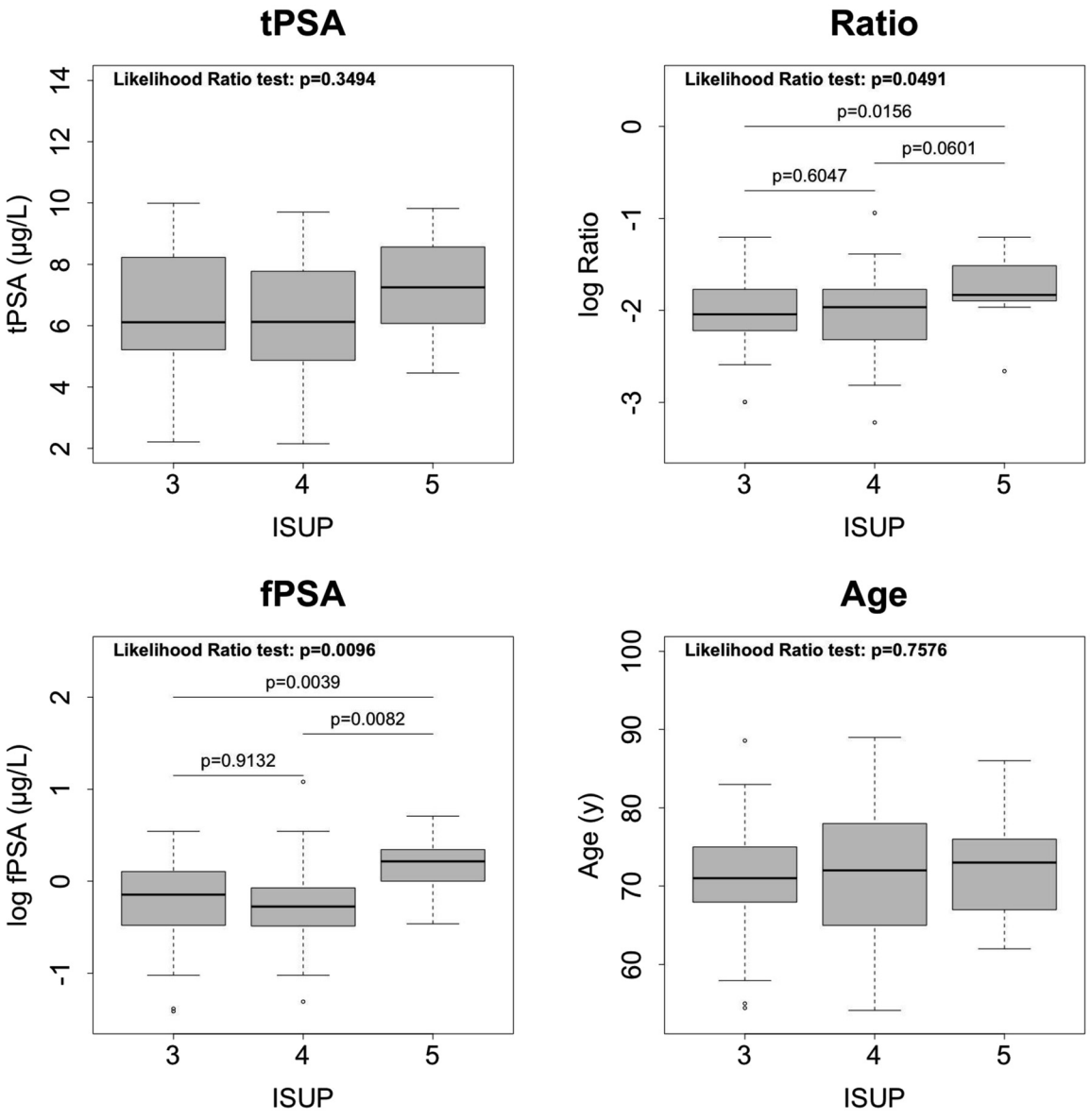

Figure 1: Comparison of age, tPSA, %f/tPSA ratio distributions between patients with ISUP 3, 4 and 5. The hypothesis tests were performed by using the analysis of variance (ANOVA) models. First a global test [i.e. likelihood ratio (LR) test] is performed to check if there is a significant difference between ISUP groups. In this case multiple comparison tests are further performed to check the difference between two groups.

probability of 0.5 (Figure 3B). The nomograms to predict the presence of: (a) high grade PCa (patients with ISUP ≥3), (b) low grade PCa (patients with ISUP <3) are reported in Figure 4A and B.

Discussion

PCa is the sixth leading cause of male cancer death (7.4%), although the largest proportion of PCas are indolent without leading to any complaints or death if left undetected [16]. These are managed by active surveillance, whereas "clinically significant" PCas (i.e. generally defined as ISUP≥2) have direct therapeutic implications as may progress, metastasize and lead to PCa-specific mortality, whose stronger predictor is histological grading (i.e. Gleason/ISUP score) [14, 19]. Over several decades, unselected PSA-based screening has increased the detection of indolent and not of high grade PCas [20, 21], resulting in rising concerns of overdiagnosis and overtreatment (radical prostatectomy/radiotherapy) and thus in an unfavourable risk-benefit ratio for the patient [2, 21]. PCas falling in the ISUP grade ≥3, mostly including a greater percentage of poorly differentiated cancer, are associated with a worse prognosis [14]. Currently, the main focus of research

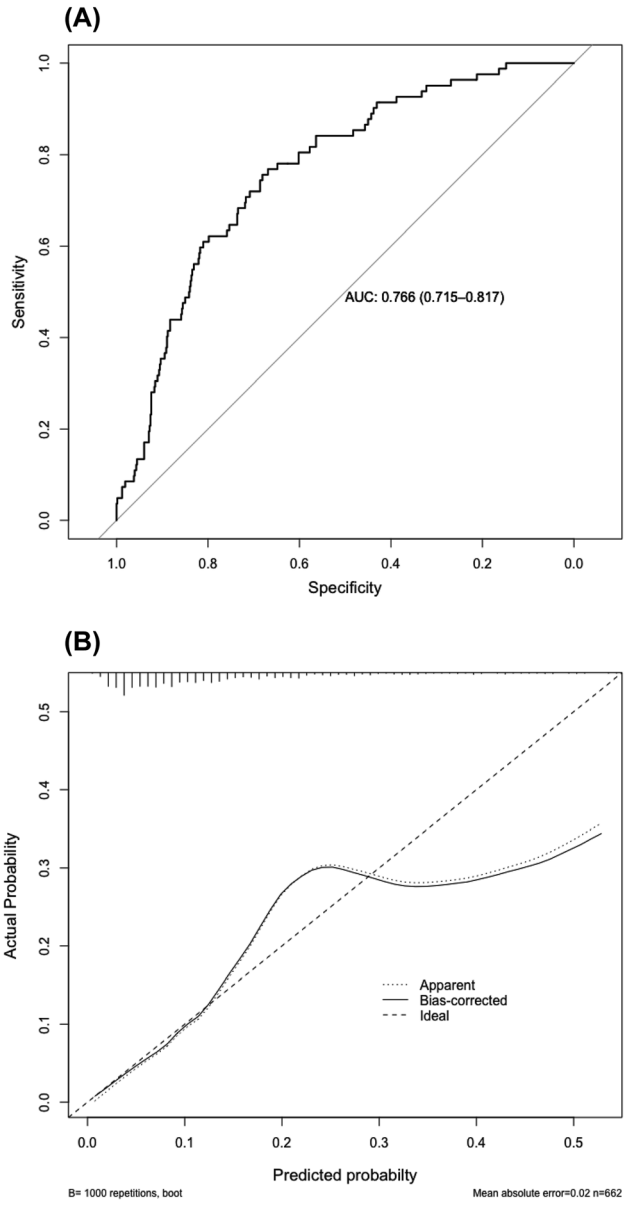

Figure 2: Receiver operating characteristic curves (A) and calibration plot of the nomogram predicting high grade cancer (B).

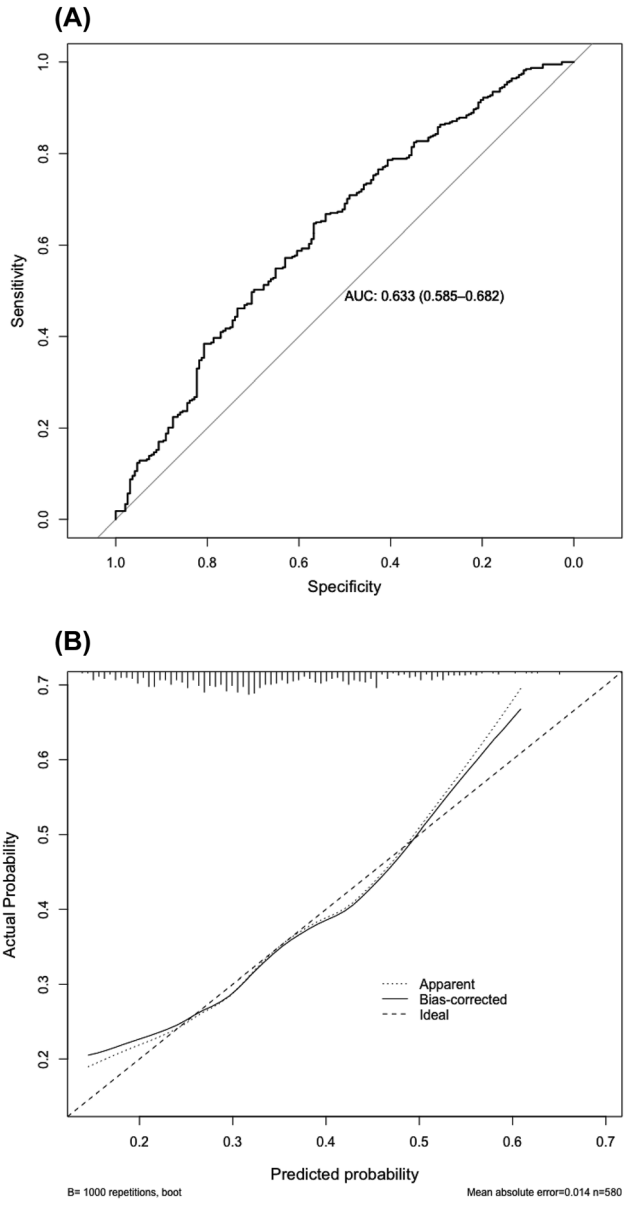

Figure 3: Receiver operating characteristic curves (A) and calibration plot of the nomogram predicting low grade cancer vs. no PCa (B).

and of the updated CPG on PCa diagnosis is for the identification of PCa of lethal potential [1]. This is the first study using tPSA and %f/tPSA obtained by one specific assay, to predict the individual risk of high grade PCa (ISUP grade ≥3), in the range of tPSA 2–10 μg/L, in which recommending biopsy/additional expensive second level tests are challenging.

The data demonstrate that low grade and high grade PCas have quite similar tPSA values, but differ for the %f/tPSA resulting lower in the latter group and likely carrying together with age a relevant diagnostic contribution. The nomogram allowing to identify patients with high grade PCas vs. those with low grade PCa and without the disease is characterized by a good (~80%) discriminating capability. However, studies reporting as secondary end-point the identification of high grade PCa (i.e. defined as Gleason score ≥7 /ISUP ≥2) the AUCs for the models fell in the range 0.70–0.77 [4, 5]. The calibration of our nomogram, however, suggests that for patients with predictive probabilities >30% of harboring a high grade PCa (ISUP grade ≥3) there is a consistent risk of underestimation. This is due to the lowest incidence of high grade PCa, falling within tPSA 2–10 μg/L, but these are also the cases that require an improved decision making process.

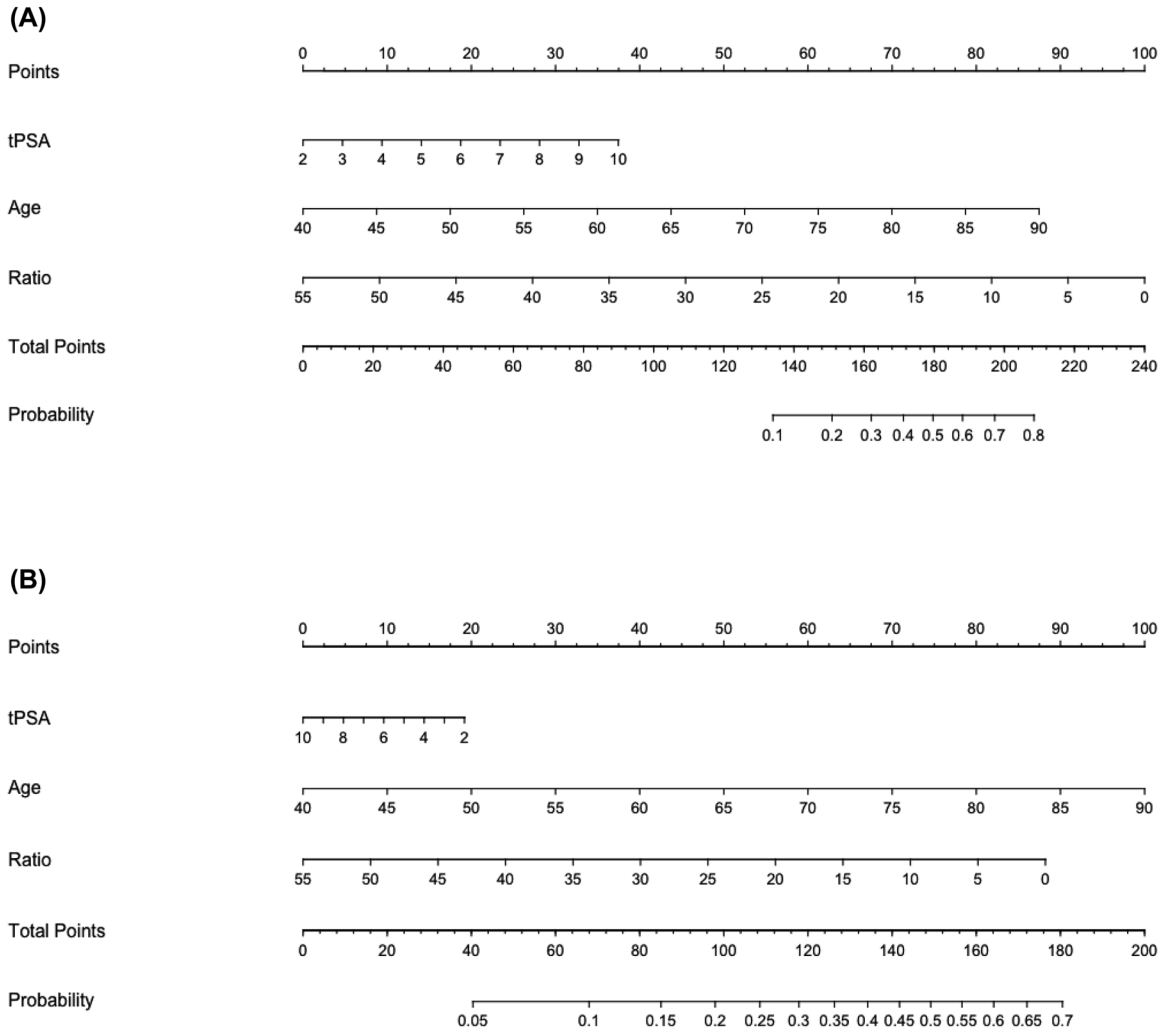

Figure 4: Nomogram prediction model for predicting high grade (A) and low grade PCa (B). The nomogram is used by first locating a patient's position for each variable on its horizontal scale and then a point value is assigned according to the points scale (top axis) and summed for all variables. Total points correspond to a probability value for having high grade PCa (A), low grade PCa (B).

A threshold for undergoing/foregoing biopsy was not provided, since in the decision-making process the decision is individualized, supported by the urologist informing the patient on the possible benefit/risk ratio of managing the disease according to: (a) the nomogram based estimated risk of high grade PCa, (b) the patient status (i.e. presence of life-threatening comorbidities, familiarity for PCa) and (c) the result of additional clinical investigations (DRE, prostate volume). Ruling out the possibility that an ISUP of high grade might early progress is challenging [19].

On the basis of the risk predicted by the nomogram, the urologist may pragmatically recommend MRI as second level test to improve the rule-in in the case of dubious DRE [1]. Current literature has shown that MRI has the most favourable diagnostic accuracy in detecting clinically significant PCa, reducing the number of insignificant PCa diagnosed [22, 23]. However, it should be remarked that the performance of MRI improve with the increase of tPSA testing characterizing the case series, and theoretically with the increased risk of having high grade PCa [22, 23]. Thus, our nomogram may be considered to refine the risk of high grade PCa in order to address and improve the cost-effectiveness of MRI [10, 24].

By considering the nomogram, predicting the probability of having low grade PCa vs. not having the disease, as expected the discriminating capability was lower than the first nomogram but acceptable and also the overestimation for predicted probability >50%, should be accounted, although likely with low clinical impact to recommend active surveillance. The progression is not a major feature of low grade PCa, but cannot be excluded [16, 19, 25] and preliminary evidence has associated a 1 unit increase of tPSA

to an approximately 2 fold increased risk of having high grade disease [9].

Thus the risk prediction according to our nomogram should be considered in light of additional clinical variables as a doubtful DRE or reinforce the clinical suspicion. It is more often neglected that the main reason of PSA variation is due to inter-individual biological variability (BV) which is higher than the intra-individual BV (42.0 vs. 6.8%). This should be accounted in the definition of the threshold of risk and might imply that in the active surveillance a reference change value of 19.5% should be theoretically accounted to estimate the significance of PSA variation at retesting. The main limitation of our study was undoubtedly due to the retrospective design. CPGs have changed over the past decade and currently new clinical tools as MRI, are available to support the recommendation for biopsy. To avoid selection bias for more recently enrolled patients, we have verified the homogeneity of clinical tools applied for recommending biopsy (according to those reported in the methods).

In conclusion, our study fulfil the current clinical need to tune risk models on the prediction of high grade PCa, with an acceptable accuracy, to identify who most likely will benefit treatment, in a range of tPSA where decision making is challenging. Our nomograms may be used in the decision making process to address MRI and active surveillance, improving the cost-effectiveness of the diagnostic pathway. The use of one method for PSA should provide a more accurate estimate of the risk predicted at the individual level, since differences between different manufacturers are evident [11, 12, 15]. Accordingly, the proposed preliminary conversion of the results from Roche into the other assays should however be cautionary considered, since the specificity of the antibodies of the different assays might generate PSA results different from those estimated by the equations [11, 12, 15]. Further observations provided in this study (presence of inflammation, markers and age patterns within high grade tumours) are consistent with the hypothesis that risk factor patterns may markedly differ for potentially lethal and indolent disease, suggesting separate etiologies and distinct disease entities [19, 25]. There is a general consensus on the evidence that later influences (i.e. diet, lifestyle, or environmental factors) [20] might be crucial to trigger disease progression among men with low grade disease, whereas earlier influences likely genetics factors may drive the development of a subtype of cancer that is more aggressive [19].

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Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The Review Board of our institution approved the study, carried out according to the Helsinki Declaration of 1975, as revised in 1996.

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