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Research Article

# Urine spermine and multiparametric magnetic resonance imaging for prediction of prostate cancer in Japanese men

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ABSTRACT

**Objectives:** To investigate the role of urine spermine and spermine risk score in predicting prostate cancer (PCa) diagnoses in combination with multiparametric magnetic resonance imaging (mpMRI).
**Methods:** Three hundred forty seven consecutive men with elevated prostate-specific antigen (PSA) with mpMRI examination were prospectively enrolled in this study. In 265 patients with PSA levels between 4 and20 ng/ml, pre-biopsy urine samples were analyzed for spermine levels with ultra-high performance liquid chromatography (UPLC-MS/MS). Transperineal image-guided prostate biopsies with 16-18 cores were performed. Logistic regressions were used to form different models for the prediction of the PCa, and the performances were compared using the area under the curve (AUC).
**Results:** The median serum PSA level and prostate volume were 7.4 ng/mL and 33.9 mL, respectively. PCa and high-grade PCa (ISUP group $\geq$2, HGPCa) were diagnosed in 66.0% (175/265) and 132/265 (49.8%) cases, respectively. The urine spermine levels were significantly lower in men with PCa (0.87 vs. 2.20, $P < 0.001$). Multivariate analyses showed that age, PSA, PV, urine spermine level, and Prostate Imaging Reporting and Data System (PI-RADS) findings were independent predictors for PCa. The Spermine Risk Score is a multivariable model including PSA, age, prostate volume, and urine spermine. Adding the Spermine Risk Score to PI-RADS improved the AUC from 0.73 to 0.86 in PCa and from 0.72 to 0.83 in high grade PCa (HGPCa) prediction (both $P < 0.001$). At 90% sensitivity for HGPCa prediction using Spermine Risk Score, 31.1% of unnecessary biopsies could be avoided. In men with equivocal MRI PI-RADS score 3, the AUC for HGPCa prediction was 0.58, 0.79, and 0.87 for PSA, PSA density, and Spermine Risk Score, respectively.
**Conclusion:** Urine Spermine Risk Score, including mpMRI could accurately identify men at high risk of HGPCa and reduce unnecessary prostate biopsies. Spermine Risk Score could more accurately predict HGPCa than PSA density in men with MRI showing equivocal PI-RADS 3 lesions.


## 1. Background

The prevalence of prostate cancer (PCa) in Japan is increasing. According to the 2011national survey of the total number of Japanese male cancers, PCa was ranked as the second most commonly diagnosed cancer, with 78,728 (15.9%), after gastric cancer. Also in Japan, it was reported that the prevalence of PCa rose very rapidly from 1982 to 2012 compared to other cancers.[1] The serum prostate-specific antigen (PSA) level is used for the screening of PCa. A PSA

*Abbreviations:* MRI, Magnetic Resonance Imaging; mpMRI, multiparametric MRI; PCa, Prostate Cancer; PSA, Prostate Specific Antigen; UPLC-MS/MS, Ultra-high Performance Liquid Chromatography with triple quadrupole Mass Spectrometer; PV, Prostate Volume; TRUS, transrectal ultrasound; PI-RADS, Prostate Imaging Reporting and Data System; AUC, Area Under Curve.

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level ≥4 ng/mL has been widely accepted as an upper limit for suggesting prostate biopsy to detect prostate cancer and is widely accepted in Japan, even though there is no consensus on the threshold value of PSA level ≥4 ng/mL.[3,4] In 2009, the European Randomized Study of Screening for Prostate Cancer (ERSPC) reported that there was no PCadetected in 76% of men who underwent prostate biopsy with an elevated PSA.[5] To address this issue, the use of additional biomarkers such as PSA-related markers, including free-to-total PSA ratio (F/T PSA), PSA density (PSAD), and PSA velocity (PSAV), was investigated.[5–7] However, the performance of these markers is still suboptimal, and new markers or approaches will be needed to improve the indication for prostatic biopsy.

In recent years, MRI has often been performed before a prostate biopsy, and its usefulness has been reported. In particular, multiparametric MRI (mpMRI), which includes T2-weighted image, diffusion-weighted image (DWI), and dynamic contrast-enhanced (DCE) sequences, has significantly improved the diagnosis of clinically significant (CS) PCa. Reports suggested that mpMRI was more sensitive (93%) than transrectal ultrasound scan (TRUS)-biopsy (48%) for the detection of clinically significant cancer.[6] Also, some reports demonstrated that MRI/US-fusion biopsy using mpMRI has a high accuracy for detecting clinically significant PCa compared to standard transrectal ultrasound-guided systematic biopsy with PSA levels in the gray zone of 4-10 ng/mL.[7]

However, there was a significant inter-observer difference in MRI reporting. To improve that, the Prostate Imaging Reporting and Data System version 1 (PI-RADS v1) was created in 2012 for systematizing and standardizing the interpretation reporting method, and currently PI-RADS version 2.1 is widely used in clinical practice.[8]

The prostate is one of the human tissues with the highest concentrations of polyamines, especially spermine. Spermine is involved in normal cell growth and function, including the secretory function of prostate epithelial cells. It is normally concentrated in benign prostate tissue with large luminal volumes.[9] As spermine is highly expressed in the prostate and is detectable in urine, there were reports suggesting a relationship between polyamines and the diagnosis of PCa. In 1975, Sanford et al. discovered that the excretion of polyamines in the urine of PCa patients was higher than in normal individuals. After that, many conflicting reports about the polyamine levels such as spermine or spermidine, in the urine sample with various detection methods in PCa patients were reported.[9–11] Recently, with the technological development of ultra performance liquid chromatography–tandem mass spectrometry (UPLC–MS/MS), the measurement of spermine became more consistent.[12] In 2016, Chan et al. suggested that a decrease in spermine levels in urine was associated with PCa and poorly differentiated PCa due to changes in cellular architecture and reduced luminal volumes.[12] In a recent study, urine spermine level and the Spermine Risk Score, which is the combination of urine spermine with clinical parameters like PSA level, prostate volume (PV), and age or digital rectal examination (DRE), could improve the detection of high-grade PCa (HGPCa).[13] Therefore, in this study, we would like to evaluate the role of urinary spermine as a biomarker for PCa and HGPCa detection by combining multiparametric MRI findings in a Japanese population.

## 2. Method

This was a prospective, single center, study under the approval of the ethics committee of Juntendo University Hospital (90-010). The inclusion criteria included men aged 18 or above, elevated PSA of 4–20 ng/mL, an MRI prostate performed, and no prior diagnosis of PCa. The exclusion criteria included men on any form of hormonal therapy or 5-alpha reductase inhibitor. All patients had an mpMRI examination as part of their pre-biopsy evaluation for cancer. The MRI prostates were reported by experienced radiologists according to the Prostate Imaging-Reporting and Data System (PI-RADS) version 2.1. Written consent was obtained from all patients. A total of 30 ml of initial stream urine was collected for spermine analysis before a transperineal ultrasound-guided prostate biopsy. A digital rectal examination or prostatic massage was not performed before urine sample collection. After the collection, the urine sample was stored at −20 °C in a deep refrigerator immediately, as described in the previous report by Chiu et al.[13] Frozen urine was then shipped by air cargo to the Chinese University of Hong Kong, Hong Kong, China. Each urine spermine level was measured as per the protocol of the previous study by UPLC-MS/MS.[13] Urine spermine values (in μmol/g) were normalized with urinary creatinine (in μmol/g) to generate normalized spermine (no unit), and all spermine analysis utilized normalized spermine values. Colleagues involved in urine laboratory work and analysis in Hong Kong were blinded to all patient information regarding clinical and pathology results.

In our hospital, transperineal prostate biopsies with 16-18 cores were performed after urine collection. Prostate volume (PV) was estimated by transrectal ultrasound using the ellipsoid formula (height × width × length and divided by 2). All pathology was reviewed by the same team of pathologists, who were blinded to the clinical information and urine spermine level. HGPCa was defined as International Society of Urological Pathology (ISUP) grade group 2 or above PCa.

The proportions of PCa were compared across age, PSA, PV, mpMRI findings (PI-RADS score), and spermine level. Then the prediction value of PCa was calculated using various clinical variables and normalized spermine values with univariate and multivariate analyses. Clinical parameters were summarized using descriptive statistics, including the median and interquartile range for continuous variables and the absolute frequency for categorical variables. The clinical parameters were compared between PCa and benign patients using T-tests for normally distributed data, Mann–Whitney U tests for non-normally distributed data, and Chi-square/Fisher exact test for categorical data.

We examined the risk models in combination with the variables that were created as a result of multivariate logistic regression analysis. The performance of variables and the combinations of risk models was compared with the area under the curve (AUC) of receiver operating characteristics (ROC). Internal validation was performed by the bootstrapping method. IBM SPSS Statistics for Windows version 26 (IBM Corp., Armonk, NY, USA) and R version 3.1.1 (The R Foundation for Statistical Computing, Vienna, Austria) were used for statistical analyses. A two-sided p value of $<0.05$ was considered significant.

## 3. Results

From August 2019 to June 2021, 347 consecutive men with suspected PCa due to elevated PSA were recruited in this study. Eighty-two patients with PSA >20 ng/mL were excluded from this analysis. The resulting 265 consecutive patients with PSA levels between 4 and 20 were analyzed for the urine spermine level. The baseline characteristics of the 265 men in this study are shown in Table 1. All 265 men (100%) had pre-biopsy multiparametric MRIs done. The median PSA and prostate volume were 7.4 ng/mL (interquartile range (IQR) 5.6–10.7 ng/mL) and 33.4 ml (IQR 22.6-47.6 ml), respectively. Most patients received systematic prostate biopsies of a median of 16 cores (IQR 16–18). In the whole cohort, PCa and HGPCa were diagnosed in 66.0% (175/265) and 132/265 (49.8%) cases, respectively. The normalized urine spermine level

**Table 1**
The Patient Characteristics with or without PCa.

| Median (interquartile range) | All $n = 265$ (100%) | Cancer patients $n = 175$ (66.0%) | Non cancer patients $n = 90$ (34.0%) | $P$ |
|---|---|---|---|---|
| Age (years) | 68 (62-73) | 70 (65-76) | 65 (59-71) | <0.001 |
| Family history of PCa in first degree relative | 7 (2.8%) | 1 (1.2%) | 6 (3.8%) | 0.244 |
| Prior negative biopsy | 14.0% (37/265) | 12.6% (22/175) | 16.7% (15/90) | 0.362 |
| PSA (ng/ml) | 7.4 (5.6-10.7) | 8.1 (5.7-11.2) | 6.37 (5.39-9.52) | 0.014 |
| Prostate volume (ml) | 33.4 (22.6-47.6) | 28.5 (20.8-39.4) | 47 (35.2-58.4) | <0.001 |
| PSA density | 0.24 (0.15-0.37) | 0.28 (0.18-0.41) | 0.16 (0.10-0.24) | <0.001 |
| Total biopsy cores | 16 (16-18) | 16 (16-19) | 16 (16-16) | 0.011 |
| PI-RADS score | | | | <0.001 |
| 2 | 36 (13.6%) | 12 (6.9%) | 24 (26.7%) | |
| 3 | 102 (38.5%) | 55 (31.4%) | 47 (52.2%) | |
| 4 | 84 (31.7%) | 71 (40.6%) | 13 (14.4%) | |
| 5 | 43 (16.2%) | 37 (21.1%) | 6 (6.7%) | |
| Creatinine (g/L) | 0.89 (0.63-1.29) | 0.89 (0.63-1.28) | 0.90 (0.67-1.29) | 0.541 |
| Spermine (umol/L) | 0.89 (0.39-2.38) | 0.71 (0.38-1.70) | 1.65 (0.60-4.97) | <0.001 |
| Normalized urine spermine (umol/g of creatinine) | 0.98 (0.47-2.63) | 0.87 (0.46-1.89) | 2.02 (0.63-5.72) | <0.001 |
| ISUP grade group | | | | |
| 1 | | 43 (24.6%) | | |
| 2 | | 44 (25.1%) | | |
| 3 | | 38 (21.7%) | | |
| 4 | | 42 (24.0%) | | |
| 5 | | 8 (4.6%) | | |

was significantly lower in PCa patients compared to those with no PCa (0.87 vs. 2.02; $t$-test, $P < 0.001$). Univariate analyses identified that the five factors age, PSA, PV, PI-RADS score, and urine spermine were predictors of both PCa and HGPCa diagnoses (Table 2 and Table 3). Multivariate analyses showed that these five factors were independent predictors for PCa and HGPCa diagnoses (Table 2, Table 3).

The Spermine Risk Score was formed from the combination of four factors: age, PSA, PV, and normalized urine spermine. The AUC of various predictors and models is shown in Fig. 1. For PCa prediction, the Spermine Risk Score (AUC 0.82) performed significantly better than the MRI PI-RADS score (AUC 0.73) using Delong's test ($p = 0.011$). Combining the Spermine Risk Score with MRI PI-RADS resulted in the best performance (AUC 0.86) in predicting PCa vs. MRI PI-RADS score (AUC 0.73) using Delong's test ($P < 0.001$) (Fig. 1). For HGPCa prediction, The AUC of MRI PI-RADS, Spermine Risk Score, and Spermine Risk Score + MRI PI-RADS was 0.72, 0.79, and 0.83, respectively. Adding Spermine Risk Score to MRI PI-RADS resulted in a significantly better AUC compared with MRI PI-RADS alone (Delong's test, $P < 0.001$) (Fig. 1). Similar results for both any grade PCa and HGPCa were observed when we divided the cohort into PSA subgroups of 4.0-9.9 ng/mL and 10.0-20 ng/mL (Supplementary Figure 1-4). For HGPCa prediction in men with PSA 4-10 ng/mL, the AUC of PSA, PSA density, MRI PI-RADS, Spermine Risk Score, and Spermine Risk Score + MRI PI-RADS was 0.62, 0.70, 0.70, 0.75, and 0.81, respectively. For HGPCa prediction in men with PSA 10-20 ng/mL, the AUC of PSA, PSA density, MRI PI-RADS, Spermine Risk score, and Spermine Risk score + MRI PI-RADS was 0.64, 0.78, 0.77, 0.85, and 0.87, respectively (Supplementary Figure 1-4). Using the 4-factor Spermine Risk Score, a cutoff of 0.33 corresponded to 90% sensitivity (missing 10%, that is 13/131 cases) for HGPCa diagnosis, with men with scores >0.33 and < 0.33 having 64.8% (118/182) and 15.9% (13/82) HGPCa diagnoses, respectively. If prostate biopsy is not offered for men with Spermine Risk Score <0.33, 31.1% (82/264) of unnecessary biopsies could be avoided.

In men with equivocal MRI findings of PI-RADS 3 lesions (n = 102), HGPCa was diagnosed in 56.3% of men with urine normalized spermine <1, but only 6.3% of men with spermine >5 (Table 4, chi-square p = 0.003). In men with PI-RADS score 3, the AUC for HGPCa prediction was 0.58, 0.79, and 0.87 for PSA, PSA density, and Spermine Risk Score, respectively. The AUC difference between PSA density and Spermine Risk Score in PI-RADS 3 patients was statistically significant (Delong's test, p = 0.027). Internal validation with bootstrapping was performed for PCa and HGPCa using the Spermine Risk Score including 5 factors (PSA, normalized spermine, age, PV, and PI-RADS score) (Fig. 2). Good validation in terms of AUC, intercepts. and slopes was observed for both PCa and HGPCa.

## 4. Discussion

The prevalence of PCa is increasing worldwide. Currently, serum PSA examination is accepted as a good screening tool for PCa.

**Table 2**
Univariate and multivariate analyses for prediction of PCa.

| | Univariate analyses OR (95% CI) | $P$ | Multivariate analyses OR (95% CI) | $P$ |
|---|---|---|---|---|
| Age (Years) | 1.09 (1.05-1.12) | $P < 0.001$ | 1.08 (1.04-1.13) | $P = 0.001$ |
| PSA[a)] | 1.80 (1.14-2.86) | $P = 0.012$ | 1.91 (1.03-3.52) | $P = 0.039$ |
| Prostate volume[a)] | 0.25 (0.16-0.40) | $P < 0.001$ | 0.27 (0.16-0.47) | $P < 0.001$ |
| PI-RADS score | | $P < 0.001$ | | $P < 0.001$ |
| PIRADS 1-2 (reference) | 0.54 (0.12-2.52) | $P = 0.432$ | 0.71 (0.13-4.03) | $P = 0.702$ |
| PIRADS 3 | 1.64 (0.49-5.50) | $P = 0.425$ | 1.76 (0.43-7.14) | $P = 0.431$ |
| PIRADS 4 | 7.65 (2.10-27.81) | $P = 0.002$ | 8.68 (1.93-39.14) | $P = 0.005$ |
| PIRADS 5 | 8.63 (2.05-36.28) | $P = 0.003$ | 6.56 (1.23-35.14) | $P = 0.028$ |
| Normalized spermine[a)] | 0.71 (0.61-0.83) | $P < 0.001$ | 0.74 (0.61-0.91) | $P = 0.003$ |

[a)] Natural logarithm transformed.

**Table 3**
Univariate and multivariate analyses for prediction of high grade PCa (ISUP grade group 2 or above).

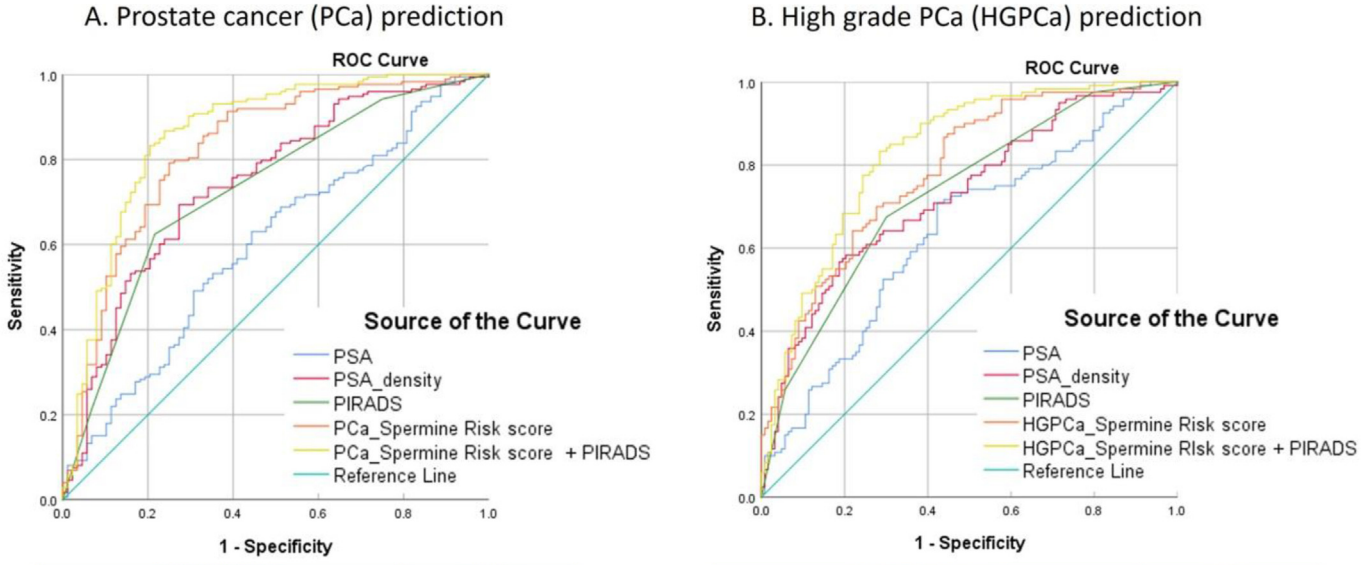
| | Univariate analyses OR (95% CI) | *P* | Multivariate analyses OR (95% CI) | *P* |
|---|---|---|---|---|
| Age (Years) | 1.08 (1.04-1.12) | $P < 0.001$ | 1.06 (1.02-1.11) | $P = 0.002$ |
| PSA[a)] | 2.14 (1.38-3.30) | $P = 0.001$ | 2.21 (1.28-3.82) | $P = 0.005$ |
| Prostate volume[a)] | 0.35 (0.23-0.52) | $P < 0.001$ | 0.38 (0.24-0.60) | $P < 0.001$ |
| PI-RADS score | | $P < 0.001$ | | $P < 0.001$ |
| PIRADS 1-2 (reference) | 0.63 (0.08-5.17) | $P = 0.663$ | 0.89 (0.10-8.04) | $P = 0.920$ |
| PIRADS 3 | 3.23 (0.67-15.50) | $P = 0.144$ | 3.28 (0.62-17.32) | $P = 0.161$ |
| PIRADS 4 | 8.13 (1.67-39.48) | $P = 0.009$ | 7.95 (1.48-42.78) | $P = 0.016$ |
| PIRADS 5 | 18.89 (3.50-102.02) | $P = 0.001$ | 14.14 (2.31-86.48) | $P = 0.004$ |
| Normalized spermine[a)] | 0.76 (0.66-0.88) | $P < 0.001$ | 0.81 (0.68-0.97) | $P = 0.020$ |

[a)] Natural logarithm transformed.

However, there are still some limitations for serum PSA in clinical usage. In men with elevated PSA of 4-20 ng/mL, up to 50-80% of patients actually did not have PCa (false positive).[2,3] Therefore, to avoid unnecessary biopsies, especially in the elderly, we need to develop additional biomarkers to improve the detection rate of PCa. Currently, mpMRI imaging is one of the most common tools to improve PCa diagnosis moreover, MRI/US-fusion biopsy has been reported as the more efficient procedure to detect clinically significant prostate cancer in patients with PSA 4–10 ng/mL(7). Other candidates of these biomarkers were the Prostate Health Index[1], 4-kallikrein panel[2], urine PCA3[3], or select MDx [4].

In this study, we examined the prediction values of a new urine marker, urine spermine, with a combination of mpMRI findings for PCa detection. Our results show that the urine spermine level was significantly lower in PCa patients than in patients without cancer. The combination of urine spermine, age, PV, PSA, and PI-RADS score showed excellent discriminative ability for PCa (AUC 0.86) and HGPCa (AUC 0.83) predictions. This study showed that adding Spermine Risk Score to mpMRI PI-RADS could further improve PCa and HGPCa predictions and have additional benefit in PCa detection. Using the urine Spermine Risk Score and mpMRI as the biomarkers, unnecessary prostate biopsies can be avoided, especially in men with equivocal findings of PI-RADS score 3 lesions. This is important as most PI-RADS 3 lesions have a relatively lower risk of HGPCa compared with PI-RADS 4 or 5 lesions, and these equivocal MRIs could contribute to unnecessary biopsies. PSA density cutoffs (e.g., 15%) have been used in some centers to guide biopsy decisions in PI-RADS 3 lesions. In this study, thhe urine Spermine Risk Score was found to be more accurate than PSA density in predicting HGPCa in men with PI-RADS 3 lesions.

Spermine is mainly excreted into the urine in the form of the monoacetyl derivative of spermine, the diacetylated derivatives of spermine (DiAcSpm) had lower secretion levels in urine but with less variation in the population, this may be a more reliable biomarker. Recent reports show that a lower urine spermine level is related to the presence of PCa and a higher risk of HGPCa.[13] Besides the lower urine spermine level in the PCa patient, Chiu et al. also showed that urine spermine level was negatively associated with a higher risk of HGPCa in Chinese men. They demonstrated that a urine Spermine Risk Score can be formed by combining urine




| PCa predictors | AUC |
|---|---|
| PSA | 0.60 (0.53-0.67) |
| PSA density | 0.74 (0.68-0.81) |
| PI-RADS | 0.73 (0.67-0.80) |
| Spermine Risk score (PCa) | 0.82 (0.77-0.88) |
| Spermine Risk score (PCa) + PI-RADS | 0.86 (0.81-0.91) |

| HGPCa predictors | AUC |
|---|---|
| PSA | 0.63 (0.56-0.70) |
| PSA density | 0.72 (0.66-0.79) |
| PI-RADS | 0.72 (0.66-0.78) |
| Spermine Risk score (HGPCa) | 0.79 (0.73-0.84) |
| Spermine Risk score (HGPCa) + PI-RADS | 0.83 (0.78-0.87) |

**Fig. 1.** Areas under the curve of the calculated probabilities of prediction of the prostate cancer.

**Table 4**
Normalized spermine and risk of prostate cancer (PCa) and higher grade PCa (HGPCa) in men with MRI PI-RADS score 3.

| Normalized spermine | <1.00 | 1.00-2.99 | 3.00-4.99 | ≥5.00 | Total |
|---|---|---|---|---|---|
| Any grade PCa | 66.7% (32/48) | 63.3% (19/30) | 25.0% (2/8) | 12.5% (2/16) | 53.9% (55/102) |
| ISUP grade ≥2 PCa | 56.3% (27/48) | 33.3% (10/30) | 25.0% (2/8) | 6.3% (1/16) | 39.2% (40/102) |

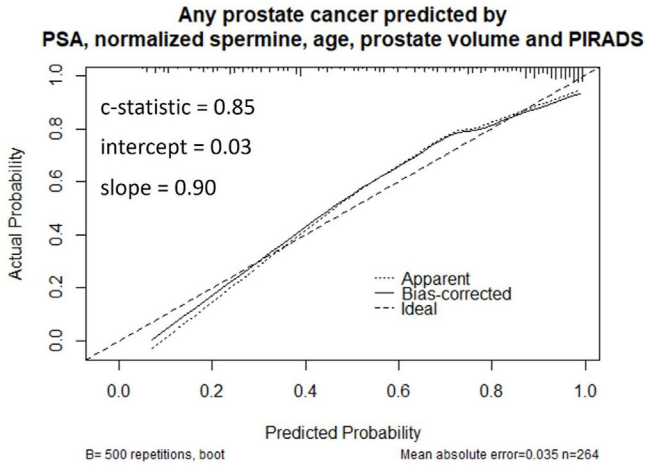
spermine with clinical factors including PSA, prostate volume (PV), and age or digital rectal examination (DRE), and the risk score could predict HGPCa better than individual clinical factors or urine spermine alone.[13]

In this study, we also observed a lower level of urine Spermine in Japanese PCa patients.[14] Further research may be needed to confirm our results using different Japanese cohorts.

There are several limitations to this study. The first limitation was the relatively small number of patients in the study, and this study was performed in a single institution, Juntendo University in Japan. Therefore, a multi-center and multi-country study may be needed to provide more strength to confirm the results of our study. A large scale study is needed to further confirm the observation as extra validation and reveal its mechanism in the future. We also have some differences in the trend of prostate biopsy in this study because of the COVID-19 crisis in Japan. There is one report that prostate biopsies decreased by around 30% as a result of the nationwide events in Japan (15). These might change the patient background so that the more selected patients have a prostate biopsy, which increases the positive rate of prostate cancer in this study. Secondly, diet control had not been performed to completely exclude the effect of food habit; despite what Vargas et al. reported before, no significant association was found between dietary polyamine intake and urinary polyamines measured. Lastly, we have not examined to compare with other prostate cancer biomarker factors that are commercially available in blood and urine, such as the Prostate Health Index (*phi*),[14] PCA3, or Select MDx.

However, despite these limitations, our study contains certain strengths. This is the first prospective study on the combined use of urine spermine and mpMRI for PCa detection. Urine spermine was detected by highly sensitive ultra-high performance liquid chromatography with a triple quadrupole mass spectrometer (UPLC-MS/MS), compared with liquid chromatography with a fluorometric detector in older studies when spermine was not well detected. Both urine sampling and mpMRI are not invasive and might be able to reduce the need for an unnecessary invasive prostate biopsy.

In conclusion, the urine Spermine Risk Score and multivariate models including mpMRI, could accurately identify men at higher risk of PCa and reduce unnecessary prostate biopsies.



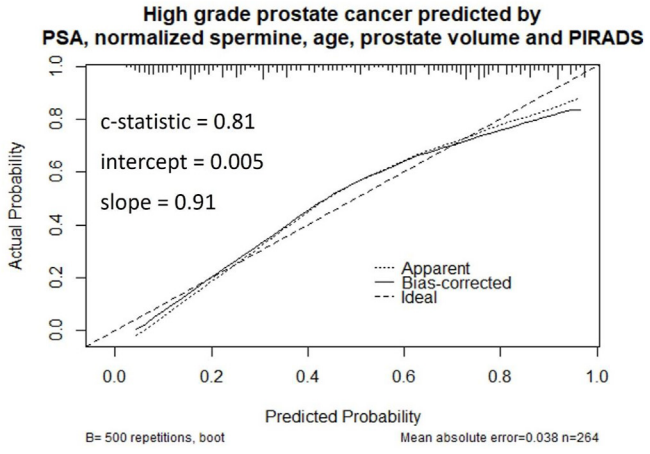




**Fig. 2.** Internal validation with bootstrapping. a. any grade of prostate cancer predicted by PSA, normalized spermine, age, prostate volume, and PI-RADS score. b. high grade prostate cancer predicted by PSA, normalized spermine, age, prostate volume, and PI-RADS score.

## Author contributions

Shuji Isotani: protocol/project development, data collection or management, data analysis, manuscript writing.

Peter Ka-Fung Chiu, Takeshi Ashizawa: Protocol/project development, data collection, data analysis, manuscript editing.

Ka-Leung Wong, Yan-Ho Fung: sample analysis.

Fumitaka Shimizu, Haruna Kawano, Toshiyuki China, Masayoshi Nagata: data collection,

Chi-Fai Ng, Shigeo Horie, Yuki Nakagawa, Satoru Muto: manuscript editing, project management.

## Conflicts of interest

KL Wong holds a patent for urinary polyamines as prostate cancer detection biomarkers (patent no. US20180172695A1). This does not alter our adherence to “prostate international” policies on sharing data and materials. The other authors declare that they have no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.prnil.2023.07.003.

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