Research Square

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Utility of PSA density velocity in diagnosing prostate cancer on prostate MR

Sabarish Narayanasamy
Mayo Clinic
Yasuhisa Kurata
Mayo Clinic
Ayumu Kido
Mayo Clinic
Hirotsugu Nakai
Kyoto University
Hiroaki Takahashi
Mayo Clinic
Jordan LeGout
Mayo Clinic in Florida
Adam Froemming
Mayo Clinic
Akira Kawashima
Mayo Clinic in Arizona
Abhinav Khanna
Mayo Clinic
Takahashi Naoki
Takahashi.Naoki@mayo.edu

Mayo Clinic

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Abstract

Purpose

To assess if PSA density (PSAD) velocity is a predictor of clinically significant prostate cancer (csPCa).

Methods

Patients undergoing prostate MR for suspected csPCa between 2017 and 2023 were included. Of these, patients who underwent two or more MR exams within 0.3 to 2 years to each other and pathological confirmation within 1 year after the last MR were identified. PI-RADS score, patient age, screening or active surveillance (AS), PSA, PSAD, PSA-velocity and PSAD-velocity were assessed if they were predictor of csPCa. For univariate analysis, all variables were assessed using student t or chi-square tests. When variables were considered significant, variables were entered into multivariate logistic regression model.

Results

23,244 MRs were performed (17,703 screening, 5,541AS). 1,174 patients (mean age: 65.9) met the inclusion criteria, and 550 patients (47%) were diagnosed with csPCa. On univariate analysis, PI-RADS score (p<.0001), age (67.0 vs 64.9, p<.0001), AS exam (67% vs 59%, p = 0.004), PSA (7.5 vs 6.6, p<.001), PSAD (0.16 vs 0.12, p<.0001) and PSAD-velocity (0.023 vs 0.012, p = 0.005) were predictors of csPCa but PSA-velocity (1.4 vs 1.2, p=.4) was not. On multivariate analysis, PI-RADS score (p<.0001), age (p<.0001), AS exam (p<.0001), PSA (p<.0001) and PSAD (p<.0001) remained significant predictors, but PSAD-velocity was not (p=.1).

Conclusions

Higher PSAD-velocity was associated with presence of csPCa on univariate analysis but not on multivariate analysis when combined with other predictors such PI-RADS score, age, and PSAD.

Introduction

Prostate cancer remains one of the most common malignancies diagnosed in men worldwide, with an estimated 300,000 new cases in the United States in 2024 [1]. Despite the widespread use of prostate-specific antigen (PSA) as a biomarker for prostate cancer detection, the accuracy of PSA alone in predicting clinically significant prostate cancer (csPCa) is limited due to its lack of specificity [2–4].

Multiparametric magnetic resonance imaging (MRI) is the standard imaging technique to diagnose csPCa [5]. Targeted biopsy of MRI-detected lesions using MRI–ultrasound fusion software, is associated

with a higher detection rate of clinically significant prostate cancer (csPCa) compared to template-based biopsy alone. To reduce unnecessary biopsies and overdiagnosis, numerous risk prediction models have been developed to evaluate the risk of csPCa and guide decisions regarding the need for biopsy. PI-RADS score (version 2.1) remains a cornerstone of these decision models [6, 7]. Prostate-specific antigen density (PSAD), calculated by PSA value divided by gland volume has been shown to have a complementary value to MRI especially in patients with negative or equivocal MRI (PI-RADS 3) [6–8]. Studies have shown that there is a low risk of csPCa in PI-RADS 3 lesions with a PSAD value < 0.10 ng/mL/mL and biopsy can be safely avoided [9].

First introduced by Carter et al. in 1993, PSA-velocity was proposed as a way to enhance the specificity of PSA screening and reduce unnecessary biopsies[10]. However, the utility of PSA-velocity is controversial [10–12]. PSAD-velocity, the change in PSAD over time, is a similar metric that accounts for the dynamic changes in PSAD over time rather than relying on static measurements for prediction of csPCa. To the best of our knowledge, the utility of PSAD-velocity in predicting csPCa has not been studied.

The aim of this study was to assess whether PSAD-velocity could serve as an independent predictor of csPCa in patients undergoing prostate MRI, in comparison to other well-established markers such as PSA, PI-RADS score, and patient age and thereby serve as a marker for biopsy.

Methods

Our institutional review board committee approved this three-center retrospective study of observational data (IRB#: 23-008038) with informed consent waiver.

Patients

This study included patients who underwent MRI of the prostate performed for suspected csPCa between 2017 and 2023. Patients with known csPCa at the time of MR were excluded. Patients without history of prostate cancer were categorized as screening and patients with known Gleason score (GS) 6 prostate cancer were considered active surveillance (AS). Following Institutional review board approval, the institutional prostate MR database across 3 centers in different states was queried. The inclusion criteria were patients who had undergone two or more MR exams. MR exam with pathological confirmation within one year after MR exam was considered index exam. When the patient had multiple pathological confirmations, the last pathological confirmation was used. MR exams performed 0.3 to 2 years prior to the index exam were defined as baseline exams. The patient must have both index MR exam and at least 1 baseline MR exam. Figure 1 shows how MR exams were selected as the index MR and baseline MR exams. Exams without prostate-specific antigen (PSA) or prostate volume values were excluded.

MR examination

MR examinations were conducted using either 3.0T or 1.5T scanners (GE Medical Systems, Illinois, U.S., Siemens, Munich, Germany). A 1.5T scanner was used in cases where patients had contraindications to the 3.0T magnet or when the scans were performed under anesthesia. All MRI exams adhered to the technical specifications outlined in PI-RADS v2.0 or v2.1.

Pathological confirmation

Ultrasound-guided MRI fusion targeted biopsies were conducted using MRI/ultrasound fusion software (UroNav, Philips Healthcare) for MRI-detected lesions of PI-RADS 3 or higher. A transrectal or transperineal approach was employed, with three to five cores sampled per suspicious lesion. Simultaneously, systematic biopsies were performed, with 10–12 cores obtained. For PI-RADS scores of 1–2, systematic biopsies were carried out only if there was a high clinical suspicion of csPCa. The presence or absence of csPCa was determined from the pathology report, from which the patient's GS was also extracted. A GS of 7 or higher was considered as csPCa.

PSAD and PSAD-velocity

The prostate volume was calculated using either prostate module of DynaCAD software (Philips Healthcare) using automated segmentation of axial or oblique axial small field of view T2-weighted images followed by radiologists' manual correction or by radiologists using the ellipsoid formula during image interpretation. In two centers, DynaCAD was used in most cases. In one center, DynaCAD was used only when suspicious (PI-RADS 3 or higher) lesion was detected. Otherwise, the ellipsoid formula was used. PSAD was defined as PSA divided by prostate volume. PSA was obtained from the radiology reports or electronic medical record, and the prostate volume was obtained from the radiology report. PSAD-velocity was defined as (PSAD of index exam – PSAD of baseline exam) divided by the time (in years) between two exams. In patients with multiple baseline MRIs (performed between 0.3 to 2 years before the index MRI), PSAD velocity was estimated using linear regression, with the slope of the regression line representing the temporal trend of PSAD. PSA-velocity was similarly calculated from PSA of two exams. Other variables including PI-RADS score, patient-age, and indication for imaging (screening vs AS) at the time of index exam were also retrieved from the radiology report.

Statistical analysis

The patients were divided into 2 groups – with and without csPCa based on pathological confirmation. Variables evaluated included PI-RADS score, patient age, indication for imaging (screening vs AS), PSA, PSAD, and PSA-velocity and PSAD-velocity. PSA and PSAD were log-transformed because data were right-sided skewed. Univariate analysis was performed using student's t-test, or chi-square test as appropriate to initially assess their relationship with csPCa. Following the univariate analysis, variables that showed statistical significance (P value < 0.05) were included in a multivariate logistic regression model. Statistical analysis was performed using Python (3.9).

Results

Patient characteristics and MR exams:

A total of 23,244 prostate MR exams (in 17,967 unique patients) were conducted during the study period, with 17,703 performed for screening without history of prostate cancer and 5,541 for AS with history of GS 6 prostate cancer. Of these, 969 exams were excluded due to lack of PSA. A total of 1,174 unique patients (mean age: 65.9 years) met the study's inclusion criteria, having undergone two or more MR exams including one index exam with pathological confirmation within one year of the last MR exam and one or more baseline MR exams 0.3 to 2 years prior to the index MRI.

Among the 1,174 patients, 550 (47%) were subsequently diagnosed with csPCa. Eighty-eight patients had 2 or more baseline MR exams. The median interval between the index and most recent baseline MR exams was 1.1 years. 440 index MR exams were screening exams, and 734 index MR exams were AS. The distribution of PI-RADS scores showed that 358 exams were classified as PI-RADS 1–2, 231 as PI-RADS 3, 411 as PI-RADS 4, and 174 as PI-RADS 5. The mean prostate-specific antigen (PSA) level across the cohort was 8.4 ng/mL, with a mean PSA-velocity of 1.3 ng/mL/year. The mean PSAD was 0.16 ng/mL/mL, and the mean PSAD-velocity was 0.018 ng/mL/mL/year.

Univariate analysis:

Results of univariate analysis are summarized in Table 1. Patients with csPCa had a higher mean age compared to those without csPCa (67.0 years vs. 64.9 years, p<.0001). Similarly, patients with csPCa were more likely to be in AS than those without csPCa (67% vs. 59%, p = 0.004). PI-RADS scores showed a clear correlation with csPCa. Higher PI-RADS scores were strongly predictive of the diagnosis of csPCa (p<.0001; Fig. 2). PSA levels were higher in the csPCa group compared to the non-csPCa group (7.5 ng/mL vs. 6.6 ng/mL, p<.001; Fig. 3). PSAD was notably elevated in patients diagnosed with csPCa (0.16ng/mL/mL vs. 0.12 ng/mL/mL, p<.0001; Fig. 4), and PSAD-velocity was similarly higher (0.023 ng/mL/mL/year vs. 0.012 ng/mL/mL/year, p = 0.005; Fig. 5). PSA-velocity, while higher in the csPCa group (1.4 ng/mL/year vs. 1.2 ng/mL/year), did not reach statistical significance (p=.4).

Table 1
Comparison of Clinical and Laboratory Variables Between csPCa and Non-csPCa Groups: Univariate and Multivariate Analysis.

Age (year)	**csPCa (n = 550)**	**Non csPCa (n = 624)**	**p-value (univariate analysis)**	**p-value (multi-variate analysis)**
	67.0 ± 7.8	**64.9 ± 6.9**	**p<.0001**	**p<.0001**
Active surveillance vs Screening *	67% [368/550]	59% [366/624]	p<.001	p<.0001
PI-RADS score **	Score 1–2: 84 Score 3: 87 Score 4: 250 Score 5: 129	Score 1–2: 274 Score 3: 144 Score 4: 161 Score 5: 5	p<.0001	p<.0001
PSA (ng/mL)	7.5 ± 5.5	6.6 ± 6.8	p<.001	p<.0001
PSA-velocity (ng/mL/year)	1.4 ± 2.8	1.2 ± 3.6	p=.4	NA
PSAD (ng/mL/mL)	0.16 ± 0.13	0.12 ± 0.09	p<.0001	p<.0001
PSAD-velocity (ng/mL/mL/year)	0.023 ± 0.07	0.012 ± 0.07	P=.005	p = 0.1

Data are mean +/- standard deviation. * Data are percentage [number of patients]. ** Data are number of patients. PI-RADS: Prostate imaging Reporting and Data System. PSA: Prostate Specific Antigen. PSAD: Prostate Specific Antigen Density.

Multivariate analysis:

Multivariate analysis included only the variables that were significant in univariate analysis. PI-RADS scores (p<.0001), age (p<.0001), undergoing an AS exam (p<.0001), PSA levels (p<.0001), and PSAD (p<.0001) remained significant predictors of csPCa (Table 1). PSAD-velocity was not a significant predictor in the multivariate model (p=.1).

Discussion

Our study showed that PSAD-velocity was associated with presence of csPCa on univariate analysis, but it was not an independent predictor of csPCa on multivariate analysis when accounting for factors such as age, PI-RADS scores and PSAD. To our knowledge, this is the first study to evaluate the role of PSAD-velocity in predicting the presence of csPCa.

The lack of significance of PSAD-velocity is likely due to confounding by stronger predictive factors. Since PSAD-velocity is derived from changes in PSAD over time, it is inherently correlated with PSA and PSAD, both of which are more robust predictors of csPCa. As these stronger variables capture most of the predictive information, PSAD-velocity contributes little additional value, resulting in its diminished significance in multivariate analysis.

Another consideration is that PSAD-velocity measurements may be less accurate than PSAD due to the phenomenon of error propagation. PSAD-velocity is calculated by dividing the difference between two PSAD values by the time interval between measurements. When deriving a value from two or more measurements, the resulting accuracy is generally lower than that of a single measurement because uncertainties from both measurements propagate into the derived value. Fluctuations in PSA levels can result from a range of biological and external factors, including prostatitis, recent sexual activity, cycling, and digital rectal examinations. Day-to-day variability in PSA has been reported to be as high as 34% [13]. In our study, prostate volume was assessed using either the DynaCAD segmentation software or the ellipsoid formula. The ellipsoid formula tends to overestimate prostate volume compared to automated segmentation methods [14]. A study showed that the difference between average of prostate volume measurement using the ellipsoid formula by multiple readers to the reference volume ranged from − 23 mL to + 6 mL [15]. While the volumes derived from automatic segmentation may have higher precision, manual adjustment of the boundary by readers is often necessary and this can introduce variability in the prostate volume measurements. Studies have shown that the Dice similarity coefficient for prostate gland segmentation is approximately 0.90 between the radiologists and a deep learning segmentation model, and approximately 0.92 between two radiologists [16–18]. This increased variability may weaken the predictive power of PSAD-velocity, further contributing to its lack of significance in multivariate analysis [10, 19, 20]. Potential variability in total prostate volume measurements among radiologists could not be assessed in this study.

In contrast to PSAD-velocity, PSAD was a statistically significant predictor of csPCa in both univariate and multivariate analysis in our study. Studies have shown that combining PSAD with the PI-RADS score on MRI can further improve diagnostic accuracy. Distler and colleagues found that PSAD combined with MRI improved the negative predictive value of PI-RADS scoring and can safely avoid about 20% of unnecessary biopsies [21]. Washino et al found that both the PI-RADS score and PSAD were independent predictors of csPca on multivariate analysis in their cohort [22]. This is consistent with our findings where both PI-RADS score and PSAD were associated with csPca on both univariate and multivariate analysis.

In our study, PSA-velocity did not reach statistical significance in predicting csPCa in univariate analysis, aligning with existing literature. Although initially proposed in 1994, the role of PSA-velocity in detecting csPCa remains controversial [10, 19]. In a large population-based cohort, Vickers and his colleagues found that PSAV does not add any additional value in evaluation of patients with an elevated PSA [23]. Instead, PSAV and PSA doubling time have been shown to be more useful in predicting prognosis and guiding treatment decisions following biochemical recurrence after prostatectomy [24]. Our study only

incorporated PSA values obtained at the time of MRI and thus was not designed as a comprehensive evaluation of PSAV's role in predicting csPCa.

A limitation of our study is that the assessment of PSA, and consequently PSA-velocity and PSAD-velocity, was based on time points only when the MR exams were performed. This restricts our ability to capture a more comprehensive trend in PSAD changes over time. Another limitation is the retrospective nature of study. Finally, there is a potential selection bias due to the single institutional study design, although spread across multiple sites in different states.

Conclusion

In conclusion, although higher PSAD-velocity was associated with the presence of csPCa in univariate analysis, it was not an independent predictor in multivariate analysis. PSAD-velocity does not offer added diagnostic information to the PSAD in predicting the presence of csPCa.

Declarations

Author Contribution

All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Y.H, A.K, H.N, H.T, J.L, A.F, A.K and N.T. The manuscript was prepared by S.N., A,K and N.T, and all authors read and approved the final manuscript.

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Figures

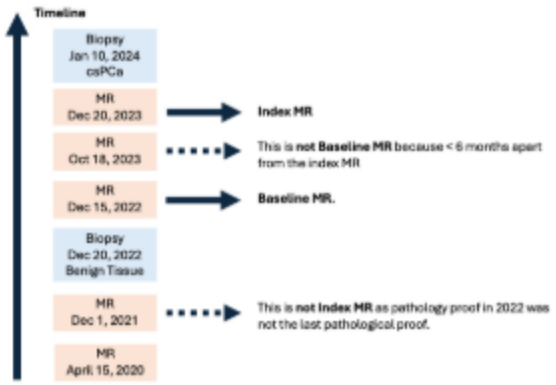


Figure 1

Diagram of MR selection. The last MR exam with pathological confirmation within 1 year after the MR was considered an index MR exam. The MRI immediately prior to the index MR exam but 0.3 to 2 years apart was considered a baseline MR exam.

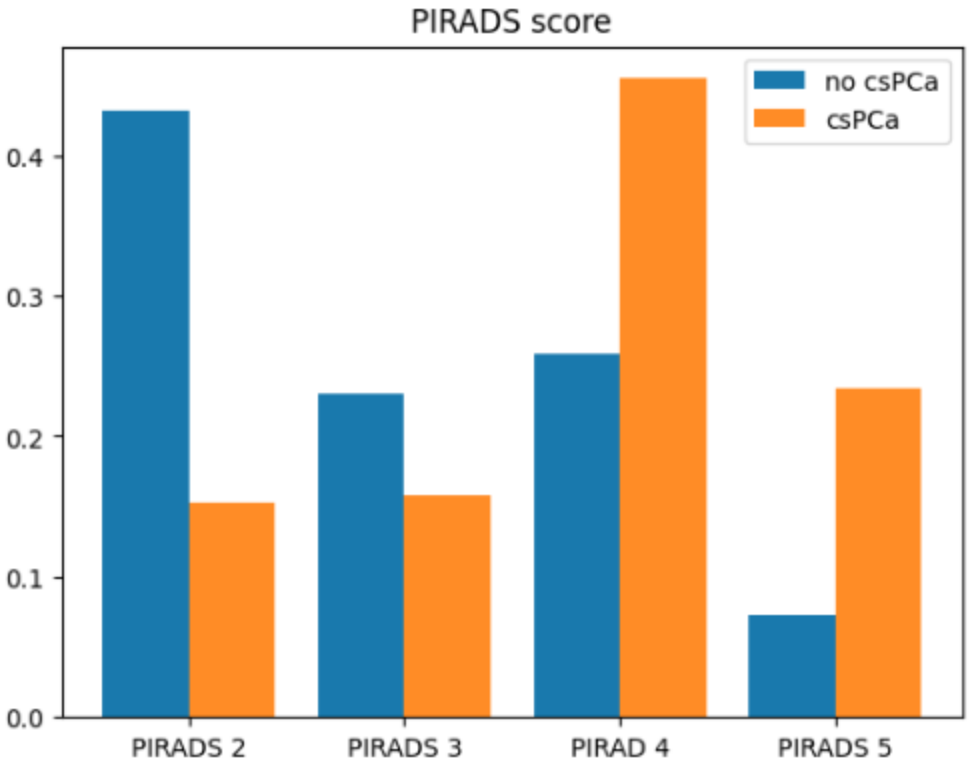


Figure 2

Histogram of PI-RADS scores in the csPCa (orange) and non-csPCa (blue) groups.

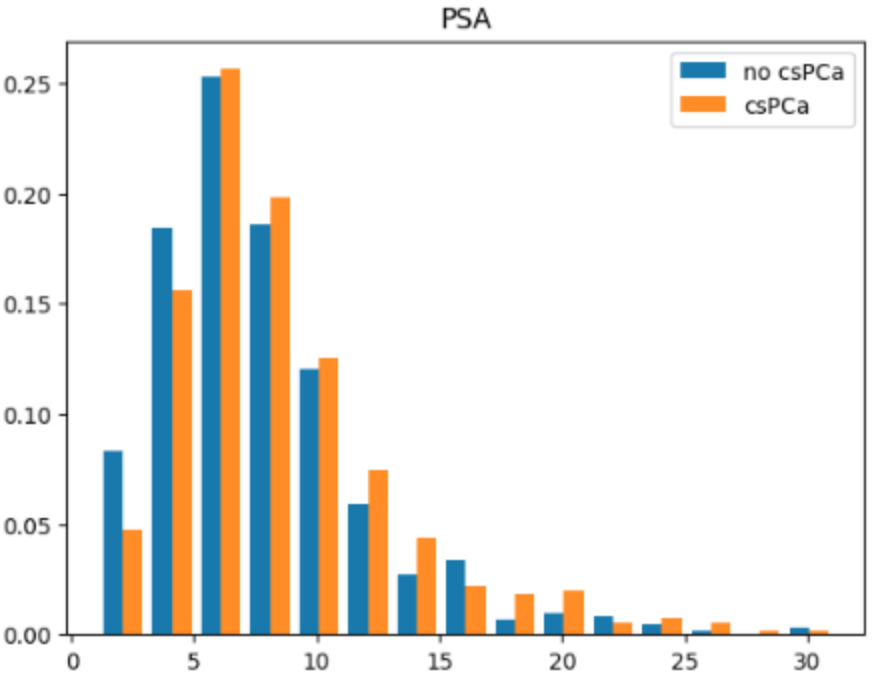


Figure 3

Histogram of PSA values (ng/mL) in the csPCa (orange) and non-csPCa (blue) groups.

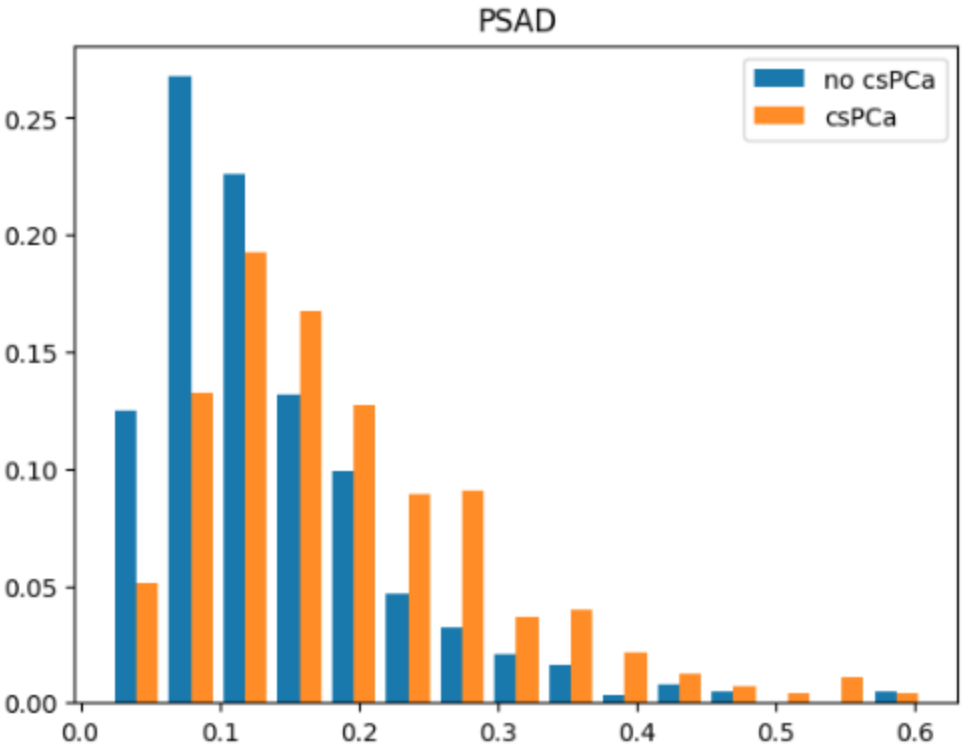


Figure 4

Histogram of PSAD (ng/mL/mL) values in the csPCa (orange) and non-csPCa (blue) groups.

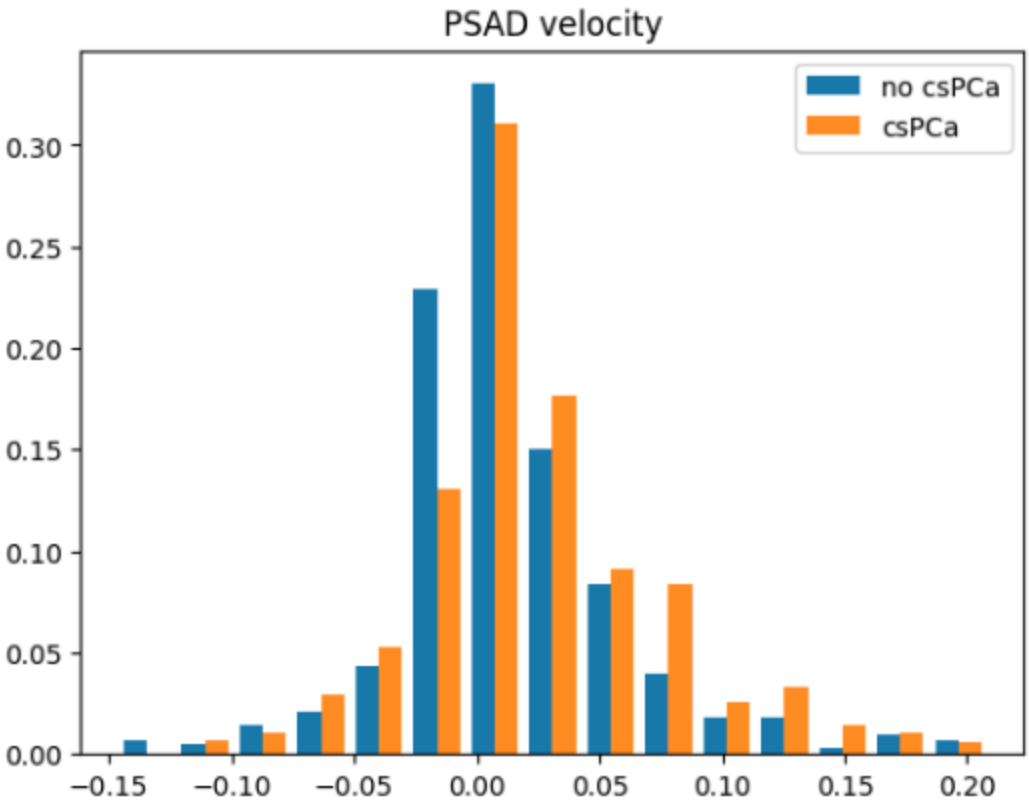


Figure 5

Histogram of PSAD-velocity (ng/mL/mL/year) in the csPCa (orange) and non-csPCa (blue) group.

Supplementary Files

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