Unlocking Precision Enhancing Prostate Cancer Detection and Reducing Unnecessary Biopsies with Combined Prostate-Specific Antigen Density and PI-RADS Score

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ABSTRACT

Objective: To determine clinically significant prostate cancer (csPCa) detection rate by combining the prostate-specific antigen density (PSAD) and prostate imaging-reporting and data system (PI-RADS) scores.

Study Design: Descriptive study.

Place and Duration of the Study: Department of Urology, University of Health Sciences, Ankara Oncology Training and Research Hospital, from January 2018 to April 2023.

Methodology: Patients who underwent prostate biopsies after multiparametric magnetic resonance imaging (mpMRI) were included in the study. PI-RADS 4 and 5 lesions were considered as MR positive. The cut-off values for PSAD were also determined to evaluate csPCa. csPCa detection rates were evaluated by grouping the patients based on the PSAD and mpMRI findings.

Results: PSAD cut-off value of 0.165 ng/mL/mL (sensitivity 80%, specificity 72%) was detected to predict csPCa (AUC = 0.81, 95% CI:0.756-0.866, p<0.001). csPCa detection rate was low (3%) in patients who have low PI-RADS scores (1-3) and a PSAD <0.165 ng/mL/mL. On the other hand, csPCa detection rate was high (50.5%) in patients who have a high PI-RADS score (4-5 lesions) and with a PSAD ≥0.165 ng/mL/mL.

Conclusion: csPCa detection rates are low in patients with PI-RADS 1-3 lesions and low PSAD values. Unnecessary biopsy may be avoided in these patients.

Key Words: *Gleason score, PI-RADS, Prostate cancer, Prostate-specific antigen, Prostate-specific antigen density.*

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INTRODUCTION

Prostate cancer (PCa) is the second most diagnosed cancer in men.[1] It is usually diagnosed by histopathological verification through prostate biopsy in suspected patients based on digital rectal examination (DRE) and / or high serum prostate-specific antigen (PSA) levels. The incidence of PCa has increased with the widespread usage of PSA. However, this increase is associated with diagnosing many insignificant or low-risk PCa which has a low risk of metastasis and disease-specific mortality. In these patients, the performing of prostate biopsy for diagnosis of PCa may increase the prevalence of probable cancer anxiety and life-threatening complications such as biopsy-related urosepsis.[1] Therefore, it is very important to reduce prostate biopsies in men who will not eventually be diagnosed with cancer or who will be diagnosed with low-risk PCa even if it is detected.

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Nowadays, the recommendation of guidelines is to reduce unnecessary biopsies and to determine clinically significant PCa (csPCa) patients.[1] To achieve this aim, the risk prediction models for the detection of csPCa have been defined.[1] Multi-parametric magnetic resonance imaging (mpMRI) plays an important role in these models. However, the PCa detection rates by mpMRI depend on some factors such as tumour volume and Gleason score.[2] Although the high negative predictive value of mpMRI for suspicion of csPCa, adding PSA density (PSAD) to mpMRI may improve the diagnostic accuracy when deciding whether to perform a biopsy or not.[3,4] There are limited studies on this topic. According to the outcomes of a current meta-analysis, the risk of having csPCa in biopsy-naive patients is higher in patients who have higher PSAD and higher prostate imaging-reporting and data system (PI-RADS) scores.[5] However, there is no consensus on an absolute cut-off value for PSAD.

This study aimed to find a cut-off value for PSAD to determine PCa and csPCa by examining the data of the hospital which is the unique oncology branch hospital of the country. It was also aimed to determine PCa and csPCa detection rates of the patient population by combining the PSAD cut-off values which the authors found with the PI-RADS score.

METHODOLOGY

This study was performed in accordance with the Declaration of Helsinki. Ethical Approval for this study was obtained from the Institutional Review Board (Approval No.: 2022-10/173).

The prostate biopsy registry was between January 2018 and April 2023 (n = 772) retrospectively. Patients who underwent cognitive guided and systematic prostate biopsies after mpMRI were included. Patients who had PCa and previous prostate biopsy history, who did not have mpMRI before biopsy and who had 5a-reductase inhibitor using history were excluded.

A power analysis was conducted using the G*Power (v3.1.9.6) software to determine the sample size. Comparing of proportions method (Z tests: Proportions: Inequality, two independent groups) was chosen. Finally, 455 patients were analysed (Figure 1).

Patients' ages, PSA value, prostate volume, PSAD, The International Society of Urological Pathology (ISUP) grades, PCa risk group (According to EAU Risk classifications), and PI-RADS (Prostate Imaging Reporting and Data System) scores were added to statistical analysis.

The prostate biopsies were taken under transrectal ultrasound (TRUS) guidance by using an 18-G needle. Twelve core systematic biopsies were performed on all patients. Two cognitive fusion-targeted biopsy cores were added for each lesion in patients who had suspicious lesions on mpMRI.

The mpMRI results were interpreted by abdominal radiologists with at least 5 years of experience in mpMRI. PI-RADS 4 and 5 lesions were considered as MR positive. Prostate volume (mL) was calculated by "0.52 x Length (cm) x Width (cm) x Height (cm)" formula according to mpMRI.

All histopathological outcomes of the prostate biopsy were evaluated. ISUP Grade ≥2 was defined as csPCa whereas ISUP Grade 1 was defined as clinically insignificant PCa.

PCa risk groups were determined according to pre-biopsy PSA value, ISUP score, and clinical stage.

Statistical analysis was conducted on the acquired data using IBM SPSS version 20 software (IBM Corporation, Armonk, NY, USA). The data suitable for normal distribution were checked with the One-Sample Kolmogorov–Smirnov test. The Chi-square test was employed to compare categorical variables. The student's t-test and Mann-Whitney U tests were used to compare independent groups of variables. Qualitative variables such as EAU risk groups, PI-RADS score, and ISUP grade were considered categorical variables. Continuous variables such as age, prostate volume, total PSA, and PSAD values were expressed as mean, median, standard deviation, and IQR. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off point for PSAD to predict PCa and csPCa. ROC curve was calculated with AUC estimates and 95% CI. For statistical significance, p-value of <0.05 was accepted.

RESULTS

The mean age of all patients was 64.3 ± 7.3 years. The median total PSA, prostate volume, and PSAD were 7.6 ng/mL, 57 Ml, and 0.13 ng/mL/mL, respectively. The median interval between mpMRI and prostate biopsy was 14 days (IQR: 3-36 days). According to biopsy results, PCa was detected in 167 (36.7%) patients. Eighty (47.9%) patients had csPCa (ISUP Grade ≥2). Based on EAU risk classification; 69 (41.3%), 42 (25.1%), and 56 (33.6%) patients had low, medium, and high-risk PCa, respectively. PI-RADS 4-5 lesions were detected in 230 (50.5%) patients. All values of the patients are given in Table I.

Patients were divided into two groups according to biopsy results. Group 1 consisted of the patients who had benign pathology whereas Group 2 consisted of the patients who had malign pathology. The age (66.7 *vs*. 62.9, p <0.001), total PSA (8.4 ng/mL *vs*. 7.02 ng/mL, p <0.001), PSAD (0.19 ng/mL/mL *vs.* 0.11 ng/mL/mL, p <0.001), and the rates of PI-RADS 4-5 lesion detection (71.8% *vs*. 38.2%, p <0.001) were statistically significantly higher in the Group 2. Prostate volume (65 mL *vs.* 45 mL, p <0.001) was statistically significantly higher in Group 1. All comparisons are given in Table I.

Patients who had malign pathology were divided into two subgroups based on ISUP grade as clinically insignificant (ISUP Grade 1) and csPCa (ISUP Grade ≥2). Of the 167 patients with malignant pathology, 87 had clinically insignificant PCa, while 80 had csPCa. Age (68.1 *vs*. 65.5, p = 0.02), total PSA (12.3 *vs.* 7.3, p <0.001), and PSAD (0.32 *vs.* 0.15, p <0.001) values were statistically significantly higher in csPCa patients. Prostate volumes in two groups were comparable (p = 0.21). The rates of PI-RADS 4-5 lesion detection were higher in csPCa patients (82.6% *vs.* 62.1%, p = 0.003). All comparisons of the subgroups are given in Table II.

The PSAD cut-off value of 0.141 ng/mL/mL (sensitivity 71%, specificity 70%) was detected to predict PCa (AUC = 0.74, 95% CI:0.691-0.786, p <0.001). On the other hand, the PSAD cut-off value of 0.165 ng/mL/mL (sensitivity 80%, specificity 72%) was detected to predict csPCa (AUC = 0.81, 95% CI:0.756-0.866, p <0.001). The ROC analyses are shown in Figure 2.

This study also involved assessing the PCa and csPCa detection rates using the mpMRI scores and PSAD cut-off levels we derived. PSAD cut-off values of 0.141 ng/mL/mL and 0.165 ng/mL/mL were used for detection PCa and csPCa, respectively. In patients who had low PI-RADS scores and with a <0.141 ng/mL/mL PSAD, PCa detection rate was low (12.8% for PI-RADS 1-3 lesions). In patients who had high PI-RADS score (PI-RADS 4-5 lesions) and with a ≥0.141 ng/mL/mL PSAD, PCa detection rate was high (71.4%).

On the other hand, in patients who had low PI-RADS (PI-RADS 1-3 lesions) score and with a <0.165 ng/mL/mL PSAD, csPCa detection rate was low (3%). In patients who had high PI-RADS score (PI-RADS 4-5 lesions) and with a ≥0.165 ng/mL/mL PSAD, csPCa detection rate was high (50.5%).

Table I: Data of all patients and comparison of the groups based on pathological results.

	All Patients (n = 455)	Group 1 (n = 288)	Group 2 (n = 167)	p-value
Age (years), mean ± SD	64.3 ± 7.3	62.9 ± 6.9	66.7 ± 7.3	*<0.001[a]
Total PSA (mg/mL), Median (IQR)	7.6 (5)	7.02 (4)	8.4 (9)	*<0.001[b]
Prostate volume (mL), Median (IQR)	57 (34)	65 (33)	45 (25)	*<0.001[b]
PSAD (ng/mL/mL), Median (IQR)	0.13 (0.12)	0.11 (0.07)	0.19 (0.21)	*<0.001[b]
ISUP Grade, n (%)				-
1			87 (52.1)	
2			31 (18.6)	
3			6 (3.6)	
4			16 (9.6)	
5			27 (16.2)	
EAU risk classification, n (%)				-
Low			69 (41.3)	
Intermediate			42 (25.2)	
High			56 (33.5)	
PI-RADS, n (%)				*<0.001[c]
1	1 (0.2)	1 (0.3)	0 0)	
2	52 (11.4)	42 (14.6)	10 (6.0)	
3	172 (37.8)	135 (46.9)	37 (22.2)	
4	177 (38.9)	98 (34.0)	79 (47.3)	
5	53 (11.6)	12 (4.2)	41 (24.5)	

*EAU, European Association of Urology; ISUP, The International Society of Urological Pathology; PI-RADS, Prostate imaging reporting and data system; PSA, Prostate specific-antigen; PSAD, Prostate specific-antigen density. *Statistically significant, [a]Student's t-test, [b]Mann-Whitney U test, [c]Chi-square test.*

Table II: Comparison of the subgroups based on clinical significance.

	Malign patients (n = 167)	ISUP Grade 1 (n = 87)	ISUP Grade ≥2 (n = 80)	p-value
Age (years), mean ± SD	66.7 ± 7.3	65.5 ± 6.7	68.1 ± 7.6	*0.02[a]
Total PSA (ng/mL), Median (IQR)	8.4 (9)	7.3 (3)	12.3 (24)	*<0.001[b]
Prostate volume (mL), Median (IQR)	45 (25)	46 (27)	45 (22)	0.21[b]
PSAD (ng/mL/mL), Median (IQR)	0.19 (0.2)	0.15 (0.1)	0.32 (0.6)	*<0.001[b]
EAU risk classification, n (%)				*<0.001[c]
Low				
Intermediate	69 (41.3)	69 (79.3)	-	
High	42 (25.2)	15 (17.2)	27 (33.8)	
	56 (33.5)	3 (3.5)	53 (66.2)	
PI-RADS, n (%)				*0.003[c]
1-2	10 (6.0)	5 (5.7)	5 (6.2)	
3	37 (22.2)	28 (32.2)	9 (11.2)	
4-5	120 (71.8)	54 (62.1)	66 (82.6)	

*EAU, European Association of Urology; ISUP, The International Society of Urological Pathology; PI-RADS, Prostate Imaging reporting and data system; PSA, Prostate specific-antigen; PSAD, Prostate specific-antigen density, *Statistically significant, [a]Student's t-test, [b]Mann-Whitney U test, [c]Chi-Square Test.*

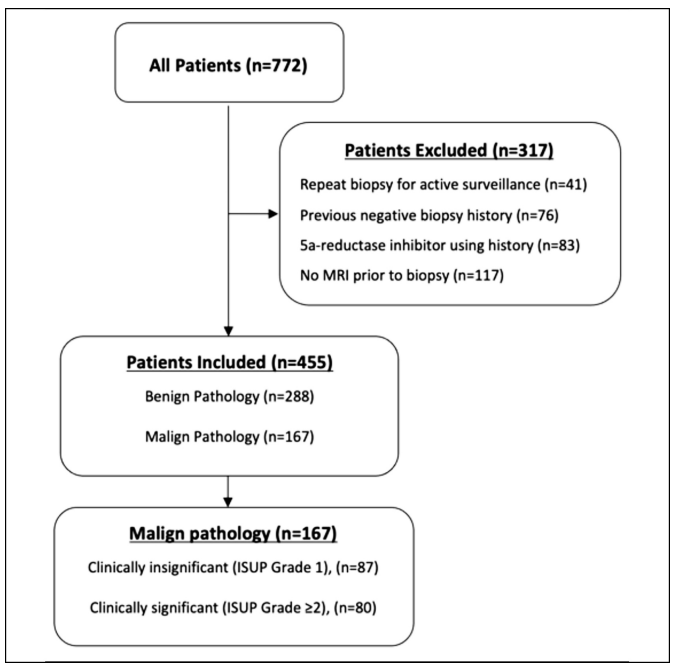

Figure 1: Flowchart of the study.

DISCUSSION

Since the PSA era, the use of certain biomarkers and risk calculators has increased for detecting PCa in the daily practice. Nowadays, biomarkers or biomarker-based calculation tools such as 4kScore, Prostate Health Index, Stockholm3, and urinary PCA3 can be used in patients with suspected prostate cancer.[6] The 4kScore and PHI have been more successful in preventing unnecessary biopsies while increasing the PCa detection rate compared to models that included PSA and age.[6] When combined with mpMRI, Stockholm3 reduced the need for biopsies and the detection of ISUP Grade 1 tumours.[7] The PCA3 has been shown to be superior to PSA in terms of specificity and predictive ability.[8] However, these biomarkers are not widely used today, especially in developing countries due to their high cost and practical difficulties.

Since PSAD was defined by Benson *et al.* in 1992, the authors believe it had not a sufficient place in routine practice, despite its role in detecting csPCa.[9] PSAD is the

significant independent predictor of csPCa in biopsy-naive patients and a significant prognostic marker for survival in PCa patients, even in advanced stages.[10,11] Moreover, PSAD can be calculated by dividing the PSA value by the prostate volume, which is easily obtained. The appealing aspects of PSAD are that it can be easily calculated with routine examinations and is cost-effective. However, differences in prostate volume measurements between imaging methods (such as ultrasound, computed tomography, and MRI) may affect the results, which could be a drawback of PSAD. It has been shown that the highest correlation between prostate weight measured by radiological imaging methods and prostate weight in the surgical specimen is determined by MRI.[12] Therefore, the authors used MRI outcomes while measuring PSAD in the study.

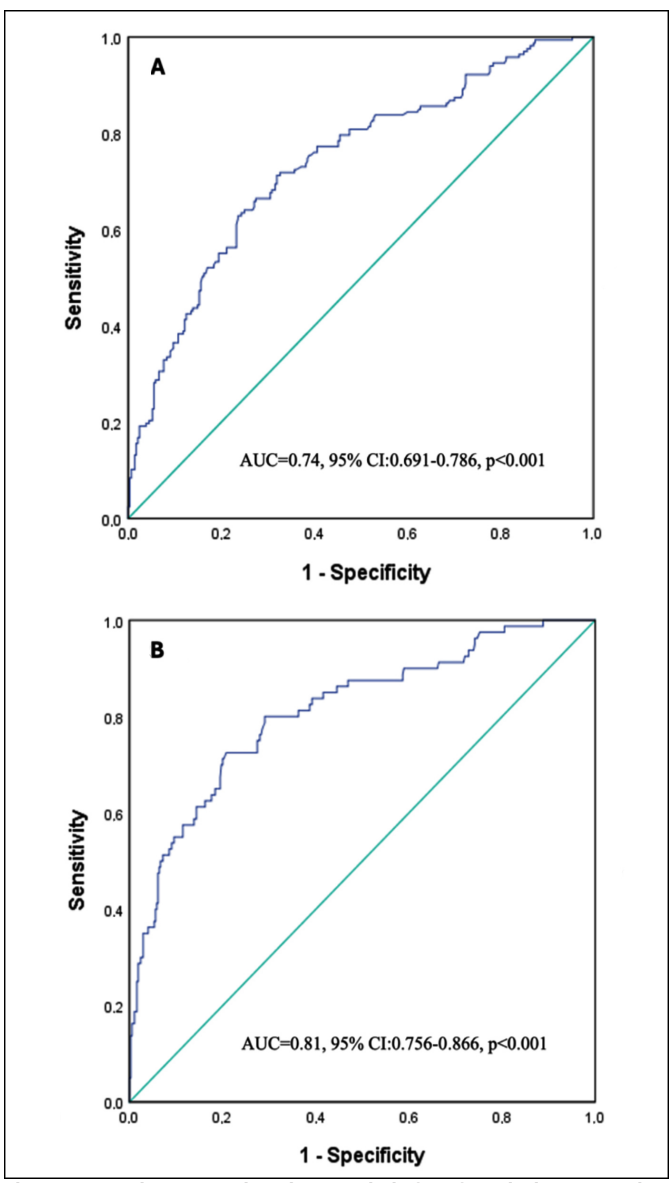

Figure 2: Receiver operating characteristic (ROC) analysis was used to find the cut-off value for PSAD to differentiate malign lesions from benign lesions (A) and clinically significant cancers from insignificant cancers (B).

In the previous studies, the values of 0.1 and 0.15 ng/mL/mL were generally accepted as cut-off values for PSAD.[13-15] Tarcan *et al.* reported that 25% of patients would miss the PSAD cut-off at 0.15 ng/mL/mL, but it would prevent 61% of unnecessary biopsies.[13] However, diagnostic improvement evaluations were not significant for 0.15 ng/mL/mL value. Similarly, in this study, when the PSAD cut-off value was taken as 0.14 ng/mL/mL, 32% of PCa patients were missed, but 63% of unnecessary biopsies were prevented. Nordstrom *et al.* evaluated the optimal PSAD cut-off value for csPCa detection in their study.[14] csPCa (ISUP Grade ≥2) detection rates were 77% and 49%, when they took PSAD cut-off value as 0.10 ng/mL/mL and 0.15 ng/mL/mL, respectively. In this study, the detection rate of ISUP Grade ≥2 PCa was found as 77.5% when cut-off value of 0.16 ng/mL/mL was used.

Catalona *et al*., in the first study to challenge the commonly accepted PSAD values of 0.1 - 0.15 ng/mL/mL, reported a PCa detection rate of 59% when using a PSAD value of 0.15 ng/mL/mL.[15] However, they highlighted that 95% of PCa patients would be detected when PSAD cut-off value was accepted as 0.078 ng/mL/mL.[15] Therefore, they recommended that the cut-off value should be 0.078 ng/mL/mL for detecting PCa. Upon deeper evaluation, they found that 84% of diagnosed PCa patients had a Gleason score below 7 (ISUP Grade 1 in the new classification).[15] In this study, only 13 (17.8%) of 73 patients with a PSAD value below 0.078 ng/mL/mL had PCa. Additionally, one of these patients had high-risk (ISUP Grade 4) PCa despite having a PSAD value of 0.05 ng/mL/mL. Based on the present findings, the authors concluded that lowering the PSAD cut-off values (<0.1 - 0.15 ng/mL/mL) might not enhance the detection rate of PCa but could also diminish the detection rate of csPCa.

Risk-adapted approaches to avoid unnecessary biopsy procedures have gained popularity in recent years. Schoots and Padhani, based on a meta-analysis of 3006 biopsy-naive patients, defined a risk-adapted table using a combination of PI-RADS scores (1-2, 3, and 4-5) and PSAD values (<0.1, 0.1 - 0.15, 0.15 - 0.2, and >0.2 ng/mL/mL).[5] They found the likelihood of detecting ISUP Grade ≥2 PCa in patients with PI-RADS 4-5 score and with a PSAD >0.2 ng/mL/mL is 77 %.[5] Conversely, this probability is much lower in patients (3%) with PI-RADS 1-2 and PSAD <0.1 ng/mL/mL. Despite the promising nature of this risk-based classification, several issues remain contentious. Firstly, the prevalence of ISUP Grade ≥2 PCa in the study population was reported as 35%, which the authors consider to be high and possibly requiring adjustment for different population prevalence. Therefore, further studies involving larger sample sizes and different ethnic populations are warranted.

The prevalence of csPCa (ISUP Grade ≥2) of this study's population is 17.5% (80 out of 455) which the authors believe more accurately reflects rates in the general population. In the present study, the rate of csPCa (ISUP

Grade ≥2) was found as 3% in biopsy-naive men with PI-RADS 1-3 and PSAD <0.165 ng/mL/mL. The authors observed that the rate of csPCa (ISUP Grade ≥2) was 14.7% in biopsy-naive men with PI-RADS 1-3 and PSAD ≥0.165 ng/mL/mL. The data of this study suggested that PI-RADS 1-3 lesions with low PSAD levels may not require biopsies due to low csPCa detection rates. The rate of csPCa (ISUP Grade ≥2) was 50.5% in biopsy-naive men with PI-RADS 4-5 and PSAD ≥0.165 ng/mL/mL. According to these findings, the authors' recommendation for these patients is to undergo biopsy.

The second contentious issue in Schoots and Padhani's meta-analysis[5] is that they divided the patients into 4 groups according to the PSAD value. The authors believe this approach could pose practical challenges. Moreover, categorising patients into multiple groups may reduce the statistical power of the analysis. Therefore, in this study, the authors opted to categorise the population into two groups using identified PSAD cut-off values.

Another question concerns the choice of radiological method used to measure actual prostate size when calculating PSAD. The lack of standardisation in prostate volume measurement across various radiological imaging modalities is seen as a limiting factor for PSAD's widespread use. Previous studies predominantly measured prostate volume using TRUS.[13-16] As highlighted by Gok *et al.* in their study, the authors also advocate that MRI results offer more accurate measurements of actual prostate size.[12] One distinguishing feature of this study from previous research is the calculation of prostate volume based on MRI results rather than TRUS.

The study has several limitations, including its retrospective and single-centred nature. Due to the absence of an mpMRI fusion biopsy device, the authors conducted cognitive-guided and systematic prostate biopsies. This limitation may have impacted the study's prostate cancer detection rates. However, the debate over whether fusion biopsy is superior to cognitive biopsy in detecting prostate cancer in biopsy-naive men remains contentious.[1]

CONCLUSION

The present study demonstrates low detection rates of csPCa in patients with PI-RADS 1-3 lesions and low PSAD (<0.165 ng/mL/mL). Consequently, unnecessary biopsies could potentially be avoided in patients with PI-RADS 1-3 and low PSAD (<0.165 ng/mL/mL) values. Nevertheless, more optimised PSAD cut-off values or biopsy decision models should be developed based on multicentric and prospective studies.

ETHICAL APPROVAL:
This study was approved by the Ethics Committee of University of Health Sciences, Ankara Oncology Training and Research Hospital (Decision Date: 06.10.2022, Decision Approval No: 2022-10/173).

PATIENTS' CONSENT:
Written informed consent was taken from all patients.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
NH: Conception and design of the study, data interpretation and manuscript writing.
TU: Data collection, data analysis, and data interpretation.
AD: Statistical analysis, data collection, data analysis, and data interpretation.
HB: Critical revision of the manuscript and supervision.
All authors approved the final version of the manuscript to be published.

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