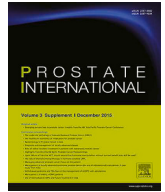




Contents lists available at ScienceDirect

Prostate International

journal homepage: <https://www.journals.elsevier.com/prostate-international>

Research Article

Predictors of false-positive results in men with Prostate Imaging–Reporting and Data System 4 lesions

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ARTICLE INFO

Article history:

Received 25 February 2026

Received in revised form

5 March 2026

Accepted 10 March 2026

Available online xxx

Keywords:

Biopsy

Magnetic resonance imaging

Prostate cancer

ABSTRACT

Background: To identify predictive factors of false-positive results in men with Prostate Imaging–Reporting and Data System (PI-RADS) 4 lesions on multiparametric MRI and to evaluate potential factors for improving risk stratification in this high-risk category.

Methods: We retrospectively analyzed 811 men with PI-RADS 4 lesions who underwent prostate biopsy (November 2020–February 2025). Clinical data [age, PSA, PSA density (PSAD), prostate volume] and radiographic features [anatomical location [peripheral zone (PZ) vs. transitional zone (TZ)], multiplicity] were assessed. Multivariate logistic regression analysis identified independent predictors of false-positive results. Interaction between location and multiplicity was evaluated for zone-specific risk profiles.

Results: Of the 811 patients, 523 (64.5%) had benign pathology (false-positive). Independent predictors of false-positive results included younger age, lower PSAD, prior negative biopsy, and TZ location. TZ lesions had significantly higher odds of a false-positive result compared to PZ lesions (OR: 6.919, 95% CI: 4.440–10.781, $P < 0.001$). A divergent pattern was observed between location and multiplicity: in the PZ, multiplicity did not affect cancer risk, whereas in the TZ, multiple lesions showed a trend toward benign pathology ($P = 0.087$), with the lowest predicted cancer probability (10.0%) in patients with multiple TZ lesions.

Conclusion: False-positive PI-RADS 4 assessments were associated with features characteristic of BPH, particularly TZ localization and lower PSAD. Current biopsy recommendations may be suboptimal for patients with these benign-favoring features. Incorporating lesion localization and volume-adjusted metrics into risk stratification could potentially reduce unnecessary biopsies.

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1. Introduction

Prostate cancer remains one of the most frequently diagnosed malignancies and is a leading cause of cancer-related death in men worldwide.^{1–3} The diagnostic pathway for prostate cancer has evolved significantly in recent years, shifting from a reliance on systematic biopsy to a more risk-stratified approach utilizing advanced imaging. Multiparametric magnetic resonance imaging (mpMRI) has become a cornerstone in the early detection and localization of prostate cancer. Its ability to identify suspicious lesions has proven invaluable for detecting clinically significant prostate cancer (csPCa) while simultaneously reducing the

number of unnecessary biopsies and the overdiagnosis of an indolent disease.^{4–6} Reflecting this utility, major clinical guidelines, including those from the European Association of Urology (EAU) and the National Comprehensive Cancer Network (NCCN), now recommend pre-biopsy MRI for men with clinical suspicion of prostate cancer.^{7,8}

Central to the interpretation of mpMRI is the Prostate Imaging–Reporting and Data System (PI-RADS).⁹ Biopsy indications have evolved over the years with the widespread adoption of this system. Generally, for lesions with a PI-RADS score of ≤ 2 , immediate biopsy is not primarily recommended. For PI-RADS 3 lesions, guidelines recommend a decision based on secondary clinical variables such as family history, PSA density (PSAD), and digital rectal examination (DRE). In contrast, a PI-RADS score of ≥ 4 is in itself considered a strong indication for biopsy. Consequently, prostate biopsies are routinely performed in patients with PI-RADS scores of ≥ 4 , typically without considering other clinical variables.

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<https://doi.org/10.1016/j.pnrl.2026.03.002>

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However, the diagnostic outcomes for PI-RADS 4 lesions differ markedly from those of PI-RADS 5.¹⁰ While PI-RADS 5 lesions demonstrate a consistently high positive predictive value for malignancy, the cancer detection rate for PI-RADS 4 lesions is comparatively suboptimal and is associated with a high false-positive rate. This discrepancy implies that, unlike PI-RADS 5 where biopsy is almost always justified, there is significant room within the PI-RADS 4 category to refine selection criteria and reduce unnecessary procedures.

In this study, we investigated predictive factors for false-positive results in patients with PI-RADS 4 lesions who underwent prostate biopsy. By analyzing these predictors, we aimed to identify factors to improve the diagnostic performance and risk stratification for men presenting with PI-RADS 4 lesions.

2. Methods

2.1. Study population and design

This retrospective study was approved by the institutional review board of our institution. We queried our prospectively maintained prostate biopsy database to identify patients who underwent prostate biopsy at our institution between November 2020 and February 2025. The inclusion criteria were men with a pre-biopsy mpMRI demonstrating at least one lesion with a PI-RADS score of 4 as the highest-scoring lesion. Patients presenting with any PI-RADS 5 lesions were strictly excluded from the study. For each patient, the following clinical and demographic data were extracted: age, serum prostate-specific antigen (PSA, ng/mL) level, PSA density (PSAD, ng/mL²), prostate volume (mL), specific anatomical location of the lesion [peripheral zone (PZ), transitional zone (TZ), and both], lesion multiplicity (single vs. multiple), and histopathologic findings (ISUP grade group in case of malignancy). For the purposes of this analysis, lesion multiplicity was defined as the presence of two or more PI-RADS 4 lesions; patients with a single PI-RADS 4 index lesion and secondary lesions scored as PI-RADS 3 or lower were classified as having a single lesion. Prostate volume was calculated from mpMRI.¹¹ PSAD was calculated as PSA (ng/mL) divided by prostate volume (mL). csPCa was defined as ISUG Gleason grade group³ 2. All patients underwent transperineal prostate biopsy via either MRI-ultrasound fusion (BioJet; MTT GmbH; Germany) or cognitive targeting. Our detailed biopsy protocol has been described previously.¹² Briefly, procedures were predominantly performed under general anesthesia, with local anesthesia utilized in a minority of cases based on physician discretion. The standard procedure involved a grid-based approach using a brachytherapy template (Template Grid 18G; MTT GmbH) attached to a transrectal ultrasound (bkSpecto1300; GE Healthcare; USA) to perform a 20-core systematic biopsy combined with targeted sampling. While the standard procedure involved combined targeted and systematic biopsy, systematic sampling was omitted in select cases based on clinical judgment.

2.2. Statistical analysis

All statistical analyses were performed using SPSS version 30 (IBM Corp., Armonk, NY). A two-sided $P < 0.05$ was considered statistically significant. Baseline patient and lesion characteristics were compared between patients with and without csPCa. The Mann–Whitney U test was used for continuous variables, which are presented as median (interquartile range), while the Chi-square test was used for categorical variables, presented as count (%).

To identify independent predictors of false-positive mpMRI findings, both univariate and multivariate binary logistic

regression analyses were performed. For ease of interpretation of the odds ratios, age and PSAD were scaled and entered into the model as per 10 years and per 0.1 ng/mL², respectively. To prevent multicollinearity, serum PSA was excluded from the multivariable model in favor of PSAD as the latter adjusts for prostate volume. Variables included in the final multivariable model were age, PSAD, biopsy-naïve status, lesion multiplicity, and location. Results from the regression analyses are presented as odds ratios (ORs) with 95% confidence intervals (CIs). To specifically investigate the combined effect of lesion multiplicity and location, the interaction between these two variables was formally tested. Estimated marginal means were calculated from the multivariable model to determine the adjusted predicted probability of csPCa for each subgroup and these results were visualized using a bar chart. Pairwise comparisons were conducted to assess for significant differences between subgroups.

3. Results

A total of 811 men with PI-RADS 4 lesions on pre-biopsy mpMRI were included in the study. Of these, 523 men (64.5%) were diagnosed with benign pathology, representing false-positive mpMRI findings, while 288 (35.5%) were diagnosed with csPCa. A comparison of baseline characteristics is presented in Table 1. Patients with false-positive results differed significantly from those with csPCa; they were younger (median 66 vs. 70 years), had a lower median PSA (6.4 vs. 7.2 ng/mL), and significantly larger prostate volume (45.3 vs. 35.0 mL; $P < 0.001$). Consequently, the PSAD was significantly lower in the false-positive group (0.15 vs. 0.21 ng/mL², $P < 0.001$). Notably, the false-positive group was characterized by a higher prevalence of multiple lesions (76.7% vs. 61.8%) and lesions located in the TZ (52.0% vs. 18.8%) compared to the csPCa group ($P < 0.001$).

The results of the logistic regression analysis are presented in Table 2. We identified several independent predictors associated with false-positive results. In the univariate analysis, the presence of multiple lesions appeared to be a significant indicator of a false-positive result (OR: 2.031, 95% CI: 1.486–2.776, $P < 0.001$). However, in the multivariate model, this association lost statistical significance ($P = 0.201$). After adjusting for covariates, lesion location emerged as a powerful independent predictor of false-positive findings; lesions in the TZ had nearly seven times odds

Table 1

Baseline characteristics of PI-RADS 4 patients, stratified by clinically significant prostate cancer (csPCa) status

	All	Non-csPCa	csPCa	P
N	811	523	288	
Age (years)	68 (11)	66 (10)	70 (10)	<0.001 ^a
PSA (ng/mL)	6.7 (4.6)	6.4 (4.3)	7.2 (5.2)	<0.001 ^a
Prostate size (mL)	41.0 (22.7)	45.3 (23.9)	35.0 (17.7)	<0.001 ^a
PSA density (ng/mL ²)	0.17 (0.13)	0.15 (0.10)	0.21 (0.16)	<0.001 ^a
Biopsy-naïve	691 (85.2%)	422 (80.7%)	269 (93.4%)	<0.001 ^b
Multiplicity				<0.001 ^b
Single	232 (28.6%)	122 (23.3%)	110 (38.2%)	
Multiple	579 (71.4%)	401 (76.7%)	178 (61.8%)	
Location				<0.001 ^b
PZ	238 (29.3%)	88 (16.8%)	150 (52.1%)	
TZ	326 (40.2%)	272 (52.0%)	54 (18.8%)	
Both	247 (30.5%)	163 (31.2%)	84 (29.2%)	

csPCa, clinically significant prostate cancer; PI-RADS, Prostate Imaging Reporting & Data System; PSA, prostate specific antigen; PZ, peripheral zone; TZ, transitional zone.

^aContinuous variables: median (interquartile range); categorical variables: n (%).

^a Mann–Whitney U test.

^b Chi-square test.

Table 2

Univariate and multivariate regression analysis on predictors of false-positive results in patients with PI-RADS 4 lesions

	Univariate		Multivariate	
	OR (95% CI)	P value	OR (95% CI)	P value
Age (per 10 years)	0.519 (0.422-0.639)	<0.001	0.504 (0.397-0.639)	<0.001
PSAD (per 0.1 ng/mL ²)	0.576 (0.502-0.661)	<0.001	0.616 (0.533-0.711)	<0.001
Biopsy-naïve	0.295 (0.177-0.493)	<0.001	0.396 (0.222-0.707)	0.002
Multiplicity				
Single	Reference		Reference	
Multiple	2.031 (1.486-2.776)	<0.001	1.330 (0.859-2.058)	0.201
Location				
PZ	Reference		Reference	
TZ	8.586 (5.795-12.720)	<0.001	6.919 (4.440-10.781)	<0.001
Both	3.308 (2.280-4.799)	<0.001	2.758 (1.701-4.470)	<0.001

CI, confidence interval; OR, odds ratio; PI-RADS, Prostate Imaging Reporting & Data System; PSAD, prostate specific antigen density; PZ, peripheral zone; TZ, transitional zone.

of yielding false-positive results compared to the PZ (OR: 6.919, 95% CI: 4.440-10.781, $P < 0.001$). Additionally, younger age, lower PSAD, and a history of prior negative biopsy were identified as significant independent predictors of false-positive results.

The interaction between lesion location and multiplicity on the predicted probability of csPCa is illustrated in Fig. 1, with the exact model-adjusted probabilities provided in Supplementary Table 1. Adjusted for age, PSAD, and biopsy-naïve status, the anatomical location emerged as the dominant differentiator of diagnostic performance. Lesions in the PZ carried a substantial risk of malignancy (48.1% for single, 50.0% for multiple). In contrast, lesions in the TZ were associated with high false-positive rate, with predicted cancer probabilities dropping to 18.0% for single lesions and

only 10.0% for multiple lesions. Within the PZ, lesion multiplicity did not significantly alter the probability of csPCa ($P = 0.762$). However, within the TZ, the presence of multiple lesions showed a trend toward a lower probability of malignancy compared to single lesions ($P = 0.087$). Full results of all pairwise comparisons are detailed in Supplementary Table 2.

4. Discussion

A PI-RADS score of 4 and 5 is currently recognized as a substantial risk factor in itself, routinely serving as a direct indication for prostate biopsy under major clinical guidelines. However, in contrast to the robust predictive value of PI-RADS 5, PI-RADS 4

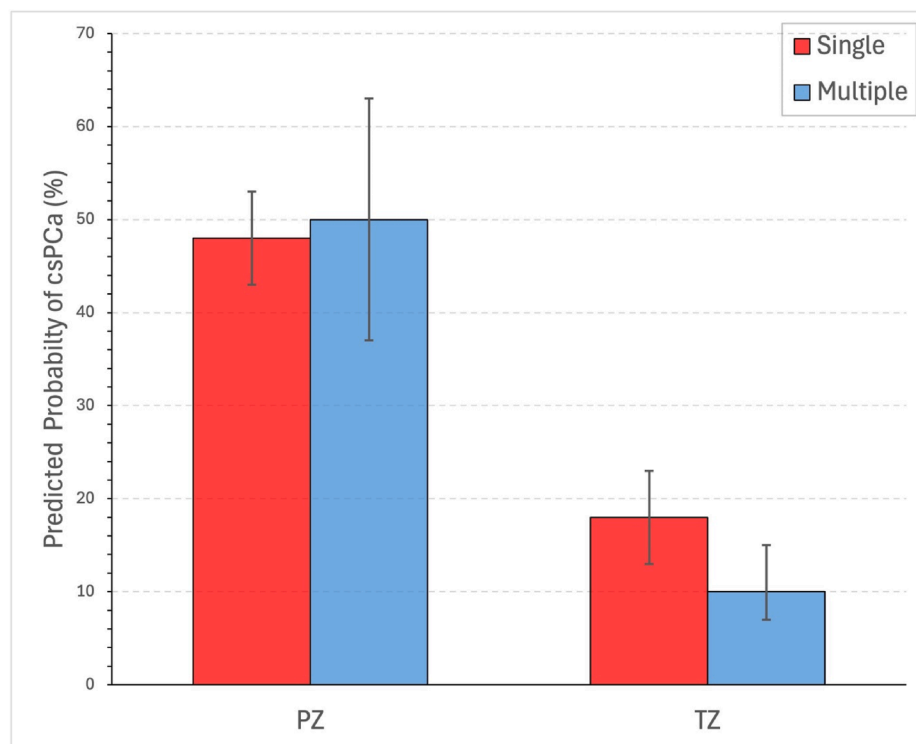


Figure 1. Predicted probability of clinically significant prostate cancer (csPCa) in PI-RADS 4 lesions according to anatomic location and multiplicity. The bar chart displays the estimated marginal means for the probability of csPCa, derived from the multivariable logistic regression model and adjusted for patient age, PSA density, and biopsy-naïve status. Error bars represent 95% confidence intervals. The analysis highlights a distinct disparity in diagnostic performance: lesions located in the transition zone (TZ) showed a significantly lower probability of csPCa compared to the peripheral zone (PZ; $P < 0.001$), reflecting a substantially higher false-positive rate in the TZ. While lesion multiplicity did not affect the probability of malignancy within the PZ ($P = 0.762$), multiple lesions in the TZ demonstrated a trend toward the lowest predicted probability of malignancy (10.0%) compared to single lesions (18.0%; $P = 0.087$). This suggests that the combination of TZ location and multiplicity identifies a subgroup where PI-RADS 4 assessment is most prone to overestimating cancer risk.

lesions are associated with a significantly higher false-positive rate. A recent diagnostic performance benchmark study for PI-RADS v2.1 reported a cancer detection rate (CDR) of 54% for PI-RADS 4 lesions, contrasting with the 84% CDR observed in PI-RADS 5 lesions—a significant gap of 30 percentage points.¹⁰ This performance gap is even more pronounced in the current cohort of real-world data, where the CDR of PI-RADS 4 lesions was lower at 35.5%. This discrepancy is largely due to the retrospective nature of the study (lacking rigid enrollment criteria, with biopsy decisions subject to clinician discretion) and the inclusion of men with a prior history of negative biopsies, which inherently lowers the overall CDR. Ultimately, both the established benchmarks and our real-world findings highlight the PI-RADS 4 category as a critical area for improvement in diagnostic precision.

In the present analysis of men with PI-RADS 4 lesions, we identified distinct independent predictors associated with false-positive results, including localization to the TZ, lower PSAD, younger age, and a history of prior negative biopsy. When interpreting the dominant influence of TZ location alongside the observed patterns in PSAD and lesion multiplicity, it is reasonable to infer that benign prostatic hyperplasia (BPH) may act as one of the primary drivers of these false-positive assessments.

Our rationale for including lesion location and multiplicity in this study stems directly from this inference. Our analysis proceeds from the premise that current multiparametric MRI technology and interpretation criteria cannot yet perfectly differentiate between malignant tumors and atypical BPH nodules classified as PI-RADS 4 in the TZ. Given that BPH predominantly originates in the TZ and characteristically presents as multifocal nodular hyperplasia, we hypothesized that these two radiographic features - anatomical location and lesion multiplicity - could act as one of the key indicators of benign pathology. To the best of our knowledge, this is the first study to specifically evaluate the interaction of these factors as a strategy to identify false-positive findings within the PI-RADS 4 population.

Our results regarding the interaction between lesion location and multiplicity further corroborate this hypothesis. It is important to note that while lesion multiplicity was not an independent predictor of false-positive results across the entire cohort, its diagnostic value is highly contextual. We observed a zone-dependent divergence in risk profiles. In the peripheral zone, lesion multiplicity had no impact on the probability of malignancy; the risk remained substantial (~50%) regardless of whether lesions were solitary or multiple. This finding aligns with the known multifocal nature of prostate cancer, where the presence of satellite tumors is common and does not diminish the likelihood of significant disease. Conversely, in the transition zone, multiplicity emerged as a potential indicator of benignity. The subset of patients with multiple TZ lesions exhibited the lowest predicted probability of malignancy (10.0%), showing a trend toward a lower risk compared to those with solitary TZ lesions ($P = 0.087$). This pattern likely reflects the typical architecture of BPH, which often manifests as multinodular hyperplasia, distinguishing it from the more discrete, focal appearance often associated with true TZ tumors.

The diagnostic difficulty of PI-RADS 4 lesions in the TZ highlighted by our results underscores a fundamental limitation of the current PI-RADS system: it does not account for prostate volume and the background prevalence of BPH. The clinical population undergoing MRI for elevated PSA predominantly consists of older men, a demographic in which variable degrees of BPH are ubiquitous.¹³ In these patients, BPH frequently manifests as multiple atypical nodules within the TZ. Such hyperplastic changes are widely recognized to drive serum PSA elevation but also present confounding morphological features on MRI that may be

misinterpreted as malignancy, potentially leading to a high rate of unnecessary biopsies. Although the 2019 revision to PI-RADS v2.1 introduced modifications to improve the characterization of TZ nodules, it remains silent on the integration of prostate volume or the extent of background hyperplasia into the risk stratification process.

Various attempts have been made to overcome the limitations of the PI-RADS system and optimize risk assessment for csPCa. One of the methods is to use risk calculators, which includes clinical data such as age, DRE, PSA, prostate volume to integrate with PI-RADS.^{14–16} However, the broad application of such risk calculators is frequently hindered by issues of miscalibration due to prevalence dependency. Another commonly studied parameter to integrate with PI-RADS is PSAD. Numerous studies have demonstrated that combining PSAD with MRI findings significantly enhances diagnostic performance by accounting for prostate volume, effectively adjusting for the confounding influence of BPH.^{14,15,17–20} Reflecting this body of evidence, current guidelines, including those from the EAU, recommend utilizing PSAD as a secondary stratification tool, specifically for equivocal (PI-RADS ≤ 3) lesions.²¹ This recommendation serves as an implicit acknowledgment that the PI-RADS system alone is limited by its lack of volume integration. Crucially, however, this PSAD-adjusted stratification has largely been restricted to equivocal cases (PI-RADS ≤ 3); for PI-RADS 4 lesions, the radiographic score itself is still considered a definitive indication for biopsy regardless of PSAD or any other parameters.

Collectively, our findings suggest that the current approach to PI-RADS 4 lesions may benefit from refinement. We identified that false-positive results in our PI-RADS 4 population are associated with clinical and radiographic features that strongly overlap with typical characteristics of BPH, particularly TZ localization and lower PSAD. Based on these insights, we suggest that a more tailored risk stratification strategy - one that integrates lesion location and quantitative volume-adjusted metrics - could improve diagnostic efficiency in this population. As an illustrative example from our cohort of PI-RADS 4 patients, applying a PSAD threshold of 0.15 ng/mL² to TZ lesions would have reduced the number of biopsies by approximately 18.5% at the cost of missing 4.2% of csPCa in our dataset, highlighting the potential trade-off between maximizing cancer detection and minimizing unnecessary procedures. Naturally, we do not advocate for the immediate adoption of this specific threshold without further validation. However, we believe our findings may serve as a foundational framework for future prospective studies aimed at optimizing the balance between reducing biopsy burden and minimizing missed csPCa in men with PI-RADS 4 lesions.

Our study has several limitations. First, the retrospective, single-center design introduces inherent selection bias and limits the generalizability of our findings to institutions with different patient demographics. Second, mpMRI interpretations were performed by multiple radiologists in a real-world clinical setting without a central consensus review. In routine practice, there can be a conservative tendency to over-score equivocal lesions (e.g., upgrading PI-RADS 3 to 4), which inherently increases the false-positive rate. While this potential for overdiagnosis and inter-reader variability are well-documented, inherent limitations of the PI-RADS system, this potential bias may be partially mitigated by the fact that our institution is a high-volume center with extensive experience in standardized PI-RADS reporting.^{22,23} Third, while we focused on BPH as a possible primary driver of false-positive results based on anatomical location and volume metrics, we did not specifically subanalyze the contribution of inflammatory conditions. Prostatitis is a well-established mimic of prostate cancer on mpMRI, and we could not definitively

distinguish between BPH nodules and focal inflammation as the etiology of the false-positive signal in all cases. Fourth, our data did not include the exact size of the individual lesions. The lack of lesion size data prevents us from analyzing whether size variations within the PI-RADS 4 category independently impacted the probability of false-positive results. Fifth, our histopathological outcomes were analyzed at the patient level (combined targeted and systematic biopsy results) rather than at the lesion level (targeted cores only). While this aligns with our clinical objective of predicting overall biopsy necessity, it prevents us from calculating the pure radiological false-positive rate of the specific PI-RADS 4 lesions as we could not isolate cases where the targeted lesion was benign but concurrent systematic sampling detected csPCa. Finally, due to the lack of uniform longitudinal follow-up data, we cannot entirely exclude the possibility that some cases diagnosed as benign BPH actually harbored missed malignancies (sampling error).

In conclusion, our study indicates that false-positive diagnoses in men with PI-RADS 4 lesions are significantly associated with specific clinical and radiographic features, particularly TZ localization and lower PSAD. These findings support the inference that benign hyperplastic conditions may be one of the key factors likely contributing to the overestimation of cancer risk in this specific subgroup. Our data suggest that the current approach of indiscriminately biopsying all PI-RADS 4 lesions may have limitations and that considering these independent predictors could offer a pathway to reduce unnecessary procedures. Future prospective studies are warranted to validate these associations and determine how lesion location and quantitative metrics might be best utilized to optimize patient selection for prostate biopsy.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used Gemini (Google) in order to improve readability and language. The authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Conflict of Interest

All authors have no potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pnrl.2026.03.002>.

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