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Does ADC Stratification Within PI-RADS Influence the Benefit of Random Biopsy? Insights From a Middle Eastern MR/US Fusion Biopsy Cohort

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Abstract

Purpose:

Multiparametric magnetic resonance imaging and PIRADS scores transformed prostate cancer diagnostics by enabling targeted biopsy. Within each PI-RADS category, apparent diffusion coefficient (ADC) values vary considerably. We hypothesized that ADC thresholds could serve as an additional predictor to identify patients likely to benefit from the addition of random biopsies to MRI-targeted sampling.

Methods

Trans-perineal biopsy database of MRI targeted biopsies and systematic biopsies yielded 306 biopsy sessions. ADC values, PI-RADS score, and pathological results were obtained. Lesions were stratified by PI-RADS category (3–5) and ADC threshold (<750 vs ≥750×10^{-6} mm^2/s). Detection rates between targeted and Systematic biopsies were compared using McNemar tests.

Results:

Among 306 men, cancer was detected by targeted biopsy alone in 163 cases (53.2%) and by Systematic biopsy in 175 cases (57.2%) (p=0.001).

When stratified based on PIRADS score, the benefit of adding random biopsy was shown in PIRADS 4 lesions, with an increased detection by 5.7% (p = 0.004). No statistically significant difference was observed in PIRADS 3 or 5 lesions (p=0.5 and 1.000).

Within PIRADS 4 lesions, there was a 6.7% increase in cancer detection in high ADC (≥ 750) lesions (TB: 38.84% vs SB: 45.45%) (p=0.016). However, in low ADC (<750) lesions, SB did not significantly contribute to prostate cancer detection (TB: 73.0% vs SB: 75.68%) (p=1.000)

Conclusion:

ADC values above 750×$10^{-6}$$mm^2/s$ identified PI-RADS 4 patients benefit from random biopsies. Overall, random biopsy cores remain valuable in PI-RADS 4 lesions, and ADC stratification could guide biopsy decisions in selected patients.

Introduction

Prostate cancer remains the most frequently diagnosed non-cutaneous malignancy and the second leading cause of cancer related mortality among men in the United States (1). Histopathological confirmation requires ultrasound-guided needle biopsy via the transrectal or transperineal route. Over the past decade, the diagnostic pathway has been restructured around pre-biopsy multiparametric MRI (mp-MRI). In the PROMIS study, mp-MRI achieved a sensitivity of 93% for clinically significant prostate cancer (csPCa), compared with 48% for standard transrectal biopsy, and its use as a triage test would have

allowed 27% of men to avoid primary biopsy (2). The PRECISION trial subsequently demonstrated that an MRI-directed pathway with targeted sampling increased csPCa detection from 26% to 38% while reducing the detection of clinically insignificant disease from 22% to 9%, relative to systematic biopsy alone (3). On this evidence, contemporary guidelines recommend mp-MRI before biopsy, with targeted sampling of suspicious lesions (4). Lesion suspicion is standardized by the Prostate Imaging Reporting and Data System (PIRADS), a five-point assessment in which diffusion-weighted imaging sequence is the determining sequence for the peripheral zone and T2-weighted imaging for the transition zone (5). In parallel, the transperineal route has been increasingly adopted. By avoiding transrectal needle passage it reduces infectious complications and antibiotic requirements, and it affords more reliable access to the anterior and apical regions of the gland (6).

The widespread adoption of targeted biopsy (TB) has raised the question whether systematic cores still need to be added this is due to their modest incremental yield of csPCa (7). Omitting them is not without risk, as demonstrated in a large paired series, targeted biopsy alone would have missed 8.8% of clinically significant cancers (8). This residual benefit is unlikely to be uniform across lesion categories, and identifying which patients still require systematic sampling has become a central question (7).

PIRADS 4 is the category in which the score is least informative. Its positive predictive value is modest and varies widely between centers (9). Also, with lesions carrying an identical score possibly differing substantially in cancer yield, a limitation inherent to a qualitative, ordinal scale. The apparent diffusion coefficient (ADC) offers a quantitative alternative hypothesis. Derived from diffusion-weighted imaging, it reflects the degree of restricted water diffusion and correlates inversely with tumor cellularity and grade (10). In fact, values below approximately 750 $\times 10^{-6}$ mm²/s have been shown to improve discrimination of csPCa when combined with the PIRADS score (11, 12). However, this numeric value is generated in every prostate MRI and then set aside when the extent of biopsy sampling is planned. Thus, this study examines whether lesion ADC, dichotomized at 750 $\times 10^{-6}$ mm²/s, identifies which patients with a PIRADS 4 lesion benefit from the addition of systematic biopsy to targeted biopsy in a Middle Eastern transperineal MRI–ultrasound fusion cohort from a single tertiary care center.

Methods

Study design and population:

We conducted a retrospective cohort study of patients who underwent transperineal MRI–ultrasound fusion prostate biopsy at our institution between March 2019 and January 2024. Patients were eligible if pre-biopsy multiparametric MRI demonstrated a lesion assigned a PIRADS score of 3–5, an ADC value was available for the index lesion, and both targeted and bilateral systematic sampling were performed during the same session. Patients with negative or unavailable MRI, missing PIRADS assessment, absent systematic cores, or unavailable ADC classification were excluded. Of 522 transperineal fusion biopsy records screened, 127 were excluded for the absence of a PIRADS 3–5 lesion (126 without a PIRADS-scored lesion and 1 with a PIRADS 2 lesion), 32 for absent systematic sampling, and 57 for

unavailable ADC classification, yielding 306 biopsy sessions. In patients with multiple lesions (140 of 264 with documented lesion counts, 53.0%), analyses were based on the index lesion, defined as the largest lesion with the highest PIRADS score. The population included biopsy-naïve men (209 of 251 with documented history, 83.3%) as well as patients with a prior negative biopsy (n = 24) or a prior diagnosis of prostate cancer on active surveillance (n = 18). The full cohort of 306 sessions was used to characterize the incremental yield of systematic biopsy across PIRADS categories. The primary analysis population comprised the 158 sessions with a PIRADS 4 index lesion, of which 37 had an ADC < 750 $\times 10^{-6}$ mm²/s and 121 an ADC ≥ 750 $\times 10^{-6}$ mm²/s.

MRI protocol and ADC measurement

MRI protocol and ADC measurement
Multiparametric MRI was performed on a 3.0-Tesla scanner and included T2-weighted, diffusion-weighted, and dynamic contrast-enhanced sequences. Experienced radiologists scored the lesions according to PIRADS version 2.1 (5). A numeric ADC value was recorded for the index lesion. Lesions were dichotomized at an ADC of 750 $\times 10^{-6}$ mm²/s, based on previously published thresholds for discriminating clinically significant prostate cancer (11, 12).

Biopsy technique and histopathological evaluation

All procedures were performed transperineally six attending urologists using the KOELIS Trinity® MRI–transperineal ultrasound fusion platform. Patients were placed in the lithotomy position and received light sedation from the anesthesia team; a minority of procedures were performed under local anesthesia with a periprostatic block. Following preparation of the perineal skin and infiltration of local anesthetic at the intended needle-entry sites, the transrectal ultrasound probe was secured to a stepper and positioned in the rectum. A brachytherapy square or linear grid was then mounted on the probe approximately 1 cm from the perineal skin. A median of 5 targeted cores (interquartile range [IQR] 4–7) was obtained from the index lesion, followed by bilateral systematic sampling with a median of 7 systematic cores in total (IQR 5–9). Experienced uropathologists reported the histopathological findings according to the International Society of Urological Pathology (ISUP) consensus recommendations using the Grade Group (GG) system (13). Clinically significant prostate cancer was defined as GG ≥ 2 (Gleason score > 6) (13).

Outcomes

The primary outcome was the incremental detection of prostate cancer with the addition of systematic cores to targeted biopsy in PIRADS 4 lesions, stratified by ADC group (< 750 vs ≥ 750 $\times 10^{-6}$ mm²/s). Secondary outcomes were the incremental detection of prostate cancer across PIRADS categories 3–5, and Grade Group upgrading. Detection of clinically significant prostate cancer (GG ≥ 2) was analyzed post hoc.

Statistical analysis

All analyses were performed using IBM SPSS Statistics, version 28 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality by visual inspection of histograms and Q–Q plots and summarized as mean ± standard deviation or median and interquartile range (IQR), as appropriate. Categorical variables were reported as frequencies and percentages. Since each patient underwent both targeted and systematic sampling within the same session, cancer detection by targeted biopsy alone was compared with combined biopsy using the McNemar test for paired proportions. Absolute differences in detection rates were reported with 95% confidence intervals. Agreement and discordance in Grade Group assignment between the two strategies were examined by cross-tabulation, with upgrading reported descriptively. Subgroup analyses were performed by PIRADS category (3, 4, and 5) and, within PIRADS 4, by ADC group. All tests were two-sided, with $p < 0.05$ considered statistically significant. For the analysis we did Wilcoxon and McNemar tests for the additional detection of prostate cancer in random biopsies compared to the target.

Ethical considerations

The study was approved by the Institutional Review Board of our institution (IRB number: BIO-2024-0101). The requirement for informed consent was waived given the retrospective design and use of de-identified data. All procedures conformed to institutional standards and the Declaration of Helsinki.

Results

Patient selection

Of 522 transperineal fusion biopsy records screened, 127 were excluded for the absence of a PIRADS 3–5 lesion, 32 for absent systematic sampling, and 57 for unavailable ADC classification, yielding 306 biopsy sessions (Fig. 1). The index lesion was PIRADS 3 in 51 sessions (16.7%), PIRADS 4 in 158 (51.6%), and PIRADS 5 in 97 (31.7%). Overall, 193 lesions (63.1%) had an ADC ≥ 750 $\times 10^{-6}$ mm²/s and 113 (36.9%) an ADC < 750 $\times 10^{-6}$ mm²/s; the ADC-stratified analysis was restricted to PIRADS 4 lesions. Within the PIRADS 4 group, 37 lesions had an ADC < 750 $\times 10^{-6}$ mm²/s and 121 an ADC ≥ 750 $\times 10^{-6}$ mm²/s.

Baseline characteristics

Mean age was 66.4 ± 8.4 years and mean BMI 28.2 ± 3.9 kg/m². Median PSA was 6.9 ng/mL (IQR 4.6–9.7), median prostate volume 55 mL (IQR 40–74), median PSA density 0.11 ng/mL² (IQR 0.08–0.18), and median index lesion diameter 1.2 cm (IQR 0.9–1.7). The index lesion was located in the peripheral zone in 81.7% of sessions, and 83.3% of sessions with documented history were in biopsy-naïve men. Hypertension was present in 50.7% of patients, diabetes mellitus in 19.3%, dyslipidemia in 19.3%, and coronary artery disease in 16.0%; 26.1% were smokers. Mean lesion ADC was 842 ± 261.5 $\times 10^{-6}$ mm²/s. (shown in Table 1a)

Table 1
Baseline characteristics of the study cohort (N = 306 biopsy sessions).

Characteristic	Value
Age, years, mean ± SD	66.4 ± 8.4
Body mass index, kg/m², mean ± SD	28.2 ± 3.9
PSA, ng/mL, median (IQR)	6.9 (4.6–9.7)
Prostate volume, mL, median (IQR)	55 (40–74)
PSA density, ng/mL², median (IQR)	0.12 (0.08–0.18)
Index lesion diameter, cm, median (IQR)	1.2 (0.9–1.7)
Index lesion in peripheral zone, %	81.7
Biopsy history, n (%)	
Biopsy-naïve	209 (83.3)
Prior negative biopsy	24
Active surveillance	18
Comorbidities, n (%)	
Hypertension	155 (50.7)
Diabetes mellitus	59 (19.3)
Dyslipidemia	59 (19.3)
Coronary artery disease	49 (16.0)
Current smoking	80 (26.1)
PIRADS category of index lesion, n (%)	
PIRADS 3	51 (16.7)
PIRADS 4	158 (51.6)
PIRADS 5	97 (31.7)
Index lesion ADC, $\times 10^{-6}$ mm²/s, mean ± SD	842 ± 261.5
ADC ≥ 750 $\times 10^{-6}$ mm²/s, n (%)	193 (63.1)

ADC, apparent diffusion coefficient; IQR, interquartile range; PIRADS, Prostate Imaging Reporting and Data System; PSA, prostate-specific antigen; SD, standard deviation. Continuous variables are summarized as mean ± SD or median (IQR) according to distribution. Comorbidity and PIRADS counts are of all 306 sessions. For other variables, denominators are smaller than 306 owing to incomplete documentation; percentages are of available data. The biopsy-naïve percentage is of the 251 sessions with documented history.

Table 1
b. Baseline characteristics of PIRADS 4 lesions stratified by index-lesion ADC.

Characteristic	ADC < 750 ×10⁻⁶ mm²/s (n = 37)	ADC ≥ 750 ×10⁻⁶ mm²/s (n = 121)
Age, years, mean ± SD	67.4 ± 9.9	65.7 ± 7.4
Body mass index, kg/m², mean ± SD	29.2 ± 4.1	28.1 ± 3.8
PSA, ng/mL, median (IQR)	6.4 (3.1–8.1)	7.0 (5.0–9.3)
Prostate volume, mL, median (IQR)	56 (38–72)	59 (49–79)
PSA density, ng/mL², median	0.11	0.11
Index lesion diameter, cm, median (IQR)	1.1 (0.8–1.2)	1.0 (0.7–1.3)
Index lesion in peripheral zone, %	85.3	92.6
Biopsy-naïve, %	77.4	85.7
Index lesion ADC, ×10⁻⁶ mm²/s, mean ± SD	582 ± 103	986 ± 172

ADC, apparent diffusion coefficient; IQR, interquartile range; PIRADS, Prostate Imaging Reporting and Data System; PSA, prostate-specific antigen; SD, standard deviation. Descriptive comparison only; no between-group statistical testing was performed. Denominators for some variables are smaller than the group totals owing to incomplete documentation; percentages are of available data.

Baseline characteristics of PIRADS 4 lesions stratified by ADC group are shown in Table 1b. In the ADC < 750 ×10⁻⁶ mm²/s and ADC ≥ 750 ×10⁻⁶ mm²/s groups respectively, mean age was 67.4 ± 9.9 and 65.7 ± 7.4 years, mean BMI 29.2 ± 4.1 and 28.1 ± 3.8 kg/m², median PSA 6.4 ng/mL (IQR 3.1–8.1) and 7.0 ng/mL (IQR 5.0–9.3), median prostate volume 56 mL (IQR 38–72) and 59 mL (IQR 49–79), median PSA density 0.11 ng/mL² in both groups, and median index lesion diameter 1.1 cm (IQR 0.8–1.2) and 1.0 cm (IQR 0.7–1.3). The index lesion was peripheral in 85.3% and 92.6% of sessions, and 77.4% and 85.7% of patients were biopsy-naïve. Mean ADC was 582 ± 103 and 986 ± 172 ×10⁻⁶ mm²/s.

Overall biopsy findings

Targeted biopsy alone detected prostate cancer in 163 of 306 sessions (53.3%), and combined biopsy in 175 (57.2%), corresponding to 12 additional diagnoses (absolute difference 3.9%, 1.7–6.1]; p = 0.001). In the post hoc analysis of clinically significant disease, targeted biopsy detected csPCa in 145 sessions (47.4%) and combined biopsy in 155 (50.7%), corresponding to 10 additional diagnoses (+ 3.3%, [1.3–5.3]; p = 0.002).

Results by PIRADS category

In PIRADS 3 lesions (n = 51), cancer was detected in 5 sessions (9.8%) by targeted biopsy and in 7 (13.7%) by combined biopsy, an incremental yield of 2 sessions (+ 3.9%, [− 1.4–9.2]); p = 0.5. In PIRADS 4

lesions (n = 158), detection increased from 74 (46.8%) to 83 (52.5%), an incremental yield of 9 sessions (+ 5.7%, [2.1–9.3]; p = 0.004. In PIRADS 5 lesions (n = 97), detection increased from 84 (86.6%) to 85 (87.6%), an incremental yield of 1 session (+ 1.0%, [− 1.0–3.0]; p = 1.000). The incremental yield of systematic sampling was therefore statistically significant only in PIRADS 4 lesions. (shown in Table 2)

Table 2
Prostate cancer detection by targeted versus combined biopsy according to PIRADS category.

PIRADS	n	Targeted biopsy, n (%)	Combined biopsy, n (%)	Added by systematic cores, n (%)	95% CI (%)	p
3	51	5 (9.8)	7 (13.7)	2 (3.9)	[− 1.4–9.2]	0.5
4	**158**	**74 (46.8)**	**83 (52.5)**	**9 (5.7)**	**[2.1–9.3]**	**0.004**
5	97	84 (86.6)	85 (87.6)	1 (1.0)	[− 1.0–3.0]	1.000
All	**306**	**163 (53.3)**	**175 (57.2)**	**12 (3.9)**	**[1.7–6.1]**	**0.001**

CI, confidence interval; PIRADS, Prostate Imaging Reporting and Data System. Combined biopsy denotes targeted plus systematic cores obtained in the same session. Added detections are sessions in which cancer was identified by systematic cores only; the absolute difference in detection rate is given with its 95% CI. p values from the McNemar test for paired proportions. Bold indicates p < 0.05.

Main PIRADS 4 ADC analysis

Among PIRADS 4 lesions with an ADC < 750 $\times 10^{-6}$ mm²/s (n = 37), targeted biopsy detected cancer in 27 sessions (73.0%) and combined biopsy in 28 (75.7%); systematic cores alone accounted for 1 additional diagnosis (+ 2.7%, [− 2.5–7.9]; p = 1.000). Among lesions with an ADC ≥ 750 $\times 10^{-6}$ mm²/s (n = 121), targeted biopsy detected cancer in 47 sessions (38.8%) and combined biopsy in 55 (45.5%); systematic cores alone accounted for 8 additional diagnoses (+ 6.6%, [2.2–11.0]; p = 0.016). Of the 9 additional cancers detected by systematic sampling in PIRADS 4 lesions, 8 occurred in the ADC ≥ 750 $\times 10^{-6}$ mm²/s group. (shown in Table 3)

Table 3
Prostate cancer detection by targeted versus combined biopsy in PIRADS 4 lesions, stratified by index-lesion ADC (primary analysis).

ADC group ($\times 10^{-6}$ mm²/s)	n	Targeted biopsy, n (%)	Combined biopsy, n (%)	Added by systematic cores, n (%)	95% CI (%)	p
< 750	37	27 (73.0)	28 (75.7)	1 (2.7)	[− 2.5–7.9]	1.000
≥ 750	**121**	**47 (38.8)**	**55 (45.5)**	**8 (6.6)**	**[2.2–11.0]**	**0.016**
All PIRADS 4	**158**	**74 (46.8)**	**83 (52.5)**	**9 (5.7)**	**[2.1–9.3]**	**0.004**

ADC, apparent diffusion coefficient; CI, confidence interval; PIRADS, Prostate Imaging Reporting and Data System. p values from the McNemar test for paired proportions, comparing targeted biopsy alone with combined biopsy within each group. No statistical comparison of incremental yield between ADC groups was performed. Bold indicates p < 0.05.

Grade Group analysis

Grade Group assignments by the two biopsy strategies are cross-tabulated in Table 4. Of the 12 cancers detected exclusively by systematic cores, 2 were GG1 and 10 were GG ≥ 2 (7 GG2, 1 GG3, and 2 GG4). Within PIRADS 4, there was an incremental yield of csPCa in a single patient in the ADC < 750 $\times 10^{-6}$ mm²/s group corresponding to GG3 PCa (1 of 37 sessions; +2.7%; p = 1.000). In the ADC ≥ 750 $\times 10^{-6}$ mm²/s group, systematic biopsy detected 8 additional cancers comprised of 1 GG1, 5 GG2, and 2 GG4. 7 of 8 (87.5%) were clinically significant corresponding to an incremental yield of csPCa in 7 of 121 sessions (+ 5.8%, [1.6–9.9]; p = 0.016). Among sessions with cancer on targeted biopsy, systematic cores upgraded the Grade Group in 5 of 163 patients corresponding to 3.1% (three GG2→GG3 and two GG3→GG4). In total, systematic sampling changed either the diagnosis or the Grade Group in 17 of 306 sessions (5.6%). (shown in Tables 4–5)

Table 4

Cross-tabulation of highest Grade Group by targeted biopsy versus combined biopsy (N = 306).

Targeted biopsy	Combined biopsy						
	No cancer	**GG1**	**GG2**	**GG3**	**GG4**	**GG5**	**Total**
No cancer	131	**2**	**7**	**1**	**2**	0	143
GG1 (3 + 3)	0	18	0	0	0	0	18
GG2 (3 + 4)	0	0	39	**3**	0	0	42
GG3 (4 + 3)	0	0	0	65	**2**	0	67
GG4 (8)	0	0	0	0	24	0	24
GG5 (9–10)	0	0	0	0	0	12	12
Total	**131**	**20**	**46**	**69**	**28**	**12**	**306**

GG, International Society of Urological Pathology Grade Group (Gleason score in parentheses). Shaded diagonal cells denote concordant results. Bold off-diagonal cells denote sessions in which systematic cores changed the result: 12 cancers detected only by systematic cores (first row; 2 GG1, 7 GG2, 1 GG3, 2 GG4) and 5 Grade Group upgrades among targeted-biopsy-positive sessions (three GG2→GG3, two GG3→GG4). In total, systematic sampling altered the diagnosis or Grade Group in 17 of 306 sessions (5.6%).

Table 5

Clinically significant prostate cancer (Grade Group ≥ 2) detected by targeted versus combined biopsy: post hoc analysis. A. Detection of clinically significant prostate cancer

Population	n	Targeted biopsy, n (%)	Added by systematic cores, n (%)	Combined biopsy (targeted + added), n (%)	95% CI	p
All sessions	**306**	**145 (47.4)**	**10 (3.3)**	**155 (50.7)**	**[1.3–5.3]**	**0.002**
PIRADS 3 and 5	148	85 (57.4)	2 (1.4)	87 (58.8)	[− 0.5–3.2]	0.500
PIRADS 4, all	**158**	**60 (38.0)**	**8 (5.1)**	**68 (43.0)**	**[1.6–8.5]**	**0.008**
ADC < 750	37	25 (67.6)	1 (2.7)	26 (70.3)	[− 2.5–7.9]	1.000
ADC ≥ 750	**121**	**35 (28.9)**	**7 (5.8)**	**42 (34.7)**	**[1.6–9.9]**	**0.016**
B. Grade Group of the cancers detected only by systematic cores						

Discussion

In this cohort of 306 transperineal MRI–ultrasound fusion biopsy sessions, the addition of systematic cores to targeted biopsy increased prostate cancer detection by 3.9% overall, and this benefit was confined to PIRADS 4 lesions. Within PIRADS 4, eight of the nine additional cancers occurred in lesions with an ADC ≥ 750 $\times 10^{-6}$ mm²/s, in which combined biopsy increased detection by 6.6%, whereas lesions with ADC < 750 $\times 10^{-6}$ mm²/s didn't show any measurable gain. In the post hoc analysis of clinically significant disease, the majority of the additional cancers were GG ≥ 2 (10 of 12 overall, and 7 of 8 in the higher-ADC group), indicating that the incremental yield of systematic sampling in this cohort was not driven by the detection of indolent disease. This distinction is clinically consequential: whereas GG1 disease is typically managed by active surveillance, GG2 and above generally warrant active treatment with surgery or radiotherapy (4), so the cancers added by systematic sampling in this cohort were largely those that would alter management.

A plausible mechanism underlies this pattern. Lesions with low ADC values are densely cellular, conspicuous on imaging, and well delineated, allowing accurate targeting; in our cohort, targeted biopsy alone was positive in 73.0% of low-ADC PIRADS 4 lesions, leaving little residual disease for systematic cores to capture. Lesions with higher ADC values are less conspicuous and more heterogeneous, so registration and sampling errors become more consequential (20, 21), and these patients may also harbor MRI-occult disease elsewhere in the gland that only systematic sampling can detect (14, 15, 22). Notably, ADC also stratified baseline risk within the same PIRADS category; cancer yield on targeted biopsy was 73.0% versus 38.8% on either side of the threshold. This illustrates concretely the biological heterogeneity concealed within a single PIRADS 4 score.

Our findings align with and extend the existing literature on the added value of systematic sampling. Combined biopsy remains the reference standard precisely because targeted cores alone miss a minority of cancers (14, 15), yet the magnitude of this benefit varies by lesion category: in a secondary analysis of the Trio study, systematic biopsy contributed most in PIRADS 3 and 4 lesions and added only 2.5% in PIRADS 5 (16), and a large multicenter side-specific analysis reached comparable conclusions (17), and our results reproduce this gradient. The single additional cancer among 97 PIRADS 5 sessions is consistent with the minimal benefit reported by others (16, 17), although our PIRADS 3 group was small and selectively biopsied, limiting conclusions in that category. Efforts to rationalize systematic sampling have also explored reduced templates, with targeted-plus-perilesional approaches missing approximately 3% of clinically significant cancers compared with full bilateral sampling (18), and contralateral cores contributing only modest additional yield (19). The present study adds a quantitative dimension to this literature within PIRADS 4, with the benefit concentrated in lesions with higher ADC values.

The 750 $\times 10^{-6}$ mm²/s threshold itself derives from studies of diagnostic discrimination, in which ADC values below this range improved the identification of clinically significant cancer when combined with the PIRADS score (11, 12). The present study repurposes this diagnostic threshold as a sampling-strategy tool, asking not whether a lesion harbors cancer, but whether targeted cores alone will suffice to

find it. Since the numeric ADC value is generated in every prostate MRI yet currently overlooked at the point of biopsy planning, this represents information available at no additional cost.

The clinical implication of our findings is a case for retaining systematic sampling in PIRADS 4 lesions with an ADC ≥ 750 ×10⁻⁶ mm²/s, in which combined biopsy yielded meaningful additional detection of predominantly significant disease. The converse question, whether systematic cores may be safely omitted in low-ADC PIRADS 4 lesions, cannot be answered by these data: the subgroup was small (37 sessions, one additional cancer), the incremental yield between ADC groups was not formally compared, and the subgroup analyses were exploratory. Our findings therefore do not justify omitting systematic biopsy in any subgroup at present; they generate a hypothesis that warrants prospective, multicenter evaluation.

Strengths of this study include the study design in which each patient served as his own control; a consecutive real-world cohort biopsied with a uniform transperineal fusion technique; ADC classification of the index lesion in all sessions; and, to our knowledge, the first evaluation of lesion ADC as a selector for the added value of systematic biopsy, and the first such data from a Middle Eastern population. The two ADC groups were also broadly similar in age, PSA, PSA density, prostate volume, and lesion size, arguing against gross confounding of the observed pattern.

This study is not without limitations. First, it is a retrospective single-center chart review, without randomization or central review of imaging and pathology, and inter-reader variability in PIRADS assignment and ADC measurement cannot be excluded (23). Second, the number of discordant biopsy pairs was small, yielding wide confidence intervals, and no adjustment for multiple comparisons was applied, so the subgroup findings should be interpreted as exploratory. Third, PIRADS 3 lesions were biopsied selectively on clinical grounds (24), introducing selection bias and limiting inference in that category. Fourth, a small number of patients contributed more than one biopsy session. Finally, the ADC threshold, although literature-derived (11, 12), requires external validation before clinical application.

Conclusion

In this transperineal MRI–ultrasound fusion cohort, the added value of systematic biopsy was confined to PIRADS 4 lesions and concentrated in those with an ADC ≥ 750 ×10⁻⁶ mm²/s, with most of the additional cancers being clinically significant. Lesion ADC, which is a quantitative measure already generated in every prostate MRI, may help identify which patients with a PIRADS 4 lesion still benefit from combined biopsy. Prospective, multicenter validation is required before systematic biopsy can be safely omitted in any subgroup.

Legend:

Figure 1: Participant flow diagram.

Declarations

Competing interests:

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Author Contribution

O.N. contributed to Conceptualization, Methodology, Writing—Original Draft, and Writing—Review & Editing. D.E. contributed to Writing—Original Draft, Data Analysis, and Writing—Review & Editing. R.T.S. contributed to Methodology, Data Analysis, and Writing—Original Draft. W.O. contributed to Data Collection and Writing—Original Draft. M.F. contributed to Data Collection and Writing—Review & Editing. M.B. contributed to Conceptualization, Methodology, Writing—Review & Editing, and Supervision. R.N., A.E.H., M.A., R.K, B.G.B., W.W., H.M., and R.Khouzami contributed to Writing—Review & Editing and Manuscript Review. All authors reviewed and approved the final manuscript.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy and ethical restrictions related to patient confidentiality.

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Figures

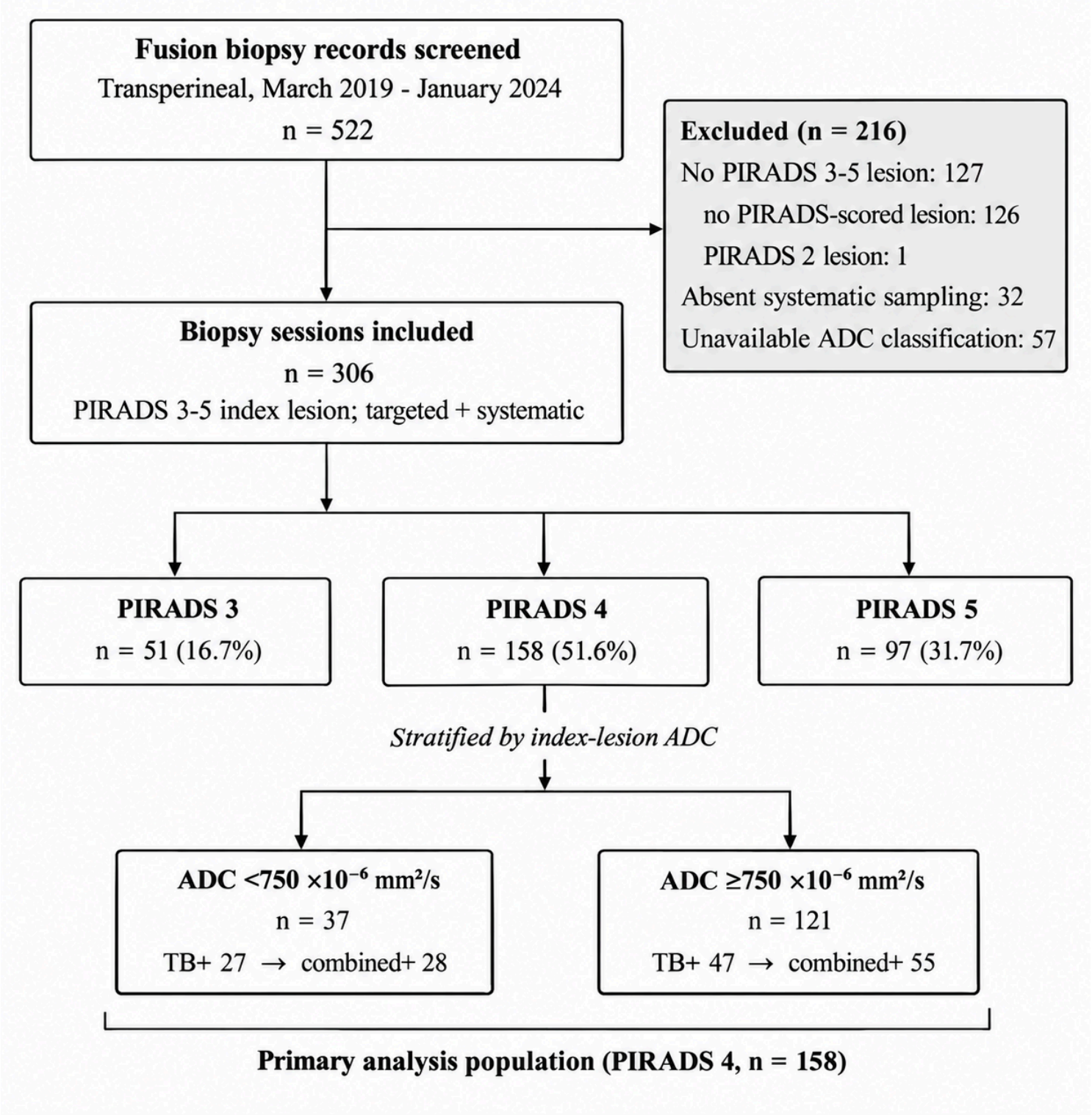


Figure 1

Participant flow diagram.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1aBaseline.docx
- Table1bPIRADS4byADC.docx
- Table2DetectionbyPIRADS.docx
- Table3PIRADS4ADCPrimary.docx
- Table4GradeGroupCrosstab.docx
- Table5ADCv2.docx