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Combined Use of PI-RADS, PSA Density, and the Free-to-Total PSA Ratio for Prostate Cancer Diagnosis in the PSA Gray Zone: A Narrative Review

Tao Liu

The First Affiliated Hospital of Yangtze University, Jingzhou 434000, Hubei, China

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Abstract: When total prostate-specific antigen (tPSA) is between 4 and 10 ng/mL, the result alone often cannot distinguish prostate cancer from benign prostatic disease. The combination of the Prostate Imaging Reporting and Data System (PI-RADS) score and PSA density (PSAD) provide additional information for biopsy decisions in this population. The free-to-total PSA ratio (f/tPSA) is another commonly used adjunct, although some evidence supporting its diagnostic value predates the widespread use of magnetic resonance imaging (MRI). This narrative review examines studies of these three measures, with particular attention to age, model composition, and biopsy outcomes. Available evidence supports combining PI-RADS with PSAD to improve risk stratification. The f/tPSA ratio has also shown diagnostic value in certain age groups and MRI-defined populations. However, good performance of a multivariable model does not establish that every included predictor provides additional information. In men aged ≥ 60 years with tPSA levels of 4–10 ng/mL, direct comparisons of models with and without f/tPSA are needed. Reporting both the number of biopsies avoided and the number of clinically significant cancers missed would help clarify the clinical value of the three-variable approach.

Keywords: Prostate cancer; PSA gray zone; PI-RADS; PSA density; Free-to-total PSA ratio; Combined diagnostic assessment

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1. Introduction

An elevated total prostate-specific antigen (tPSA) level is a common reason for further investigation of suspected prostate cancer. PSA is organ-specific, but its cancer specificity is limited: benign prostatic hyperplasia and inflammation can also increase serum concentrations. At tPSA levels of 4–10 ng/mL, commonly described as the PSA gray zone, the distributions observed in benign and malignant disease overlap. Identifying which patients should undergo biopsy is therefore a central purpose of research on

adjunctive diagnostic measures [1].

The free-to-total PSA ratio (f/tPSA) has long been used to assess patients in this range, principally as a supplement to tPSA testing [2]. With the introduction of prebiopsy magnetic resonance imaging (MRI), risk assessment has expanded to include lesion characteristics and prostate volume. The Prostate Imaging Reporting and Data System (PI-RADS) score describes the degree of suspicion on MRI, while PSA density (PSAD) relates tPSA to gland volume. Clinicians consequently have more information available than serum PSA measurements alone.

This change in practice raises a specific question about f/tPSA: once PI-RADS and PSAD are known, does the ratio improve risk estimates sufficiently to change biopsy decisions? Its sensitivity or specificity in isolation cannot answer that question. Age-stratified studies provide a rationale for examining men aged ≥ 60 years with PSA levels in the gray zone. This review considers that evidence alongside studies of combined diagnostic approaches and discusses the issues that affect their interpretation.

2. Literature sources and scope

This narrative review draws on literature concerning the PSA gray zone, MRI scoring, PSAD, f/tPSA, and age-stratified diagnosis. Study details were checked using PubMed-indexed records, full-text articles available through PubMed Central, and journal and guideline websites. The literature search for the review topic extended through September 9, 2026. Search terms included “prostate cancer”, “PSA gray zone”, “PI-RADS”, “PSA density”, “free-to-total PSA”, “percent free PSA”, “age”, and “prediction model”.

The discussion focuses on original studies involving patients with tPSA levels of 4–10 ng/mL. Studies of broader populations were also considered where they helped explain the performance of combined approaches; their eligibility criteria were taken into account when assessing applicability. This review did not include an exhaustive systematic search, independent duplicate screening, or a new quantitative synthesis.

3. The contribution of PSAD after MRI assessment

PI-RADS v2.1 assigns scores from 1 to 5 to describe the likelihood that an MRI finding represents clinically significant prostate cancer (csPCa). Diffusion-weighted imaging is the dominant sequence for peripheral-zone assessment, whereas T2-weighted imaging is dominant in the transition zone [3]. Standardized scoring supports communication of imaging findings and helps guide subsequent biopsy sampling.

The PRECISION trial enrolled 500 biopsy-naïve men with suspected prostate cancer. Clinically significant cancer was detected in 38% of patients assigned to the MRI pathway and 26% assigned to standard systematic biopsy [4]. These findings support the use of MRI before biopsy. However, the trial was not restricted to patients in the PSA gray zone, so its detection rates should not be treated as expected rates for that subgroup.

MRI does not resolve every biopsy decision. A PI-RADS score of 3 indicates an equivocal finding, and a negative MRI still requires interpretation alongside other clinical information. PSAD offers an additional measure in these circumstances and is calculated as follows:

PSAD = tPSA (ng/mL) / prostate volume (cm^3).

Patients with the same tPSA concentration may have substantially different PSAD values because their prostate volumes differ. Volume therefore helps place an elevated PSA result in context. The performance of PSAD nevertheless depends on the selected cutoff. In a meta-analysis of 39 studies, Wang et al. reported pooled sensitivities of 0.87, 0.61, and 0.42, and corresponding specificities of 0.39, 0.69, and 0.82, at PSAD thresholds of 0.10, 0.15, and 0.20 ng/mL/cm^3 in patients with PI-RADS or Likert scores of 3 [5]. Raising the cutoff reduced false-positive results but left more clinically significant cancers below the threshold.

Evidence more directly relevant to the gray zone comes from Wen et al., who retrospectively studied 453 patients. In the validation subset obtained by random splitting, the area under the receiver operating characteristic curve (AUC) for predicting csPCa was 0.871 for PI-RADS combined with PSAD, compared with 0.829 for PI-RADS alone and 0.677 for PSAD alone [6]. The results support the complementary value of imaging and density measurements. Because the validation data came from the same study cohort, performance at other centers remained unestablished.

The meta-analysis by Haj-Mirzaian et al. examined the implications for biopsy decisions. Strategies that omitted biopsy in patients with PI-RADS scores ≤ 3 and PSAD below 0.10 or 0.15 ng/mL/cm^3 could avoid approximately 30% and 48% of unnecessary biopsies, respectively, while maintaining overall strategy sensitivities of approximately 97% and 95% [7]. These estimates describe the strategies evaluated in the included populations. They do not imply that all patients with negative MRI findings have equivalent risk. Individual risk factors and arrangements for subsequent monitoring remain relevant when applying such strategies [1].

4. Earlier evidence for f/tPSA and the influence of age

4.1. From an adjunct to PSA testing to reassessment in the MRI era

The f/tPSA ratio expresses free PSA as a proportion of total PSA and may be reported as a decimal or percentage. Catalona et al. studied men with tPSA levels of 4–10 ng/mL and a nonsuspicious digital rectal examination. A percent-free PSA cutoff of 25% detected approximately 95% of cancers while avoiding approximately 20% of unnecessary biopsies [2]. This study provided an early basis for using f/tPSA in the PSA gray zone.

Its clinical setting matters when interpreting the findings. The outcome was detection of any prostate cancer, and contemporary MRI-based stratification was not part of the assessment. The study established that f/tPSA could supplement tPSA testing; it did not test its contribution after PI-RADS and PSAD had already been considered. As the information available for diagnosis expands, the additional contribution of an individual measure may change. Earlier diagnostic performance therefore cannot, by itself, establish that a three-variable approach is superior to a model using PI-RADS and PSAD.

4.2. Age-related findings in Chinese populations

Studies in Chinese populations have not produced entirely consistent results. Huang et al. evaluated 558 men with PSA levels of 2.5–20 ng/mL. Although cancer prevalence increased as percent-free PSA decreased, its AUC was not superior to that of PSA. Analyses stratified by age and prostate volume also did not demonstrate a clear advantage [8]. An association with cancer was therefore present without evidence of better discrimination than the existing test.

In contrast, the multicenter study by Chen et al. restricted PSA to 4–10 ng/mL and included 2,310 men undergoing an initial biopsy. The authors found that f/tPSA provided additional diagnostic value in men aged ≥ 60 years, whereas the same benefit was not observed in those aged 40–59 years [9]. Differences in PSA ranges, age categories, and patient composition prevent the disagreement between these studies from being attributed to a single factor. The latter study more closely matches the population of interest for research in older men with gray-zone PSA levels, but its principal comparison was still against PSA testing.

Another age-stratified study selected percent-free PSA cutoffs to detect 90% of prostate cancers. The resulting thresholds were 24%, 27%, and 32% for men aged 60–69, 70–79, and ≥80 years, respectively [10]. These differences suggest that a fixed cutoff may not perform equally across age groups. However, the thresholds were derived for a particular detection target in a specific sample and should not be adopted directly as universal biopsy criteria after MRI.

Together, these findings justify examining age while leaving an unresolved question: how much of the contribution observed for f/tPSA in men aged ≥ 60 years remains after PI-RADS and PSAD are included? Addressing this requires comparisons using the same patients and diagnostic outcome. Potential overlap between cohorts should also be checked when studies originate from the same research consortium and cover similar recruitment periods.

5. What studies of combined approaches can establish

5.1. Overall model performance and the contribution of an individual predictor

The term “combined” covers several different approaches in this literature. Some studies use a set of cutoffs to define biopsy rules; others develop multivariable prediction models or compare complete diagnostic pathways. Although each uses multiple measures, they do not necessarily answer the same question.

Baruah et al. prospectively enrolled 104 men with PSA levels of 4–10 ng/mL and lower urinary tract symptoms. They assessed different rules combining PI-RADS with PSAD or percent-free PSA, some of which improved specificity [11]. Their definition of csPCa incorporated Gleason score and cancer core length, and systematic biopsy served as the reference. The findings therefore describe the performance of particular decision rules rather than the incremental performance of a three-variable regression model.

Zhang et al. developed a nomogram containing age, PSAD, f/tPSA, and PI-RADS. Its validation-cohort AUC was 0.891, and the study reported improvement in net reclassification improvement (NRI) [12]. These findings might appear to establish the value of using all three diagnostic measures. However, the key comparison involved adding PI-RADS to an existing clinical model. The observed improvement primarily evaluated the inclusion of imaging information. To determine whether f/tPSA itself was needed, the appropriate comparison would retain the other predictors and remove only f/tPSA.

Liang et al. developed separate transition-zone and peripheral-zone models for patients with PI-RADS 3 findings. The transition-zone model retained age, f/tPSA, and PSAD, while the peripheral-zone model retained age, PSA, and prostate volume [13]. The different predictor sets suggest that the role of f/tPSA may depend on patient and lesion characteristics. Selection into a final model offers a reason for further investigation, but it does not quantify the clinical benefit obtained by adding the predictor.

Ding et al. developed a model in 155 patients with PSA levels in the gray zone that included f/tPSA, PI-RADS, and an elastography measure [14]. Because additional imaging information was incorporated, the results apply to that particular combination. Ranking the AUCs of models from separate studies would

confound differences in patient composition, outcome definitions, and predictor sets.

5.2. Changes in cancer detection accompanying biopsy avoidance

Diagnostic pathway studies can show the relationship between biopsy use and cancer detection more directly than AUC alone. Jin et al. evaluated 1,018 patients, including 378 with csPCa. The MRI-plus-PSAD pathway could avoid 302 biopsies while detecting 364 clinically significant cancers. The pathway that also incorporated f/tPSA could avoid 403 biopsies while detecting 357 clinically significant cancers [15].

Calculated from the reported counts, the three-measure pathway avoided 101 additional biopsies but detected seven fewer clinically significant cancers than the two-measure pathway. Adding f/tPSA therefore changed patient allocation, with reduced biopsy use accompanied by a loss in detection. Both outcomes are necessary to interpret the result. Net benefit was broadly comparable across the MRI-based combinations evaluated, and the study population was not restricted to the conventional PSA gray zone. The findings consequently do not establish which pathway should be preferred in men aged ≥ 60 years with PSA levels of 4–10 ng/mL.

Neither "f/tPSA adds no value" nor "the three-measure combination is better" adequately describes the current evidence. The incremental value depends on the population, comparator, decision threshold, and acceptable degree of missed cancer detection.

6. Factors affecting interpretation of combined diagnostic performance

Differences between studies begin with the diagnostic outcome. Any prostate cancer and csPCa are not interchangeable endpoints. Even studies reporting csPCa may use different definitions: some apply an International Society of Urological Pathology (ISUP) Grade Group threshold of ≥ 2, whereas others incorporate tumor volume or cancer core length [7,11,13]. Systematic and targeted biopsy also differ in sampling, which can affect the reference diagnosis. These features should be checked before comparing diagnostic performance.

Measurement methods are another source of variation. PSAD depends on prostate volume estimation, f/tPSA is calculated from two serum measurements, and PI-RADS assessment is influenced by image quality and interpretation [1,3]. Data used for combined modeling should, where possible, correspond to the same diagnostic episode, with relevant investigations and medication use recorded. For example, a study of finasteride observed a reduction in tPSA without a significant change in percent-free PSA [16]. A change in tPSA alone therefore does not establish that f/tPSA changes in the same direction.

PSAD and f/tPSA are separate predictors, but both calculations involve tPSA. They should not be assumed to be statistically independent. Model development should examine their relationship and the stability of coefficients after the additional predictor is introduced. A statistically significant regression coefficient does not necessarily mean that prediction has improved enough to alter clinical management.

AUC describes discrimination, whereas calibration assesses agreement between predicted probabilities and observed outcomes. NRI and integrated discrimination improvement (IDI) can provide additional descriptions of change, but their interpretation depends on how they are calculated and the evaluation settings. Neither establishes clinical value on its own [17]. Reporting model development, missing-data handling, and validation in accordance with TRIPOD + AI can help readers assess the reliability and applicability of the findings [18].

7. Research priorities in men aged ≥ 60 years with PSA levels in the gray zone

Existing evidence provides a rationale for investigating the incremental value of f/tPSA in men aged ≥ 60 years with tPSA levels of 4–10 ng/mL. A direct approach would use PI-RADS and PSAD in a baseline model and then add f/tPSA to construct an extended model. Both models should use the same patients, outcome definition, and validation data. If other clinical predictors are included, they should be handled consistently so that the comparison isolates the contribution of f/tPSA.

Results should be presented in terms that correspond to biopsy decisions. At a similar sensitivity for csPCa, how many additional biopsies could the extended model avoid? Alternatively, at a similar biopsy rate, could it detect more clinically significant cancers? These comparisons are more informative for clinical use than reporting a high AUC for the three-variable model alone.

Patients with negative MRI findings or PI-RADS 3 lesions are relevant groups for further analysis, provided that sample size and the number of outcome events are sufficient. An improvement in overall model performance should also be examined to determine whether the benefit is concentrated within a particular PI-RADS category. A result confined to one subgroup should not be generalized to all patients.

Study design must distinguish retrospective estimates from actual clinical implementation. Calculating the number of potentially avoidable biopsies from historical biopsy results represents a simulated decision within an existing cohort. Whether patients whose biopsies are deferred subsequently experience delayed cancer detection requires follow-up data. Guidelines allow biopsy omission to be considered in selected low-risk patients while retaining a requirement for monitoring [1]. Subsequent research should therefore assess outcomes among patients who defer biopsy, alongside model validation.

8. Conclusions

Evidence supports combining PI-RADS and PSAD to improve risk stratification in patients with PSA levels in the gray zone. The f/tPSA ratio has shown diagnostic value in some age groups and MRI-defined populations, but consistent direct evidence for its contribution beyond PI-RADS and PSAD remains limited. In men aged ≥ 60 years with gray-zone PSA levels, the relevant question is how adding f/tPSA changes risk estimates and biopsy decisions. Evaluation should consider discrimination and calibration together with biopsies avoided and clinically significant cancers missed to establish the clinical value of the three-variable approach.

Disclosure statement

The author declares no conflict of interest.

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