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Research Article

Negative magnetic resonance imaging cannot be used to omit an initial prostate biopsy - An ambispective study

Kevin Arulraj^a, Sanjay Sharma^b, Chandan J. Das^b, Amllesh Seth^a, Rajeev Kumar^{a,*}^a Departments of Urology, All India Institute of Medical Sciences, New Delhi, India^b Radiodiagnosis and Interventional Radiology, All India Institute of Medical Sciences, New Delhi, India

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ABSTRACT

Introduction: Up to 40% of patients with suspected prostate cancer (PCa) have a negative prebiopsy magnetic resonance imaging (nmMRI), and up to 15% of them may have clinically significant PCa (csPCa). The ability to predict the presence of csPCa despite nmMRI may help avoid unnecessary biopsies. We aimed to determine the negative predictive value (NPV) of mpMRI, the influence of MRI reporting patterns in clinical practice, and the factors that might predict csPCa among men with an nmMRI.

Methodology: In an IRB-approved, ambispective study, men who underwent prostate biopsy from 2016 to 2023 and had a prebiopsy MRI, were included to determine the presence of csPCa. The reporting patterns of institutional and noninstitutional MRI were evaluated. Age, digital rectal examination (DRE) findings, prostate specific antigen (PSA), PSA density (PSAD), and MRI reports were evaluated for their ability to predict csPCa in men with nmMRI.

Results: 1660 patients who underwent prostate biopsy were assessed for eligibility, and 685 patients were enrolled in the study. The median age, PSA and PSAD were 60 years, 11.63 ng/ml and 0.23 ng/ml/cm³, respectively. 62 (9%) men had an nmMRI, among which csPCa, non-csPCa, and negative biopsy were found in 34%, 5%, and 61% of men, respectively. 61% had an institutional MRI, while 39% had a noninstitutional MRI. The sensitivity and NPV of any MRI for csPCa were 93% and 66%, respectively, which improved to 96% and 81% for institutional MRI. Univariate and multivariate analyses showed abnormal DRE and PSAD ≥ 0.25 ng/ml/cc as predictive factors for csPCa in men with an nmMRI.

Conclusion: 34% of men with negative MRIs were found to harbor csPCa on prostate biopsy. The NPV of institutional MRI was higher than for noninstitutional MRI. Men with an abnormal DRE or PSAD ≥ 0.25 ng/ml/cc had a higher incidence of csPCa despite an nmMRI.

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1. Introduction

Prostate specific antigen (PSA)-based screening is the most widely used method to identify patients who need a prostate biopsy for the detection of prostate cancer (PCa). However, this is associated with over-detection, and prostate biopsies are associated with infectious complications requiring hospitalization in up to 6.3% of men.¹ Multi-parametric magnetic resonance imaging (mpMRI) is a valuable additional tool in selecting men for a prostate biopsy.^{2–4} Current guidelines recommend performing an mpMRI prior to biopsy when there is a suspicion of localized prostate cancer, and when mpMRI is positive, a targeted biopsy (TB) along with the standard systematic biopsy (SB) is recommended.^{5–8}

Although mpMRI improves the detection of csPCa and limits over-detection, there is a risk of missing csPCa. Multiple factors influence the sensitivity and specificity of mpMRI, and there is a wide variation in reporting among different centers.⁵ In addition, there is high inter-observer variability in the reporting of mpMRI with a concordance rate of only 50% for Prostate Imaging Reporting and Data System (PIRADS) 4 lesions.⁶

About 20% to 40% of patients with suspected PCa have a negative prebiopsy MRI (nmMRI), and these men may defer a primary biopsy.^{2,3,7} In a recent meta-analysis, the negative predictive value (NPV) of mpMRI has been found to be 85% to 95%.⁹ Hence, there is a risk of missing 15% of csPCa when biopsy is avoided in patients with an nmMRI, and omission of biopsy in men with nmMRI is still debated.^{10,11} Considering the widespread availability of MRI and the variability in expertise of reporting prostate MRI, it becomes important to evaluate whether it is safe to omit biopsies in men with elevated prostate-specific antigen (PSA) but an nmMRI.

* Corresponding author. All India Institute of Medical Sciences, New Delhi, India.
E-mail address: rajeev.urology@aiims.edu (R. Kumar).

The ability to predict which men are likely to harbour csPCa despite an nMRI would help in deciding which patient should be biopsied despite an nMRI. A PSA density (PSAD) of more than 0.15 ng/ml/cc can help predict the presence of csPCa in patients with nMRI.¹² This is particularly relevant in the Indian subcontinent, where PCa detection rates are lower (25%) than in the western population (36%).¹³

We therefore aimed to find the NPV of mpMRI for csPCa in Indian men, the MRI reporting patterns in clinical practice, and the factors that predict the presence of csPCa among men with an nMRI.

2. Materials and methods

We conducted an ambispective study of all patients who underwent prostate biopsy from January 2016 to July 2023 in our department. Institutional ethics committee approval was obtained prior to the study (IECPG-485/25.08.2021). The retrospective arm included men who underwent prostate biopsy from January 2016 to July 2021. The prospective arm included men who underwent a prostate biopsy from July 2021 to July 2023. All patients who underwent biopsy for suspected prostate cancer (PSA >4 ng/ml and/or abnormal digital rectal examination, DRE) and had a prebiopsy mpMRI were included after obtaining written and informed consent to participate in the study. We excluded patients with a history of previous biopsy, prior history of PCa, prior surgical treatment for benign prostatic hyperplasia (BPH), or variant histology of PCa on biopsy. Patients with inadequate MRI data were also excluded from the study. In the retrospective arm, MRI reports of patients were collected through the institute picture archiving and communication system (PACS) database. Institutional MRI scans were done with a 1.5 or 3 Tesla system and were reported by one of two urologists with experience in prostate MRI reporting. Scans done outside our center and not available in the hospital PACS were retrieved by contacting the patients telephonically, and the PIRADS score mentioned in those reports was collected. No scans were re-evaluated or re-reported for the purpose of the study.

All scans were assessed for their adequacy in reporting and adherence to PIRADS version 1 or 2. Histopathology reports of prostate biopsies were retrieved from the institute's histopathology database. Parameters such as the Gleason score, Gleason grade group, number of cores involved, and percentage of cores involved were collected from biopsy reports. Histopathological examination (HPE) was classified as benign, nonclinically significant PCa (non-csPCa), and clinically significant PCa (csPCa) as per the Epstein criteria.¹⁴ MRI reports were classified as positive for cancer (PIRADS 3-5 on report or reported as suspicious for malignancy without a PIRADS scoring) or negative for cancer (all other reports, PIRADS 1-2). Age, PSA, prostate volume on MRI, PSAD, DRE findings, and biopsy type (SB or TB) were collected from the records. In patients who underwent TB, two additional cores were sampled for each target lesion along with SB.¹⁵ In the prospective arm, all the data as mentioned above were prospectively recorded. No study-specific extra investigations were performed.

The primary outcome was the incidence of csPCa in biopsy-naïve men with nMRI. The secondary outcomes were to identify predictors of risk for csPCa in men with an nMRI and to assess the MRI reporting patterns in prostate cancer (institutional vs noninstitutional). All patient data were collected through a data collection proforma. The data were processed using SATA, version 14.0 software (Satacorp, College Station, Texas, USA). Categorical variables were expressed as numbers and percentages. Quantitative variables were expressed as means \pm standard deviations.

3. Results

A total of 1660 patients underwent transrectal ultrasound guided (TRUS) biopsy for suspected PCa between January 2016 and July 2023. Thirty-eight patients who had undergone a repeat biopsy were excluded from analysis. PCa was reported in 1079 (66%) out of 1622 patients who underwent primary biopsy.

MRI data were available for 685 patients (42%) out of the 1622 who underwent a primary biopsy (Fig. 1). All the available MRIs were reported with PIRADS v2.1 or older. The clinical characteristics of these 685 patients are given in Table 1. Sixty-two patients (9%) had an nMRI. Among these, PCa was reported on biopsy in 24 patients (39%), of whom 21 had csPCa (34%). MRI was positive for cancer in 623 patients (91%), among which 303 (49%) patients had csPCa (Table 2).

Of the 685 patients, institutional MRI was performed and retrieved from the PACS in 420 patients. 265 patients had noninstitutional MRI reports. The overall incidence of csPCa among men with nMRI was 34%. In patients who had an institutional MRI, nMRI was reported in 37 (9%) patients, and 7 (19%) of them had csPCa. Among the patients with noninstitutional MRI, 25 (9%) patients had an nMRI, and 14 (56%) of them had csPCa (Table 2, Fig. 2).

The overall sensitivity and specificity of MRI in detecting csPCa were 93.5% (95% CI 90%–95%) and 11.4% (95% CI 8.4%–14.9%), respectively, with an NPV of 66.1% (95% CI 54%–77%). The sensitivity, specificity, and NPV of institutional MRI for csPCa were 96.2% (95% CI 92%–98%), 12.8% (95% CI 8%–17%) and 81.1% (95% CI 66%–91%), respectively. The sensitivity, specificity, and NPV of noninstitutional MRI for csPCa was 89% (95% CI 84%–94%), 8.7% (95% CI 4.6%–14%) and 44% (95% CI 25%–63%), respectively.

Among the patients with an nMRI (Table 3), patients with biopsy-positive csPCa had a significantly higher PSA (21.6 ± 2.3 ng/ml vs 9.7 ± 5.4 ng/ml, $P = 0.046$), a higher number of patients with suspicious DRE (hard prostate: $P = 0.004$; presence of a nodule: $P < 0.001$), and were more likely to have had a noninstitutional MRI scan ($P = 0.003$). The prostate volume was significantly lower in patients with csPCa (39 ± 17.7 ml vs 65 ± 29 ml, $P < 0.001$). Consequently, the PSA density was higher in the csPCa group compared to the biopsy-negative cohort (0.61 ± 0.7 vs 0.19 ± 0.23 , $P < 0.001$). The type of biopsy (systematic vs fusion) and DRE grade were comparable between the two groups.

The ability of PSAD to predict patients who had an nMRI was analysed. The area under curve (AUC) in the receiver operator characteristics (ROC) analysis was 82% (95% CI 71%–93%). The optimal threshold of PSAD for the diagnosis of csPCa was ≥ 0.25 ng/ml/cc (Youden's index). The sensitivity, specificity and NPV for a PSAD ≥ 0.25 ng/ml/cc in predicting csPCa were 76% (95% CI 52%–91%), 82% (95% CI 67%–92%), and 87% (95% CI 87%–72%), respectively. Similarly, a PSAD ≥ 0.25 ng/ml/cc was found to predict csPCa in the overall cohort of patients who had an MRI prior to biopsy with sensitivity and specificity of 78%, and 74%, respectively (AUC 0.83).

Age, serum PSA, DRE findings (grade, consistency, and presence of nodules), prostate volume, and PSAD were analysed for the prediction of csPCa in the nMRI cohort. At univariate analyses, hard prostate on DRE (OR 2.8, 1.4–5.5, $P = 0.003$), presence of a nodule on DRE (OR 3.9, 1.7–8.7, $P = 0.001$), higher PSA (OR 1.01, 1.01–1.02, $P < 0.001$), and PSAD (OR 5.4, 2.2–12.8, < 0.0001) were significantly associated with csPCa in biopsy-naïve patients with an nMRI. At multivariate analysis, Grade 1 prostatomegaly on DRE (OR 3.5, 1.12–10.9, $P = 0.03$), presence of nodules on DRE (OR 2.3, 1 – 5.4, $P = 0.043$), and PSAD ≥ 0.25 ng/ml/cc (OR 3.8, 1.5–9.7, $P = 0.005$) were found to be significant predictors for csPCa.

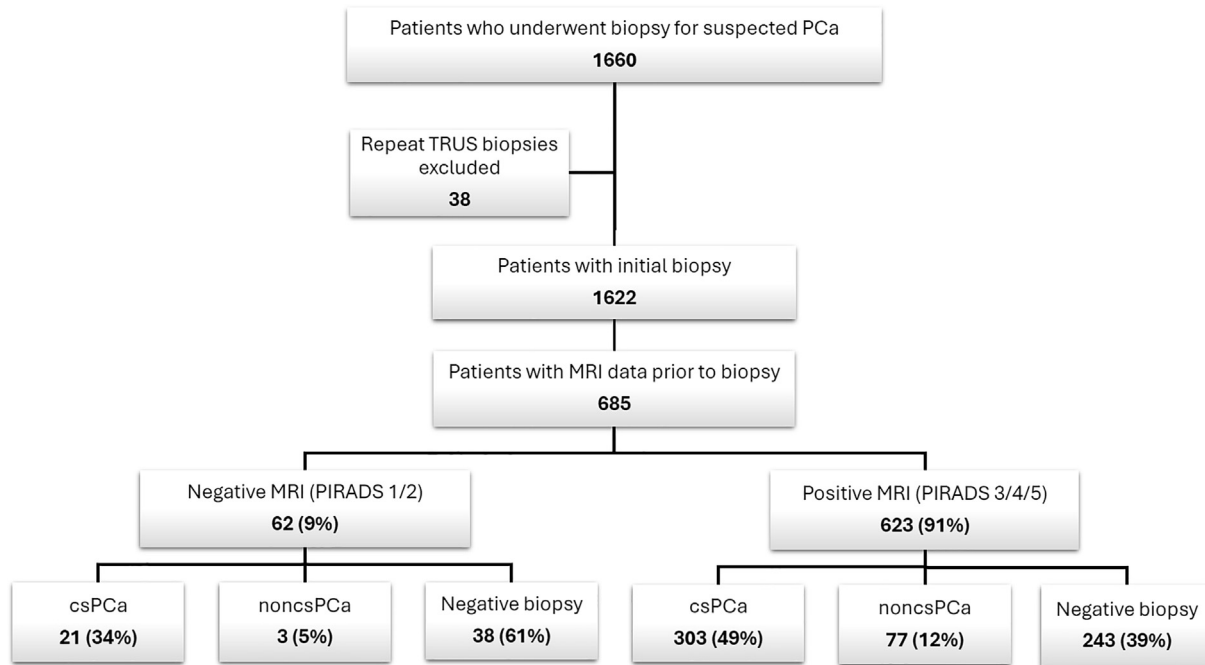


Figure 1. Patient inclusion and exclusion chart with HPE results. HPE, histopathological examination.

Table 1
Characteristics of patients with available prebiopsy MRI ($n = 685$)

Variable	Value
Median age (IQR)	60 (56–62)
Median PSA, ng/ml (IQR)	11.6 (7.17–11.63)
Median prostate volume, ml (IQR)	37 (28–48)
Median PSA density, ng/ml/cc (IQR)	0.23 (0.13–0.45)
csPCa, n (%)	324 (47)
ISUP grade distribution, (n)	
GG2	75
GG3	65
GG4	124
GG5	59
Non-csPCa, n (%)	80 (12)
Benign, n (%)	281 (41)
MRI type, n (%)	
Institutional	420 (61)
Noninstitutional	265 (39)

csPCa, clinically significant prostate cancer; IQR, interquartile range; ISUP, International Society of Uro pathology; MRI, magnetic resonance imaging; PSA, prostate specific antigen; GG, Gleason grade group.

Table 2
MRI reporting patterns and biopsy outcomes

MRI reporting pattern	noncsPCa, n (%)	csPCa, n (%)	Benign, n (%)
Overall, $n = 685$			
Negative MRI, $n = 62$	3 (5)	21 (34)	38 (61)
Positive MRI, $n = 623$	77 (12)	303 (49)	243 (39)
Institutional MRI, $n = 420$			
Negative MRI, $n = 37$	1 (3)	7 (19)	29 (78)
Positive MRI, $n = 383$	48 (12)	178 (47)	157 (41)
Noninstitutional MRI, $n = 265$			
Negative MRI, $n = 25$	2 (8)	14 (56)	9 (36)
Positive MRI, $n = 240$	29 (12)	125 (52)	86 (36)

csPCa, clinically significant prostate cancer; MRI, magnetic resonance imaging; noncsPCa, non clinically significant prostate cancer.

4. Discussion

Among 685 patients who had a pre biopsy MRI, an nMRI was reported in 62 patients (9%), among whom 34% had csPCa on biopsy. Thus, MRI had an overall NPV of 66% for csPCa, which improved to 81% for institutional MRI. An abnormal DRE and PSAD ≥ 0.25 ng/ml/cc predicted csPCa in men who had an nMRI.

There is significant variability in the incidence of nMRI for prostate cancer.¹⁶ Ahmed et al reported 27% nMRI at a mean PSA of 7.1 ng/m² while Leest et al had a higher proportion of 49% of patients with nMRI at a median PSA of 6.4 ng/ml.¹⁷ The median PSA in our population was 11.6 ng/ml, but the incidence of a nMRI (9%) was lower than the average incidence of 33% in the literature.¹⁶ This may be explained by a higher incidence of chronic prostatitis in Indian men who undergo TRUS biopsies.¹⁸ Prostatitis can mimic malignancy in MRI, and as a result, higher PIRADS scores are assigned to men with prostatitis.^{19,20} Men with prostatitis may have a positive MRI, despite harbouring no malignancy. Further, there was heterogeneity in the reporting of MRIs. Although institutional scans were reported by one of the two experienced radiologists, noninstitutional MRIs were reported by independent radiologists, and their experiences might vary. There can also be a defensive reporting pattern among radiologists, where a higher proportion of MRIs were reported positive to avoid missing PCa in doubtful cases.

We found that, among men with an nMRI, 34% had csPCa, 5% had noncsPCa, and 61% had benign histopathology. The incidence of csPCa in men with nMRI in our study is higher compared to the 5% to 15% reported previously in the literature.^{2,4,9} However, there are studies where a higher incidence of PCa was found in patients with an nMRI.^{21–24} Medina et al in their retrospective study, found that among men who have an nMRI, 35% showed csPCa on biopsy. The mean PSA in this group was 10.34 ng/ml (SD 9.37 ng/ml).²² Slot et al showed that in men with an nMRI, whose mean PSA was 19.6 ng/ml, 30.8% were found to have PCa.²³ Similarly, Gaziev et al reported

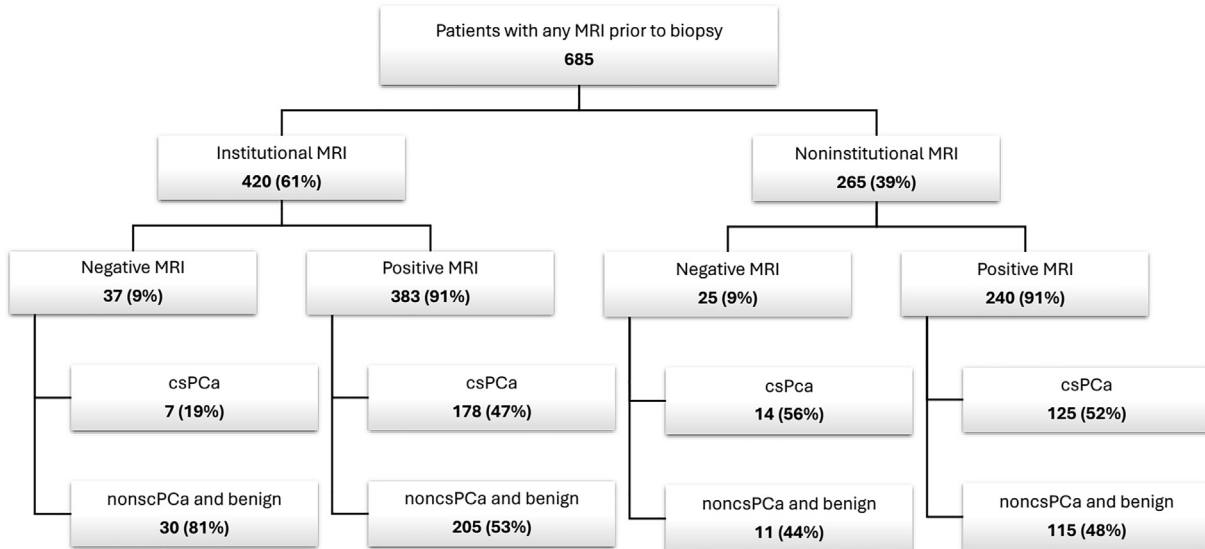


Figure 2. MRI reporting pattern with HPE results. HPE, histopathological examination; MRI, magnetic resonance imaging.

a 33% biopsy positivity rate in men with an nMRI whose mean PSA was 11 ng/ml.²⁴ Further, studies comparing MRI with post radical prostatectomy (RP) HPE have shown that MRI might miss significant csPca. Branger et al studied RP specimens in men with nMRI and found that 60% had an unfavorable pathology.²⁵ A similar rate of 60% missed Gleason 3 + 4 lesions and 21% missed Gleason 4 + 4 lesions were reported by Kim et al in men undergoing RP who had an nMRI.²⁶ Rosenkrantz et al showed that nMRI can miss a Gleason 7 or higher lesion in 36% of cases. Lee et al found that 30% of Pca lesions in prostatectomy specimens were missed by MRI.²⁷ These studies show that, despite having an nMRI, a significant proportion of men harbour csPca, which can possibly be due to interobserver variability among radiologist,²⁸ and the presence of an MRI-invisible tumor that has been shown to be associated with Black race and elevated PSA (18 ± 33 ng/ml).²⁹

We found that the incidence of csPca in nMRI varied with the pattern of MRI reporting. The proportion of men who had an nMRI was similar in institutional as well as noninstitutional scans (9%), but the incidence of csPca varied between the groups. Incidence of csPca in men with institutional nMRI was 19%, which increased to 59% in noninstitutional nMRI. This discordance can be explained with the high interobserver variability in MRI reporting, quality of scans, and radiologist experience. Li et al reported a concordance rate of only 60% between noninstitutional MRI and re-reporting them in a tertiary care centre. They found an 18% downgrade and an 8% upgrade in the PIRADS scoring after a second read of noninstitutional MRIs.³⁰ Kohistani et al found high interobserver variability when scans are done outside high-volume centres with an average agreement of 40% for PIRADS 3 or more lesions, which improved to 51% for PIRADS 4 or more lesions.⁶ Sung et al analysed the temporal changes in PIRADS scores and correlated the results with RP specimens. They found a significant change in PIRADS reporting, including a twofold increase in PIRADS 1-3 reporting over time, which correlated with pGG \leq 2 tumors.³¹ The presence of a high interobserver variability between experienced and inexperienced radiologists can impact the csPca rates after a biopsy. Patients with an MRI where all the necessary sequences are not performed have the risk of a missed csPca. Likewise, inaccurate reporting by general radiologists who are not well versed with mpMRI reporting can result in csPca being missed. These

differences in scan results can be minimized by strict adherence to the PIRADS while reporting and, when possible, being reported by an experienced radiologist.

We found that MRI had an overall sensitivity of 93.5% in diagnosing csPca with a NPV of 66%. The reported sensitivity in our study is comparable with previous studies.^{9,11,21} However, the NPV is lower than the widely accepted range of 85 to 95%.^{9,11,21} The NPV is highly variable between previous studies, with a range of 18% to 100% according to a meta-analysis by Zhen et al and there can be multiple factors at play.²¹ First, the prevalence of csPca was 47% in this study. The disease prevalence and NPV are inversely associated. As the prevalence of Pca increases, the NPV of MRI for csPca reduces.⁹ Second, MRI reports from noninstitutional sources were also accepted in addition to institutional MRI, which could affect the overall accuracy of reporting as noninstitutional MRI reports are not standardized and are performed with different magnetic strengths different sequences, with the reporting being done by different radiologists.²¹ Moreover, the experience of radiologists reporting the noninstitutional MRIs is not known and this can affect the overall NPV.

The prostate volume was significantly lower in patients with csPca (39 ± 17.7 ml vs 65 ± 29 ml, $P < 0.001$). This is in line with the available literature that men with smaller prostates have been found to have a higher incidence of Pca.^{32,33} Patients with BPH have benign nodules which can compress and reduce the volume of the peripheral zone. However, in men with large prostates, there can be a possibility that significant cancer can be missed due to under-sampling by TRUS biopsy. We found the mean PSAD in the biopsy-negative group was 0.19 ng/ml/cc. This is higher than the traditional threshold of 0.15 ng/ml/ml. However, we also found that PSAD ≥ 0.25 ng/ml/cc had an NPV of 87% for csPca and this could be clinically useful in selecting patients with nMRIs for a biopsy. While a PSAD ≥ 0.15 ng/ml/cc is traditionally used as a cut-off for predicting Pca in men with an nMRI, Yusim et al found that a PSAD ≥ 0.2 ng/ml/cc could predict csPca.³⁴ Similarly, Raheem et al in their study of 265 patients had arrived at a PSAD threshold of 0.27 ng/ml/cc to detect csPca.³⁵ Satoshi et al had proposed a PSAD ≥ 0.3 ng/ml/cc in men with PIRADS 3 lesions to detect csPca. In Indian men, Patil et al in their retrospective study, suggested an increased PSA density cut off.¹³

Table 3
Characteristics of men with nMRI

Variable	csPCa Present	csPCa Absent	P
Number, n	21 (34)	41 (66)	0.839
Age, years (mean ± SD)	62.4 ± 8.9	62 ± 4.8	
PSA, ng/ml (mean ± SD)	21.6 ± 23	9.7 ± 5.4	0.046
DRE grade, n (%)			
1	2 (9.5)	2 (5)	0.047
2	13 (62)	23 (56)	
3	6 (28.5)	16 (39)	
Consistency, n (%)			
Firm	9 (43)	33 (80)	0.004
Hard	12 (57)	8 (20)	
Nodule, n (%)			
Absent	6 (29)	32 (78)	<0.001
Present	15 (71)	9 (22)	
MRI, n (%)			
Institute	7 (33)	30 (73)	0.003
Noninstitutional	14 (67)	11 (27)	
PV, ml (mean ± SD)	39 ± 17.7	65 ± 29	<0.001
PSA density, ng/ml/cm ³ mean ± SD	0.61 ± 0.7	0.19 ± 0.23	<0.001
Biopsy type, n (%)			
Systematic	16 (56)	30 (73)	0.817
TRUS-Fusion	5 (24)	11 (27)	
Gleason, n (%)			
GG2	6 (28.5)		
GG3	4 (19)		
GG4	9 (43)		
GG5	2 (9.5)		

csPCa, clinically significant prostate cancer; DRE, digital rectal examination; nMRI, negative magnetic resonance imaging; PSA, prostate specific antigen; PV, prostate volume; SD, standard deviation; TRUS, transrectal ultrasound guided; GG, Gleason grade group.

Our findings suggest that MRI may be a poor predictor of finding csPCa in our population. This may have a significant impact on clinical practice since an MRI is often used to decide whether to biopsy a patient or not. Particularly among noninstitutional MRIs, the possibility of finding csPCa was almost the same, irrespective of the MRI findings. Even among institutional MRIs, the 19% incidence of csPCa among nMRI would make it difficult to rely on nMRI to omit a biopsy. Indian men have higher serum PSA levels owing to the increased incidence of chronic prostatitis on biopsy, and the traditional PSA threshold value of 4 ng/ml when applied to our population can lead to unnecessary biopsies.^{18,36} Thus, our findings that abnormal DRE and higher PSAD can help subclassify men with nMRI who have a higher chance of csPCa may be of significant clinical relevance.

Our study is limited by its retrospective component, where complete information was not available for all men, and they had to be excluded from analysis. Our study did not have a follow up protocol in patients who had a negative biopsy. Follow-up of patients who had a negative biopsy despite high-risk predictors might enable us to find PCa detection rates if a repeat biopsy was performed. In clinical practice, noninstitutional MRI reports, if needed, were reviewed by radiologists in our centre. This led to the upstaging or downstaging of PIRADS scores, and patients were managed accordingly. This review process was not accounted for in our study to determine the real-world scenario of MRI reporting. Being a high-volume referral center, we were able to assess the quality of reporting from community scans compared to scans performed within our center. Nevertheless, a future multicenter study can further examine the differences in reporting between centers and make our results more applicable to a broader population. However, this is one of the largest studies on prostate biopsies, evaluating the value of a prebiopsy MRI and PSAD in Indian men.

5. Conclusions

The incidence of csPCa in Indian men with negative MRI was 34%. The NPV of MRI for csPCa was 66%, which improved to 81% for institutional MRI. Among men with nMRI, abnormal DRE and PSAD may help identify patients at higher risk for csPCa. Prostate biopsy should be considered in patients with abnormal DRE or PSAD $> / = 0.25$ ng/ml/cc, regardless of a negative MRI.

Conflicts of interest

None.

Sources of funding

None.

Abbreviations

mpMRI: Multiparametric Magnetic Resonance Imaging
 PCa: Prostate Cancer
 TB: Targeted Biopsy
 SB: Standard Biopsy
 csPCa: Clinically significant Prostate Cancer
 noncsPCa: Non clinically significant Prostate Cancer
 PSA: Prostate Specific Antigen
 DRE: Digital Rectal Examination
 DWI: Diffusion Weighted Imaging
 DCE: Dynamic Contrast Enhancement
 PIRADS: Prostate Imaging Reporting and Data System
 ESUR: European Society of Urogenital Radiology
 NPV: Negative Predictive Value
 PSAD: PSA Density
 nMRI: Negative MRI
 HPE: Histopathological Examination
 BPH: Benign Prostatic Hyperplasia
 TRUS: Trans Rectal Ultrasound
 ISUP: International Society of Uropathology
 GG: Gleason Grade Group
 PV: Prostate Volume
 AUC: Area Under Curve
 ROC: Receiver Operating Characteristic Curve

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