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DIAGNOSTIC ACCURACY OF IXIP INDEX AND PROSTATE MRI IN THE DIAGNOSIS OF PROSTATE CANCER: PRELIMINARY RESULTS ON A COMBINED APPROACH

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ABSTRACT

The purpose of this study was to assess whether Immune CompleX Predictive Index (iXip) improves diagnostic accuracy of multiparametric prostate MRI (mpMRI) for clinically significant prostate cancer. This study included 72 patients (mean age: 68±8 years) with suspicion of prostate cancer and available iXip score. mpMRI images were evaluated by two radiologists according to the PI-RADS v2.1. Reference standard was based on fusion biopsy and standard transperineal 12-point biopsy. Diagnostic accuracy of iXip, mpMRI and their combination were calculated. Optimal cutoff of iXip with sensitivity and specificity was identified using the Youden index. Patients with clinically significant prostate cancers had significantly higher iXip values compared to patients without clinically significant prostate cancers (median 0.411 vs 0.273; p=0.026). The AUROC for iXip was 0.795 (95% CI 0.579-1.000, p=0.026). Sensitivity and specificity were 75% and 100% respectively for mpMRI alone, and 100% and 80% respectively for mpMRI combined with iXip > 0.375. The combination of mpMRI with a cutoff value of iXip > 0.375 has a very high sensitivity for the diagnosis of prostate cancer and a moderately high specificity.

1. Introduction

Prostate cancer is the most common malignancy and the second leading cause of cancer-related death in men [1]. Early diagnosis of prostate cancer is crucial because 5-year survival is nearly 100% in patients with local or regional involvement while it drops to 30% in patients with metastatic disease at the time of diagnosis [2]. Prostate biopsy is the gold standard for the diagnosis of prostate cancer, but it is invasive and limited by false negative results and complications such as infection or hemorrhage [3]. Therefore, identification of reliable noninvasive laboratory and imaging biomarkers is crucial to reduce the number of unnecessary biopsies [4].

Serum prostate-specific antigen (PSA) and its derivatives (i.e. PSA velocity, PSA density, PSA ratio) are routinely used as a screening test for prostate cancer; however, a metanalysis showed that screening for prostate cancer using PSA at best leads only to a small reduction in disease-specific mortality over 10 years but does not affect overall mortality [5, 6]. Immune CompleX Predictive Index (iXip) – a combined algorithm integrating serum PSA values, PSA-IgM complexes, prostate volume and patient age – is a new, potentially noninvasive screening tool that seems to offer better diagnostic accuracy in the diagnosis of prostate cancer than every single parameter composing the index, showing a very high specificity (almost 100%) when a cutoff of 0.5 is used [7-10].

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Very few studies investigated its diagnostic accuracy, and its predictive ability towards the presence of a clinically significant prostate cancer is currently being studied in the on-going prospective PROXIMA trial [9-11]. Multiparametric prostate magnetic resonance imaging (mpMRI) and Prostate Imaging Reporting and Data System (PI-RADS) are now routinely in the diagnostic pathway for identification of prostate cancer and demonstrate a sensitivity of 82%, with a detection rate that increases along with higher mpMRI PI-RADS scores [12, 13]; however, specificity of mpMRI is still limited to 59% for the diagnosis of clinically significant prostate cancer [12], and therefore other MRI biomarkers (ADC values, Kurtosis, MRI texture features) have been investigated with the aim of improving diagnostic accuracy and staging [14-17].

Recently, many studies demonstrated an improved diagnostic accuracy of a combined approach using patient age, PSA, PSA density and mpMRI for the diagnosis of prostate cancer [18-23], but the results of Cuocolo et al [24] were not in favor of such a combination. Our hypothesis is that the use of iXip – that integrates four clinical and laboratory parameters – may further improve diagnostic accuracy of mpMRI for the diagnosis of prostate cancer and, to our knowledge, this hypothesis has not been investigated yet.

Therefore, the purpose of this study was to assess whether combining iXip and mpMRI could improve diagnostic accuracy in detecting and ruling out clinically significant prostate cancer in men with clinical suspicion of prostate cancer.

2. Material and methods

This dual-institution study was carried out at *blinded to reviewers* and at *blinded to reviewers*. This retrospective study was approved by the ethics committee of both structures that waived informed consent.

2.1 Study Cohort

From December 2018 to June 2019, 350 consecutive patients were referred with suspicion of prostate cancer (i.e. elevated PSA level > 4 ng/mL, high PSA kinetic, or abnormal digital rectal examination) or follow-up of prostate lesions. The following exclusion criteria were considered for this study: *i*) history of radical prostatectomy (n = 67); *ii*) history of transurethral resection of the prostate (TURP) (n = 92); *iii*) patient undergoing radiotherapy and/or hormone therapy (n = 81); *iv*) concomitant neoplasms, autoimmune diseases or active infections (n = 18). As per our standard protocol, iXip index was calculated in all patients, while mpMRI and biopsy were performed if clinically indicated based on iXip index and mpMRI results, respectively.

2.2 iXip index

iXip index was calculated based on: i) serological values of PSA in ng/ml (Hybritech Access test with UniCel DxI800® system, Beckman Coulter, Brea, CA, USA); ii) serological levels of PSA-IgM from blood sampling; iii) prostate volume measured with TRUS; iv) patient age in years.

PSA-IgM was performed before any prostatic manipulation, to avoid possible transitory changes in the biomarkers, and it was analyzed with semi-automatic instrumentation (ELISA kit Prostate-IC® XG007, Xeptagen).

TRUS were performed using an Esaote ultrasound equipment (Mylab TwiceTM ClassC, Genoa, Italy) with biplan transrectal probe (mod. TRT33) with a frequency of 3.0 / 13.0 MHz. Since the prostate is considered ellipsoid, the estimate volume (mL) was calculated using the following formula: 0.523 × width (cm) × length (cm) × height (cm) [25].

The iXip values were calculated using the dedicated online calculator (http://iXip.xeptagen.com) which provides a numerical value ranging from 0 to 1. Within this range, patients are classified into five risk groups, as follows: 1) no risk if iXip < 0.2; 2) low risk for iXip 0.2 - 0.3; 3) intermediate risk for iXip 0.3 - 0.5; 4) high risk for iXip 0.5 - 0.8; 5) very high risk if iXip ≥ 0.8 [7, 10, 11].

2.3 MRI examinations

All MRIs examinations were performed in accordance with PI-RADS version 2.1 [13], with a 1.5-T MRI scanner (Achieva, Philips Medical Systems, Eindhoven, the Netherlands) equipped with a surface phased array coil (16 channel HD Torso XL), and using the same protocol in all patients (Table 1). Before each examination, 20 mg of butylscopolamine (Buscopan®, Boehringer-Ingelheim, Ingelheim, Germany) were administered intravenously to reduce bowel peristalsis. The imaging protocol includes axial turbo-spin echo (TSE) T1-weighted sequence, axial, sagittal and coronal TSE T2-weighted sequences, oriented according to the major axis of the prostate, diffusion weighted images (DWI) performed through the acquisition of single-shot ecoplanar sequences (EPI) with a maximum b value of 1400 s/mm2. Perfusion imaging was performed after intravenous administration of gadolinium-based contrast agent, 1 mmol/kg of Gadoteric acid (Gd-DOTA, Dotarem®, Guerbet, USA) at a flow of 3 ml/sec followed by infusion of 30 ml of saline solution. Post-contrast images were acquired using 3D T1-weighed axial sequences.

2.4 MRI Analysis

Multiparametric MRI examinations were reviewed in consensus by two radiologists (with 10 and 4 years of experience in prostate imaging) on a picture archiving and communication system station (PACS - Impax, Agfa-Gevaert, Mortsel, Belgium). The readers were blinded to the iXip results or any other clinical information of the included patients. For each subject, the readers documented the presence of prostate lesions and they classified them following the PI-RADS v2.1 [13].

Parameters	T1w TSE	T2w TSE	DWI
TR (ms)	552	3091	3808
TE (ms)	12	100	58
FA (degrees)	90	90	90
Slice Thickness (mm)	5	3	4
Reconstruction Interval (mm)	0.5	0.3	0.4
Acquisition Matrix	448 × 358	256 x 215	112 × 62
Signal Averages	1	3	6
Signal-to-noise ratio	1	1	1

Table 1. MRI acquisition parameters. (Abbreviations: TSE: Turbo-Spin Echo; DWI: Diffusion Weighted Images, TR: Repetition Time, TE: Echo Time, FA: Flip Angle.

2.5 Reference standard

Reference standard was based on fusion biopsy obtained with Esaote MyLab Twice system®, (Esaote, Genoa, Italy), followed, in the same session, by a standard transperineal 12-point biopsy.

All biopsy samples were histologically analyzed by an experienced pathologist (with 15 years of experience) following the ISUP (International Society of Urological Pathology) recommendations and the lesions were Gleason-graded accordingly [23]. The diagnosis of clinically significant prostate cancer was made if Gleason score was ≥ 7.

2.6 Statistical analysis

Data were summarized as continuous variables and were expressed as mean and standard deviation (SD) or median and interquartile range (IQR), depending on the normality distribution. Categorical variables were expressed as numbers and percentages.

The Mann-Whitney U test was used to compare the iXiP values between patients with clinically significant (Gleason Score ≥ 7) and non-clinically significant (Gleason score ≤ 6) prostate cancer. Area under the receiver operating characteristics curve with 95% confidence intervals (AUROC; with 95% CI) and optimal cutoff values based on the Youden index with sensitivity and specificity were calculated to assess the diagnostic performance of iXip for the diagnosis of clinically significant prostate cancer. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence intervals (95% CI) of iXip, mpMRI (PI-RADS score ≥ 4) and combination iXip and MRI were calculated for the diagnosis of clinically significant prostate cancer. Statistical significance level was set at $p < 0.05$. Statistical analysis was conducted using SPSS software (Version 20.0. Armonk, NY, USA: IBM Corp) and MedCalc Statistical Software (version 14.8 Ostend, Belgium).

3.Results

3.1 Study Cohort

Seventy-two patients (mean age 67 ± 8 years, range 51 - 88 years) were included in this study; of these, 46 (64%) were submitted to mpMRI, and 40 (56%) to target lesion biopsy after mpMRI (Table 2).

Characteristics	
Age (years), mean ± SD (range)	67 ± 8 (51 - 88)
iXip, n (%)	72
Median (IQR)	0.313 (0.326 - 0.415)
iXip < 0.2	6 (8%)
iXip = 0.2 - 0.3	26 (36%)
iXip = 0.3 - 0.5	26 (36%)
iXip = 0.5 - 0.8	12 (17%)
iXip = ≥ 0.8	2 (3%)
mpMRI with PI-RADS classification, n (%)	46
No lesions, PI-RADS 1, PI-RADS 2	24 (52%)
PI-RADS 3	10 (22%)
PI-RADS 4	8 (17%)
PI-RADS 5	4 (9%)
Histopathological diagnosis, n (%)	40
No prostate cancer or Gleason score ≤ 6	20 (50%)
Gleason score 7 prostate cancer	14 (35%)
Gleason score 8 prostate cancer	6 (15%)

Table 2. Characteristics of the study cohort.

MpMRI relieved no prostate lesion, very low (PI-RADS 1) or low (PI-RADS 2) risk lesions in 24 (52%), PI-RADS 3 lesions in 10 (22%), PI-RADS 4 lesions in 8 (17%) (Figure 1), and PI-RADS 5 lesions in 4 (9%) patients.

Histopathological diagnosis at target biopsy included no prostate cancer or Gleason score ≤ 6 in 20 (50%) cases. Clinically significant prostate cancer was found at pathology in the remaining 20 (50%) patients, including 14 (35%) Gleason score 7 and 6 (15%) Gleason score 8.

3.2 Diagnostic performance of iXip

The median iXip in the overall population was 0.313 (IQR 0.326 - 0.415). Patients with clinically significant prostate cancers had significantly higher iXip values (median 0.411; IQR 0.372 - 0.576) compared to patients without clinically significant prostate cancers (median 0.273; IQR 0.233 - 0.439; $p = 0.026$). The ROC curve using iXip values as independent variable and the presence of clinically significant prostate cancer as dependent variable provided an area under the ROC curve of 0.795 (95% CI 0.579 - 1.000, $p = 0.026$) for the diagnosis of clinically significant prostate cancer (Figure 2). A iXip value > 0.375 demonstrated a sensitivity of 80% and a specificity of 80% for the diagnosis of clinically significant prostate cancer.

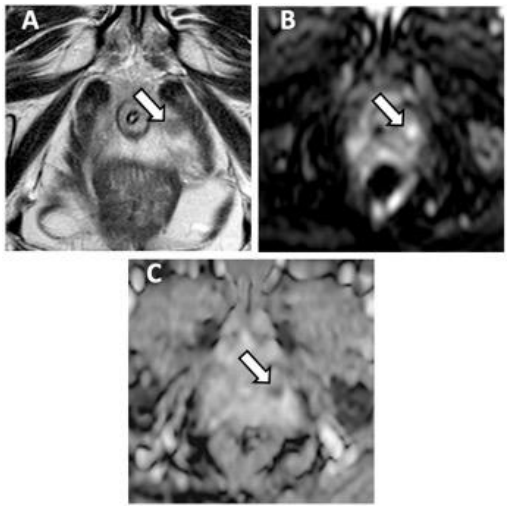

Figure 1. 74-year-old patient with iXip 0.750. Axial T2-weighted image (A) shows a homogeneous hypointense area in the left peripheral zone at the apex of the prostate with high signal on DWI at high b-value (B) and low ADC (C). This area was categorized as PI-RADS 4. A Gleason 7 (4 + 3) adenocarcinoma was found on fusion biopsy.

3.3 Diagnostic accuracy of mpMRI and iXip

Diagnostic accuracy of iXip, mpMRI and combined mpMRI with iXip is reported in Table 3. When using the cutoff of iXip ≥ 0.5 (high risk patients), sensitivity and specificity for the diagnosis of clinically significant prostate cancer were 30.0% (95% CI 8.0% - 64.6%) and 80.0% (95% CI 44.2% - 96.4%), respectively. Using a iXip cut off of 0.375 the sensitivity increased to 80% (95% CI 44.2% - 96.4%) with identical specificity (80.0%; 95% CI 44.2% - 96.4%).

The presence of PI-RADS 4 or PI-RADS 5 lesion on mpMRI had a sensitivity of 75.0% (95% CI 35.5% - 95.5%) and a specificity of 100% (95% CI 56.0% - 100%) for the diagnosis of clinically significant prostate cancer. When combining mpMRI with iXip value ≥ 0.5 the sensitivity increased to 85.7% (95% CI 46.6% - 99.3%), while the specificity decreased to 71.4% (95% CI 30.2% - 94.8%).

When combining mpMRI with iXip index > 0.375, there was a 100% (95% CI 59.7% - 100%) sensitivity (Figure 3), while the specificity was 80.0% (95% CI 44.2% - 96.4%).

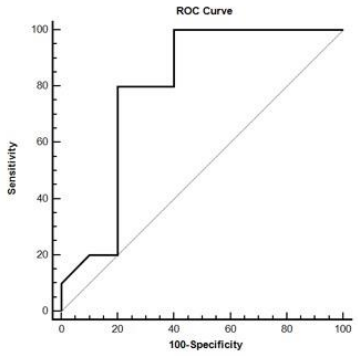

Figure 2. ROC curve for iXip index for the diagnosis of clinically significant prostate cancer (GS ≥ 7).

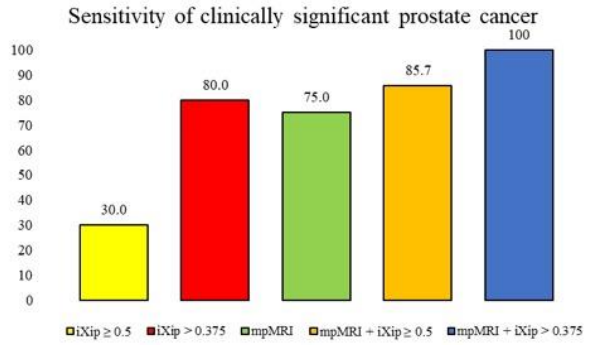

Figure 3. Graph showing sensitivity for the diagnosis of clinically significant prostate cancer (GS ≥ 7) of iXip ≥ 0.5, iXip > 0.375, mpMRI, mpMRI + iXip ≥ 0.5, mpMRI + iXip > 0.375.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
iXip ≥ 0.5	30.0 (8.0-64.6)	80.0 (44.2-96.4)	60.0 (17.0-92.7)	53.3 (27.4-77.7)
iXip > 0.375	80.0 (44.2-96.4)	80.0 (44.2-96.4)	80.0 (44.2-96.4)	80.0 (44.2-96.4)
mpMRI	75.0 (35.5-95.5)	100 (56.0-100)	100 (51.1-100)	77.7 (40.1-96.0)
mpMRI + iXip ≥ 0.5	85.7 (46.6-99.3)	71.4 (30.2-94.8)	77.7 (40.1-96.0)	83.3 (36.5-99.1)
mpMRI + iXip > 0.375	100 (59.7-100)	80.0 (44.2-96.4)	80.0 (44.2-96.4)	100 (59.7-100)

Table 3. Diagnostic performance of iXip index (≥ 0.5), multiparametric prostate MRI (PI-RADS ≥ 4) and combined iXip and multiparametric prostate MRI for the diagnosis of clinically significant prostate cancer (GS ≥ 7) with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with 95% confidence intervals (95% CI). Data are expressed as percentages, data in parenthesis are 95% confidence interval (CI). (Abbreviations: PPV: positive predictive value, NPV: negative predictive value).

4. Discussion and conclusions

This study investigates the diagnostic accuracy of iXip and mpMRI alone and in combination for the identification of patients with high probability of prostate cancer. Prior studies explored the combination of mpMRI with clinical and laboratory parameters such as PSA or PSA density [18-24], with the majority of them reporting an improvement in sensitivity and specificity compared to mpMRI alone. In agreement with prior evidences [27, 28], our results showed a sensitivity and specificity of mpMRI of 75% and 100%, respectively, for the diagnosis of clinically significant prostate cancers. To the best of our knowledge, this is the first study demonstrating that a combined approach using iXip and mpMRI improves the diagnostic accuracy in detecting and ruling out clinically significant prostate cancer in men with clinical suspicion of prostate cancer, as compared to mpMRI alone. Indeed, when integrating a cutoff of iXip index ≥ 0.5 with mpMRI results, sensitivity increased to 85.7%, with similar specificity (71.4%). Interestingly, the combination of mpMRI and a cutoff of iXip index > 0.375 maximized the sensitivity for the diagnosis of clinically significant prostate cancer to 100%, with a moderately high specificity (80%). Our preliminary results show that
a combined mpMRI and iXip approach can help to better stratify patients into those who should undergo biopsy and those who should not, as compared to mpMRI alone.

In agreement with the experience of Gallotta et al [8], our results demonstrated that patients with clinically significant prostate cancer have significantly higher iXip values (median 0.411) compared to patients without clinically significant prostate cancer (median 0.273; $p = 0.026$). iXip was recently developed as an innovative and promising tool based on the evaluation of PSA level, PSA-IgM dosage, prostate volume and patient's age [8-11]. According to prior evidences, patients with iXip values < 0.2 may avoid biopsy due to the high negative predictive value of iXip, while biopsy is strongly recommended for patients with iXip > 0.5 [8-11]. Similar to prior evidences [8, 10], in our study iXip demonstrated a fair diagnostic performance (AUROC 0.795, $p = 0.026$) for the diagnosis of clinically significant prostate cancer and none of the patients with iXip < 0.2 had prostate cancer at biopsy; therefore, iXip should be considered as a potential screening test in the general population for the identification of patients at high risk of clinically significant prostate cancer and to reduce the number of repeated biopsy in patients with previously negative biopsy.

Based on prior studies, a iXip value ≥ 0.5 is considered at high probability of having a prostate cancer [7-10]; in our study, this cutoff showed a sensitivity of 30% and specificity of 80% for the diagnosis of clinically significant prostate cancer. According to our preliminary results, the optimal iXip cutoff value calculated using the Youden index should be 0.375, with iXip values higher than 0.375 demonstrating a sensitivity of 80% and a specificity of 80% for the diagnosis of clinically significant prostate cancer.

This retrospective study has several limitations that need to be acknowledged. The main limitation is represented by the small study cohort. Moreover, we did not assess the accuracy of a combined approach of mpMRI with other noninvasive parameters such as PSA or PSA density alone. Nevertheless, this is the preliminary evidence exploring the integration of iXip with mpMRI in the detection of clinically significant prostate cancers.

Further multicenter studies with a larger population are needed to strengthen our results.

In conclusion, iXip score has a fair diagnostic performance for the diagnosis of clinically significant prostate cancer. The combination of mpMRI and iXip improves the diagnostic accuracy in detecting and ruling out clinically significant prostate cancer in men with clinical suspicion of prostate cancer, as compared to mpMRI.

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