

JMS

Journal of Morphological Sciences

Journal of Morphological Sciences

Current Archives About

Current Issue

Vol 6 No 3 (2023): JMS



ISSN 2545-4706

<https://doi.org/10.55302/JMS>

<https://doi.org/10.55302/JMS2363>

Published: 2023-12-27

Articles

LOCALLY-ADVANCED BREAST CANCER IN A MALE PATIENT: A CASE REPORT

Nedjati Jakupi, Stojan Velkov, Despot Despotovski, Ljubica Atanasova

1-3



OUR EXPERIENCE WITH INVASIVE SKIN CARCINOMA OF THE SKULL TREATED WITH A ROTATIONAL FLAP

Ana Tomevska, Mikjun Mikjunovikj, Zoran Bitrakov, Biljana Trajanoska, Slavco Ivanoski, Ana Trimoska Radeska, Emilija Mikjunovikj, Ace Dodevski

4-9



THE INFLUENCE OF ACUTE DECOMPENSATION ON ONE-YEAR SURVIVAL AND MORTALITY IN PATIENTS WITH LIVER CIRRHOSIS

Elena Curakova Ristovska, Magdalena Genadieva-Dimitrova, Beti Todorovska, Kalina Grivceva Stardelova, Ivan Rankovich, Vladimir Milivojevich, Ante Bogut, Georgi Janevski

10-20



NEPHROPROTECTIV EFFECTS OF CANDESARTAN ON DIABETIC NEPHROPATHY IN RATS

Jasmina Trojancanec, Kristina Pavlovska, Kalina Gjorgjievska, Nikola Kolovchevski, Emilija Shikole, Bojan Labachevski, Aleksandar Nikodinovski, Igor Kikerkov, Dimche Zafirov 21-33

 PDF

ACUTE MESENTERIC VENOSUS THROMBOSIS IN A PREGNANT WOMAN

Aleksandra Eftimova, Ana Kocevaska, Anamarija Shpisikj Pushevaska, Jasmina Chelebieva 34-38

 PDF

OBESITY AS A RISK FACTOR FOR ENDOMETRIAL PATHOLOGICAL CHANGES

Ana Kocevaska, Anamarija Shpisikj Pushevaska, Zoran Ilievski, Aleksandra Eftimova Kitanova, Kristina Skeparovska 39-45

 PDF

COMPARISON OF THE VALUES OF EFT (External Fixation Time) IN THE TREATMENT OF LOWER LEG OPEN FRACTURES AND NON-UNIONS WITH THE METHOD OF COMPRESSION-DISTRACTION OSTEOSYNTHESIS BY ILIZAROV

Ognen Sheshoski, Slavcho Stojmenski, Nenad Atanasov, Simon Trpeski, Petar Miloshevski 46-55

 PDF

THE ROLE OF HIGH-RESOLUTION CT IN THE DETECTION AND DIFFERENTIATION OF PULMONARY CHANGES BETWEEN UIP AND NSIP PNEUMONIA

Kristina Dimitrijevikj, Nadica Mitreska, Biljana Prgova-Veljanova, Sonja Nikolova, Milkica Pashoska 56-67

 PDF

AMYAND'S HERNIA -A RARE CASE OF RIGHT -SIDED IN INGUINAL HERNIA

Velimir Shumenkovski, Dimitar Arnaudov, Bojan Trenchikj, Svetozar Antovikj, Ljubomir Ognjenovikj, Ognen Kostovski, Goce Volchevski, Dragan Hadzi Manchev, Gjorfji Trajkovski 68-71

 PDF

CASE REPORT OF ANGELMAN SYNDROME- A CHILD WITH PATHOGENIC VARIANT c.678dup, p.(Leu227iLefster4) IN THE EXON 7 OF UBEZA GENE

Danilo Nonkulovski, Aspazija Sofijanova, Sonja Bojadzieva, Ilija Kirovski, Olivera Viktor Jordanova 72-77

 PDF

BIODISTRIBUTION STUDY OF 188Re-HEDP AS A RADIOPHARMACEUTICAL FOR BONE PAIN PALLIATION

Toni Tripunoski, Domokos Mathe, Lajos Balog, Ana Ugrinska, Maja Chochevska, Sinisa Stojanoski, Nikolina Bozinovska, Nevena Manevska, Anamarija Jankulovska, Daniela Popgjorceva 78-84

 PDF

HIGH -RESOLUTION CT PULMONARY CHANGES IN PATIENTS WITH CYSTIC FIBROSIS USING BHALLA SCORE SYSTEM CORRELATED WITH CLINICAL PARAMETERS

Kristina Dimitrijevikj, Nadica Mitreska, Violeta Vasilevska-Nikodinovska

85-98

 PDF

ADRENAL GLAND TLR EXPRESSION IN ApoE DEFICIENT HOMOZYGOUS (ApoE KO-/-) MICE WITH IMPAIRED THYROID FUNCTION

Toni Tripunoski, Sasho Panov, Jasmina Dimitrova Shumkovska, Slavica Josifovska, Irena Kostadinova Petrova, Ana Ugrinska, Sinisa Stojanoski, Nevena Manevska, Verdi Stanojevic, Bojana Stoilovska Rizova, Daniela Popgjorceva

99-108

 PDF

ACADEMIC BACKGROUND OF THE PROFESSIONS ELIGIBLE FOR VOCATIONAL TRAINING IN MEDICAL BIOCHEMISTRY IN THE REPUBLIC OF NORTH MACEDONIA

Jasna Bogdanska, Katerina Tosheska Trajkovska, Sonja Topuzovska

109-119

 PDF

FINANCIAL BARRIERS AND ACCESSIBILITY OF HEALTH SERVICES AMONG PATIENTS WITH NON-COMMUNICABLE DISEASES IN URBAN AND RURAL AREAS IN THE PELAGONIAN REGION

Svetlana Popovska Kljuseva, Vesna Velikj Stefanovska, Dragan Kochinski

120-128

 PDF

INFORMED CONSENT IN GENETIC REASEARCH

Ljupco Chakar, Aleksandar Stankov, Goran Pavlovski, Natasha Bitoljanu, Viktorija Belakaposka Srpanova, Ana Ivcheva, Rosica Siamkouri, Zlatko Jakjovski

129-134

 PDF

TRAUMATIC NECK INJURIES IDENTIFIED BY CONVENTIONAL X-RAY IMAGING-AN AUTOPSY CASE REPORT

Renata Jankova, Zoran Mitrevski

135-139

 PDF

SERUM ANTI-OXLDL ANTIBODIES IN PATIENTS WITH ANGIOGRAPHICALLY CONFIRMED CORONARY ARTERY DISEASE

Katerina Tosheska-Trajkovska, Irena Kostovska, Melda Emin, Hristina Ampova, Nikola Manev, Zan Zimbakov, Coskun Kerala, Jasna Bogdanska, Sonja Topuzovska

140-147

 PDF

PREPARATION AND IN VITRO STABILITY STUDY OF 188Re-HEDP AS A BONE SEEKING RADIOPHARMACEUTICAL

Toni Tripunoski, Domokos Mathe, Lajos Balog, Ana Ugrinska, Maja Chochevska, Sinisha Stojanoski, Elena Stanojevska, Nevena Manevska, Toni Grozdanovski, Daniela PopGjorceva

148-156

 PDF

SPONTANEOUS VISUAL RECOVERY FOLLOWING COMBINED CENTRAL RETINAL VEIN AND CILIORETINAL ARTERY OCCLUSION – CASE REPORT

Natasa Trpevska Sekerinov, Andrijana Petrusevska, Emilija Gjosevska Dastevska

157-162

 PDF

RECURRENT CENTRAL VENOUS RETINAL OCCLUSION, CLINICAL FEATURES AND TREATMENT OUTCOME

Jana Nivicka Kjaeva, Natasa Trpevska Sekerinov, Gazmend Mehmeti, Andrijana Petrusevska

163-169

 PDF

BILATERAL CONGENITAL CATARACT IN A NEWBORN- LITERATURE REVIEW AND CASE REPORT

Igor Isjanovski, Stefan Pandilov, Emilija Gjosevska Dashtevska

170-175

 PDF

DIAGNOSTIC AND THERAPEUTIC MODALITIES IN THE MANAGEMENT OF OPTIC DISC PIT MACULOPATHY- CASE REPORT AND LITERATURE REVIEW

Stefan Pandilov, Natasa Trpevska Sekerinov

176-182

 PDF

CRANBERRY, A POTENTIAL ALTERNATIVE TREATMENT FOR URINARY TRACT INFECTIONS

Liljana Labacevska Gjatovska, Marko Kostovski, Maja Jurhar-Pavlova, Danica Kovacheva-Trpkovska, Radomir Jovchevski, Kiril Mihajlov, Tatjana Grdanoska, Bojan Labachevski, Kristina Pavlovska

183-189

 PDF

ANTIMICROBIAL RESISTANCE IN GRAM NEGATIVE BACILLI ISOLATED FROM BLOOD CULTURE

Danica Kovacheva-Trpkovska, Marko Kostovski, Radomir Jovcevski, Liljana Labacevska-Gjatovska, Kiril Mihajlov, Tatjana Grdanoska, Igor Trpkovski, Branka Petrovska-Basovska, Blerta Mehmeti

190-197

 PDF

THROMBOCYTOPENIA ASSOCIATED WITH HEPATITIS B VIRUS INFECTION-CASE REPORT

Haris Sulejmani, Nenad Bogdanovski, Ivana Zafirova, Svetlana Krstevska Balkanov

198-202

 PDF

COMBINING PROSTATE HEALTH INDEX AND mpMRI DATA (MRI SPECTROSCOPY) TO MANAGE PI-RADS LESIONS AND REDUCE EXCESSIVE BIOPSY, A SINGLE CENTER STUDY

Toni Krstev, Ivica Stojanoski, Lazar Ilievski, Nerhim Tufekchioski, Biljana Prgova-Veljanova, Masha Kostova, Olivera Stojcheva-Taneva, Jasmina Trojcanec, Stefan Milenkovski

203-216

 PDF



DIAGNOSTIC PERFORMANCE OF PROSTATE HEALTH INDEX (PHI) IN PREDICTING PROSTATE CANCER ON PROSTATE BIOPSY; A SINGLE CENTER STUDY

Toni Krstev, Ivica Stojanoski, Lazar Ilievski, Nerhim Tufekchioski, Olivera Stojcheva-Taneva, Jasmina Trojancanec, Cvetanka Volkanovska Iljevska

222-233



THE ROLE OF TGF- β 1 IN THE DEVELOPMENT OF DIABETIC NEPHROPATHY EXPERIMENTALLY INDUCED BY STREPTOZOTOCIN AND THE NEPHROPROTECTIVE EFFECTS OF CANDESARTAN

Jasmina Trojancanec, Kristina Pavlovska, Emilija Shikole, Nikola Kolovchevski, Bojan Labachevski, Aleksandar Nikodinovski, Krume Jakjovski, Igor Kikerkov, Marija Petrusevska, Panche Zdravkovski, Dimche Zafirov

234-245



BIOFILM IN CHRONIC DIABETIC FOOT ULCER-CASE REPORT

Julija Mitrova Telenta, Liljana Labacevska Gjatovska, Marko Kostovski, Maja Dimova, Ivana Dohceva Karajovanov, Suzana Nikolovska, Silvija Duma, Hristina Breshkovska, Nikola Panovski

246-250



[View All Issues >](#)

Information

[For Readers](#)

[For Authors](#)

[For Librarians](#)

Journal of Morphological Sciences is an official journal of the **Macedonian Association of Anatomists**, published twice or three times a year in English.

Journal of Morphological Sciences

[Current](#) [Archives](#) [About](#)

[Home](#) / [Editorial Team](#)

Editor- in-Chief

Biljana Zafirova

Deputy editors

Biljana Trpkovska

Editorial Council

Biljana Zafirova

Niki Matveeva

Nikola Jankulovski

Sonja Topuzovska

Beti Zafirova Ivanovska

Viktorija Jovanovska

Goran Dimitrov

Sunchica Petrovska

Jasna Bogdanska

Elena Kjosevska

Nikola Labachevski

Sonja Bojadzieva

Editorial Office

Anamarija Paunkoska

Lenche Danevska

Biljana Narashanova - secretary

International Editorial Board

Ace Dodevski, R. North Macedonia

Biljana Bojadzieva Stojanoska, R. NorthMacedonia

Elizabeta Chadikovska, R. North Macedonia

Jane Netkovski, R. North Macedonia

Katerina Kubelka Sabit, R. North Macedonia

Lazo Noveski, R. North Macedonia

Slavica Kostadinova Kunovska, R. North Macedonia

Vesna Janevska, R. North Macedonia

Vladimir Popovski, R. North Macedonia

Jasmina Trojachanec, R. North Macedonia

Sanja Mancevska, R. North Macedonia

Bruno Nikolovski, R. North Macedonia

Jasna Halilovic, Bosnia and Herzegovina

Silvia Mladenova, Bulgaria

Monika Urbaniak, Poland

Ivica Grkovic, Croatia

Simon Pkhrikyan, Armenia

Igor Sladojevic, Bosnia and Herzegovina

Ljiljana Tadic, Bosnia and Herzegovina

Biljana Srdic, Serbia

Dusica Maric, Serbia

Ivana Kavecic, Serbia

Zivka Eri, Serbia

Ljiljana Vasovic, Serbia

Mirela Eric, Serbia

Slobodan Vlajkovic, Serbia

Zoran Pesic, Serbia

Filip Vukmirovic, Montenegro

Mileta Golubovic, Montenegro

Vitaly Gargin, Ukraine

Iva Petkovska, USA

Jadranka Stojanovska, USA

Information

[For Readers](#)

[For Authors](#)

[For Librarians](#)

Journal of Morphological Sciences is an official journal of the **Macedonian Association of Anatomists**, published twice or three times a year in English.

COMBINING PROSTATE HEALTH INDEX AND mpMRI DATA (MRI SPECTROSCOPY) TO MANAGE PI-RADS LESIONS AND REDUCE EXCESSIVE BIOPSY, A SINGLE CENTER STUDY

Toni Krstev¹, Ivica Stojanoski^{1,2}, Lazar Ilievski¹, Nerhim Tufekchioski¹, Biljana Prgova-Veljanova^{3,4}, Masha Kostova^{3,4}, Olivera Stojcheva-Taneva⁵, Jasmina Trojancanec^{4,6}, Stefan Milenkovski⁷

¹Department of Urology, City General Hospital 8th of September Skopje, North Macedonia.

²Faculty of Medicine, Goce Delchev University, Shtip, North Macedonia

³Department of Radiology, City General Hospital 8th of September Skopje, North Macedonia,

⁴ Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, North Macedonia.

⁵Clinic of Nephrology in Skopje, North Macedonia.

⁶Department of Preclinical and Clinical Pharmacology and Toxicology, Skopje, North Macedonia

⁷ Medical Doctor, Alkaloid AD, Skopje, North Macedonia

Abstract

To evaluate the values of PHI and PI-RADS findings in the early detection and prediction of prostate cancer, as well as their application in clinical trials, especially when values of PSA are in the „grey zone,, with negative DRE.

The 100 patients, men aged 50 years or older with prostate-specific antigen 4 to 10 ng/ml („gray zone,,) and normal digital rectal examination with suspected prostate cancer were examined, who had undergone biopsy and were divided in two groups. A group with no evidence of PCa (non PCa) and the group with PCa.

The performance of PHI and mpMRI PI-RADS score was compared to predict biopsy results and, specifically, the presence of clinically significant prostate cancer (csPCa) using multiple criteria. Among 100 subjects, 21 (21.0%) were diagnosed with PC, including 13 (61.95%) with csPC (Gleason \geq 7).

By the threshold of PHI \geq 36, the sensitivity, specificity, PPV, and NPV to predict PCa were 100%, 68.35%, 45.65%, and 100%, respectively.

The best cut-off (PHI) was 42.8% with sensitivity 85.7% and specificity 86.1%. The area under the receiver operator characteristic curve (AUC) of combining PHI and mpMRI was greater than that of PHI alone (0.993 vs. 0.954, p=0.002) and mpMRI alone (0.993 vs. 0.976, p=0.025).

Comparing the performance in the identification of clinically significant prostate cancer (csPCa), we found that PHI \geq 73.04 and PI-RADS score \geq 4 were able to identify csPCa (Gleason score \geq 7 (3 + 4)) both alone and added to a base model including age, PSA, fPSA-to-tPSA ratio and prostate volume.

If biopsy was restricted to patients with PI-RADS 5 as well as PI-RADS 3 or 4 and PHI \geq 36.0, 50% of biopsy could be avoided with one csPCa patient being missed.

The analyzed correlation between PHI and PI-RADS score was statistically significant (p<0.0001). According to the value of Spearman's coefficient, R=0.748, the correlation is positive, i.e. direct, and they showed that with an increase in the value of the prostatic health index, (PHI) the PI-RADS score increases, and vice versa.

The combination of PHI and mpMRI had higher accuracy for detection of csPC compared with PHI or mpMRI alone.

Keywords: Prostate health index, mpMRI PI-RADS, detection of prostate cancer

Introduction

Prostate cancer is the second most common cancer in men and the fifth leading cause of death worldwide [1].

Prostate specific antigen (PSA) is widely used as a serum marker to detect and monitor the progression of prostate cancer (PCa), and it has dramatically increased the rate of early detection and reduced PCa-specific mortality. However, the low specificity of PSA in determining the presence of PCa and suboptimal ability to discriminate between clinically significant and indolent cancer may lead to unnecessary prostate biopsies and overtreatment, especially in men presenting with a total PSA level of <10 ng/ml. [2,3].

Given these limitations, there is considerable interest in new biomarkers with improved clinical specificity for PCa detection. The use of biomarkers could aid in avoiding unnecessary biopsies without missing aggressive cancers [4].

The evaluation of PSA isoforms, in particular, free PSA (fPSA), and [-2] proPSA (p2PSA) has been shown to improve the specificity of PSA in the range of 4-10 $\mu\text{g/L}$.

The prostate health index (phi) combines PSA, fPSA, and p2PSA results using the equation $(\text{p2PSA}/\text{fPSA} \times \sqrt{\text{PSA}})$ to estimate the probability of finding PCa at biopsy. The assay is intended for use in men with non-suspicious digital rectal exam (DRE) findings and serum PSA concentration between 4-10 $\mu\text{g/L}$ [5]. Increasing phi scores are associated with an increased prevalence of PCa and higher grade (Gleason score ≥ 7) cancers on biopsy [6].

To complement this limitation, multi-parametric magnetic resonance imaging (mpMRI) has recently been utilized before prostate biopsy to determine not only the likelihood of cancer but also its location. [7].

mpMRI of the prostate (MRI spectroscopy) currently plays a central role in the diagnostic pathway of suspected prostate cancer (PCa) [8] and is among the gold standards for the prediction of positive biopsy [9].

Men who have a PI-RADS (Prostate Imaging Reporting and Data System score of 3 or higher) underwent biopsy [10]. However, PI-RADS 3 corresponds to csPCa. Clinically significant PCa should have histopathology ISUP grade ≥ 2 and/or volume ≥ 0.5 cc and/or have extra-prostatic extension. Only in less than 15% of patients, thus the use of mpMRI to select patients for biopsy is not ideal [11].

Therefore, the aim of the present study was to evaluate the feasibility of combining PHI and mpMRI in the prediction of positive biopsy.

Materials and methods

Study design and population

This is a prospective observational non-randomized study from 2018 to 2019 conducted at General City Hospital 8th of September in Skopje. The study included consecutive men above 50 y/o, with negative DRE, undergoing trans-rectal ultrasound-guided (TRUS) prostate biopsy for suspected PCa with TPSA level of 4-10ng/ml. Men receiving 5- α -reductase inhibitors, evidence of acute prostatitis, urinary tract infection and those with previous history of prostatic surgery for any prostatic condition were excluded from this study. Blood samples were drawn prior to TRUS biopsy. mpMRI (MRI spectroscopy) was done before TRUS biopsy. Patients then underwent TRUS biopsy according to standardized protocol; with a minimum of 12 biopsy cores taken. PCa was identified and graded according to the 2005 consensus conference of the International Society of Urological Pathology.

The primary endpoint of this study was to evaluate PHI and mpMRI in the prediction of positive biopsy. The number of potentially avoidable biopsies if these tests were used as a guide for prostate biopsy decision was calculated.

Patients were stratified into two groups: with no significant prostate cancer (non-PCa) and with cancer (PCa).

Biochemical analysis

Serum samples for TPSA, fPSA and p2PSA were collected and centrifuged within two hours of collection, aliquoted and stored at -70°C until analysis. Testing was performed on Access2 automated immunoassay analyser (Beckman Coulter, CA, USA), using Hybritech calibrators, controls, and reagents.. %fPSA (fPSA/TPSAx100), %p2PSA (p2PSA/fPSAx100) and PHI ($[\text{p2PSA}/\text{fPSA}] \times \sqrt{\text{TPSA}}$) were then obtained via calculation.

Multiparametric MRI (mpMRI) and Biopsy Protocols

mpMRI was performed using a 3-T MRI scanner Siemens MAGNETOM Vida 3 T (Siemens, Munich, Germany) acquiring diffusion-weighted imaging (DWI), dynamic contrast enhancement imaging (DCE), T1-weighted axial and T2-weighted tri planar imaging. The images were segmented to obtain and record lesion locations and PI-RADS scores.

Statistical analysis

Statistical analyses were performed using SPSS v.24 software. Continuous and categorical variables were summarized by the median and interquartile range (IQR) for skewed data and frequency measures, respectively. Mann-Whitney U test was used for comparisons of continuous variables and Chi-Square test was used for comparisons of categorical variables. Medcalc v.17.0.4 software was used to plot receiver operating characteristic (ROC). Predictive accuracy was quantified as the area under the receiver operating characteristic curve (AUC). The AUC between variables were compared using Delong’s method. A twosided p-value <0.05 was considered statistically significant in all analyses.

Ethics

This study was approved by the research ethics committee of Medical faculty, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia.

Results

100 patients consented to the study for undergoing prostate biopsy. 21% had pathologically verified prostate carcinoma(only 13 had GS≥7), 79% had no cancer (noPCa). The median age was 69.2 ± 6.8 years. No statistically significant difference was noted in the age between patients with or without PCa (69.8 ± 7.2 vs 70.8 ± 4.8 y/o, p=0.24) (Table 1).

Table 1.The age of the study population

	Ag : (y/o)		p value
	mean ± SD	min- max	
PCa	70.8 ± 4.8	61 – 77	t=1.18 p=0.24
non PCa	69.8 ± 7.2	51 – 85	

non PCa (benign prostatic conditions)

t(Student t-test)

PCa (prostate cancer)

Table 2. The basic clinical characteristics of the study population

	Descriptive Statistics		
	mean ± SD	min- max	median (IQR)
PSA	6.66 ± 1.7	4.02 – 10	
PHI	42.01 ± 26.1	8.8 – 133	34.93 (27.51 – 45.8)
fpsa	1.82 ± 1.1	0.36 – 6.81	1.47 (1.17 – 2.36)
%fpsa	26.75 ± 13.8	0.81 – 78.89	24.02 (16.34 – 34.34)
pro2psa	27.03 ± 20.9	5.41 – 156.97	22.25 (14.03 – 31.41)
%pro2psa	1.65 ± 0.9	0.4 – 5	1.4 (1.045 – 1.88)

Table 3. Correlation of PI-RADS score and PCa and non PCa patients

PI-RADS score (mpMRI)	n	PCa n (%)	Non PCa n (%)	p value
pi-rads 1 - very low unlikely to be present	5	0	5 (6.33)	***p=0.000
pi-rads 2 - low	33	0	33 (41.77)	
pi-rads 3 - intermediate	40	1 (4.76)	39 (49.37)	
pi-rads 4 - high is likely to be present	21	19 (90.48)	2 (2.53)	
pi-rads 5 - very high to be present	1	1 (4.76)	0	

non PCa (benign prostatic conditions)

Fisher's exact

;***p<0.0001 csPCa

(prostate cancer)

All values given as number (percentage, %) or median (IQR), n number, csPCa clinically significant prostate cancer, non-PCa non-clinically significant prostate, ca cancer, PSA prostate-specific

antigen, PHI prostate health index, mpMRI multi parametric magnetic resonance imaging, mpMRI is defined as PIRADS, p value shows the significance between csPC and non-csPC

Mean PSA was equal to 6.66 ± 1.7 ng/mL (range: 2 to 10 ng/mL); Median PHI was equal to 42.01 ± 26.1 (range: 8.8 to 133.0) (Table 2). Patients with csPCa and patients without PCa showed statistically more significant difference in PI-RADS score ($p < 0.0001$). PI-RADS score was equal to or greater than 4 in 21 patients and equal to 3 in 40 patients. In the diagnostic setting, a positive biopsy was observed in 21 patients (21.0%).

19 patients were registered with PI-RADS 4 (90.48%) and only 1 patient (4.76) with PI-RADS 3 and PI-RADS 5. In the group with significant PCa dominant was PI-RADS 4 score, in the group with nonsignificant PCa dominant was PI-RADS 3 score (Table 3). The analyzed correlation between PHI and PIRADS score was statistically significant ($p < 0.0001$).

According to the value of Spearman's coefficient, $R = 0.748$, the correlation is positive, i.e. direct, and they showed that with an increase in the value of the prostatic health index, (PHI) the PI-RADS score increases, and vice versa.

Table 4. Correlation of PHI and MRI PI-RADS (score)

	Spearman R	t(N-2)	p value
PHI & MRI PI-RADS (score)	0.7477	11.15	***0.0000

*** $p < 0.0001$

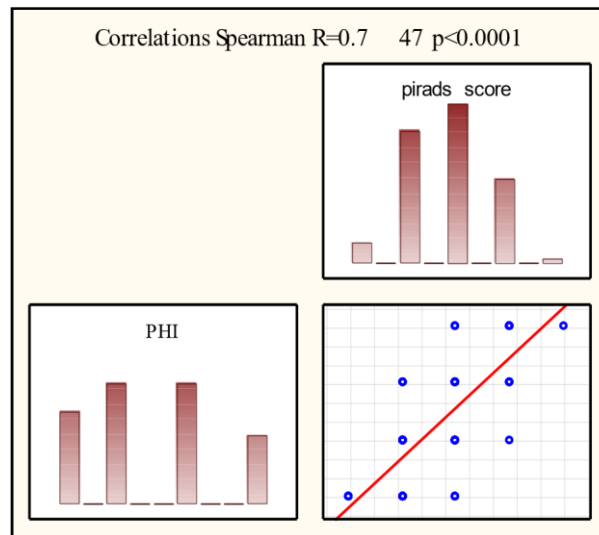


Figure 1. Correlation of PHI and MRI PI-RADS (score)

Table 5. PHI values between PI-RADS score groups

PI-RADS mpMRI	PHI			
	n	mean ± SD	min- max	median (IQR)
1	5	15.5 ± 1.4	13.9 – 17.14	15.27 (14.5 – 16.69)
2	33	28.31 ± 7.3	8.8 – 48.6	27.93 (24.7 – 31.4)
3	40	37.62 ± 9.9	20.06 – 58.82	37.07 (29.87 – 43.55)
4	21	76.74 ± 35.2	30.3 – 133.3	69.55 (43.9 – 103.1)
5	1	73.04	73.04	73.04

The groups with PI-RADS score 1 and 2, as well as the groups with score 4 and 5, were combined for statistical analysis. PHI values were significantly different between PI-RADS ratio classes ($p < 0.0001$).

All intergroup comparisons with post-hoc analysis presented significant differences.

Patients with PI-RADS score ≤ 2 and PI-RADS score equal to 3 presented significantly lower PIH values than patients with PI-RADS 4 and 5 ($p < 0.0001$ and $p = 0.000253$, respectively).

Patients with PI-RADS score ≤ 2 had significantly lower PIH values than patients with PI-RADS score equal to 3 ($p = 0.000246$). Patients with PI-RADS score ≤ 2 had significantly lower PIH values than patients with PI-RADS score equal to 3 ($p = 0.000246$). The average PIH values were 26.62 ± 8.1 , 37.62 ± 9.9 and 76.57 ± 34.4 , respectively in the groups with PI-RADS score ≤ 2 , 3 and ≥ 4 ; PIH had median values of 27.11, 37.07, and 71.295, respectively, in the PI-RADS score ≤ 2 , 3, and ≥ 4 groups.

Table 6. Distribution of study population with PHI and PI-RADS score

PI-RADS score	PHI			
	n	mean ± SD	median (IQR)	p value
2	38	26.62 ± 8.1	27.11 (21.62 – 31.35)	H=53.02 *** $p = 0.0000$ 2vs3 *** $p = 0.000246$ 2vs4 *** $p = 0.000000$ 3vs4 *** $p = 0.000253$
3	40	37.62 ± 9.9	37.07 (29.87 – 43.55)	
4	22	76.57 ± 34.4	71.29 (43.9 – 103.1)	

H (Kruskal-Wallis ANOVA), post-hoc Mann-Whitney test

*** $p < 0.0001$

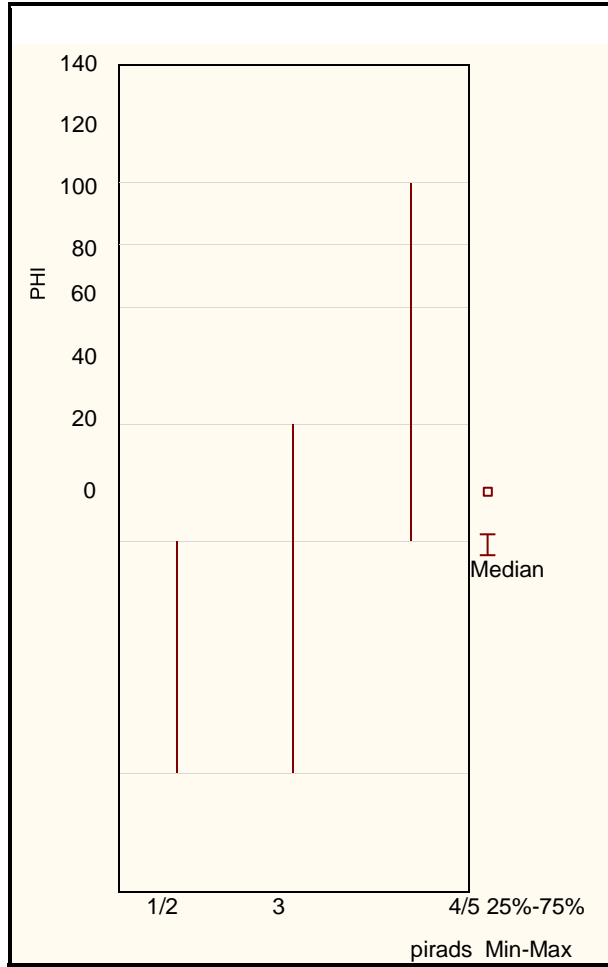


Figure 2. Distribution of study population with PHI and PI-RADS score

As a good test for detecting patients with csPCa and nonPCa, ROC analysis presented the AUC of PHI, mpMRI, and combination of PHI and mpMRI .AUC was 0.954 (AUC=0.954, CI 95% 0.913-0.995), 0.976 (95% CI 0.942– 1.000), and 0.993 (AUC=0.993, CI 95% 0.982-1.00), respectively .

Table 7. Basic characteristics of Area Under the ROC curve

	AUC	Std. Error ^a	Asymptotic Sig. ^b	95% Confidence Interval	
				Lower Bound	Upper Bound
PSA	0.656	0.063	0.029	0.532	0.780
PHI	0.954	0.021	0.000	0.913	0.995
PI-RADS mpMRI	0.976	0.017	0.000	0.942	1.000
PHI- mpMRI	0.993	0.006	0.000	0.982	1.000

The combination of PHI and PI-RADS score proved to be an excellent test for predicting prostate cancer.

The area under the ROC curve AUC (Area Under the Curve) for this combined model has a value of 0.993 (AUC=0.993, CI 95% 0.982-1.00).

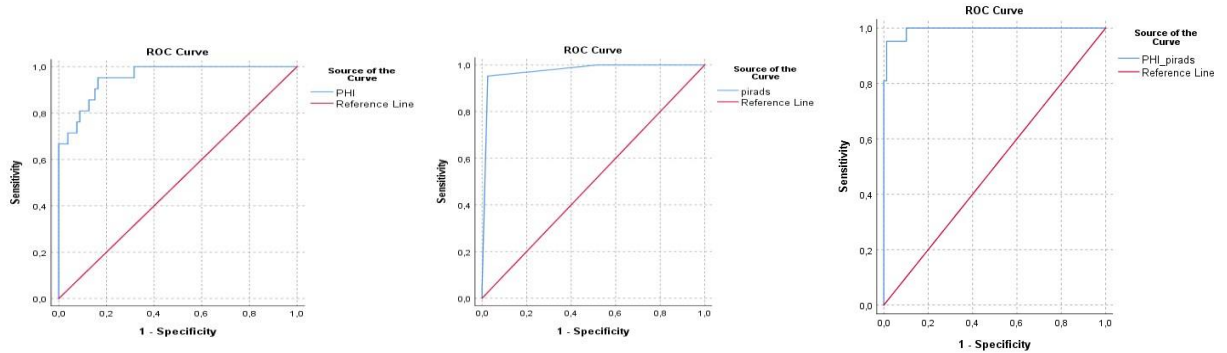


Figure 3. Basic characteristics of Area Under the ROC curve

Receiver-operating characteristic (ROC) curve analysis for PHI, mpMRI (PI-RADS score), and combination of both to predict clinically significant prostate cancer. The area under curve (AUC) of PHI, mpMRI (PI-RADS score), and combination of PHI and mpMRI were 0.954 (95% CI 0.913– 0.955), 0.976 (95% CI 0.942–1.000), and 0.993 (95% CI 0.982– 1.000). PHI, prostate health index; mpMRI, multiparametric magnetic resonance imaging

Table 8. Univariate analysis of the parameters

	Area	p value	cut off	given cut off	Sn	Sp
PSA	0.656 (0.532 – 0.780)	0.029	6.54		61.9	59.5
fpsa	0.390 (0.250 – 0.529)	0.121	1.335		38.1	39.2
%fpsa	0.345 (0.197 – 0.493)	0.029	21.91		33.3	32.9
p2psa	0.753 (0.642 – 0.865)	0.000	26.05		66.7	65.8
%p2psa	0.948 (0.904 – 0.992)	0.000	1.745		85.7	86.1
				1.36	100	63.29
				2.15	76.19	94.94
PHI	0.954 (0.913 – 0.995)	0.000	42.8		85.7	86.1
				26.99	100	29.11
				35.99	100	68.35
				54.99	66.67	96.2
PHI and pirads	0.993 (0.982 – 1.0)	0.000			95.2	94.9

All PSA-derived biomarkers, as well as PI-RADS score, were significantly associated with the risk of PCa at univariate analysis with an AUC ranging from 0.656 (95% CI: 0.532 to 0.780) for PSA to 0.954 (95% CI: 0.913 to 0.995) in case of PHI to 0.993 (95% CI: 0.982 to 1.000) (Table 8).

The optimal cut-off for PHI was 42.7% and was associated with a sensitivity 85.7% and specificity 86.1%. For the combined model of PHI and mpMRI (PI-RADS score), the largest area under the ROC curve (AUC=0.993), the highest sensitivity and specificity (95.2% and 94.9%, respectively) was obtained. This combination of markers was presented as the best tools for detection and prediction of prostate cancer.

Table 9. Correlation between Gleason score and PHI

Gleason	PHI			p value
	mean ± SD	min- max	median (IQR)	
<7	74.29 ± 36.4	41.89 – 133.3	63.61(45.89-100.1)	Z=0.47 p=0.00638
≥7	81.91 ± 32.5	36.8 – 131.82	79.43(59.4-103.1)	
	79.01 ± 33.4	36.8 – 133.3	73.04(48.31-103.1)	

Z(Mann-Whitney U Test)

Table 10. Correlation between Gleason score, PHI and mpMRI (PI-RADS score)

	Gleason			p value
	n	< 7 n (%)	≥ 7 n (%)	
PHI (36 – 54.99)	7	4 (50)	3 (23.08)	X ² = p=0.
PHI >55	14	4 (50)	10 (76.92)	
pi-rads 3 *intermediate	1	1 (12.5)	0	X ² = p=0.
pi-rads 4 *high is likely to be present	19	6 (75)	13 (100)	
pi-rads 5 very high to be present	1	1 (12.5)	0	

X² (Pearson Chi-square)

Among the 21 patients with positive biopsy, a mean age of 70.8 ± 4.8 years (range: 61 to 77) (Table 1). A clinically significant PCa (Gleason score 7 (3 + 4) or higher) was observed in 13 patients (61.9%). PHI and PI-RADS score preserved a significant association with the presence of csPCa, respectively.

PHI was higher in csPCa 79.43(59.4-103.1) vs 63.61(45.89-100.1) ($p=0.00638$) and most of the patients were with PI-RADS 4 (90.4%). The optimal cut-off for the identification of csPCa was 42.7 for PHI and PI-RADS 4 with sensitivity: 95.2 and specificity 94.9 (Table 8). If biopsy was restricted to patients with $PI-RADS \geq 3$, 33.8% of biopsy could be avoided. If biopsy was restricted to patients with $PHI \geq 42.8$, 38.2% of biopsy could be avoided, but three csPC patients would have been missed.

Furthermore, if biopsy was restricted to patients with PI-RADS 5 as well as PI-RADS 3 or 4 and $PHI \geq 42.8$, up to 50% of biopsy could be avoided with only one csPC patient being missed.

Discussion

This study allows to evaluate the values of PHI and PI-RADS findings in the early detection and prediction of prostate cancer, as well as their application in clinical trials, especially when values of PSA are in the „grey zone,, with negative DRE. The correlation of the predictive capabilities of different noninvasive procedures, including PSA, the PHI, and the mpMRI (PI-RADS score), in patients at the time of the initial biopsy has been analyzed. As shown in the literature, only few studies have evaluated the complementary role of PHI and mpMRI in detecting csPCa.

The recognition of PCa over-diagnosis and overtreatment has resulted in a change in cancer diagnostic priorities. It shifts from detecting all cancers to focusing on the identification of potentially aggressive but curable cancers and minimizing the detection and treatment of indolent disease [12].

Our study results are consistent with other studies in demonstrating a good correlation of PHI with PI-RADS score. Also, PHI and mpMRI have been suggested as biomarkers before biopsy to identify csPC and reduce unnecessary biopsy [13,14].

In NCCN guideline for PC, early detection, $PHI > 35$ was suggested to estimate high-grade cancer [15] A recent multicenter study recommended $PHI > 30$ to predict high-grade ($GS \geq 7$) cancer in Asian men, whereas the threshold should be > 40 for European men [16].

A PHI cut-off value of 42.8 has been identified as the best threshold with sensitivity 85.7% and specificity 86.1. We found that PHI significantly outperformed mpMRI in the prediction of positive biopsy. In addition, we compared the ability of PHI and mpMRI to predict the presence of csPCa . We found that

$PHI \geq 74.89$ and PI-RADS score ≥ 4 were able to identify csPCa (Gleason score ≥ 7 (3 + 4)) both alone and added to a base model including age, PSA, fPSA-to-tPSA ratio and prostate volume. The first evidence of the complementary role for PHI and mpMRI was proposed by Gnanapragasam et al [17].

The authors found that the combination of PHI and mpMRI improved predictive performance for overall and clinically significant ($GS \geq 7$) cancer detection compared with mpMRI alone (AUC 0.75 vs. 0.69). Furthermore, applying a PHI threshold of ≥ 35 among men with negative mpMRI had the highest NPV of 0.97 for excluding csPCa and could spare 42% of biopsies, while only missing a single low-volume csPC. Hsieh et al. showed an AUC of 0.87 for the PHI combined with mpMRI [18].

It is consistent with our study where AUC was 0.993 for the PHI combined with mpMRI. If biopsies were limited to subjects with PHI values ≥ 30 and PI-RADS score ≥ 3 , it was possible to save about 50% of unnecessary biopsies, missing only one csPCa [11].

In a prospective study on 345 patients at Johns Hopkins University, Tosoian et al. found that PI-RADS score ≤ 3 and PHI levels < 27 corresponded to the absence of csPCa in 15 men on first biopsy [19].

These findings correlate with our results and support the hypothesis that PHI may be a useful tool to recognize high-grade PCa beyond MRI outcome. Our study showed absence of csPCa in 23 men on first biopsy. More importantly, prostate biopsy was done for all patients, regardless of mpMRI findings or PHI level. Therefore, we can see more clearly the impact of PHI and mpMRI on cancer detection rate. Fan et al. demonstrated that PHI, among PSA-derivative biomarkers, was the best predictor of csPCa in men with PIRADS score 3 and 4/5. These findings suggested that in patients with PI-RADS 3 index lesions, which is a gray zone for PI-RADS lesions, PHI may help to identify high-risk groups for csPCa and may enable several patients to avoid unnecessary biopsy [20].

Some authors published (in study including 395 men) that adding PHI to PI-RADS significantly increased the accuracy for the prediction of any cancer and csPCa [21].

For PHI cutoff value of ≥ 27 would have allowed 34% of the patients with PI-RADS 3 lesions ($n = 35$) to avoid a targeted biopsy, with both sensitivity and NPV of 100% [22]. The proportion of men who harbor csPCa was very different in PI-RADS 3 and in PI-RADS 4/5 [8].

American Urological Association (AUA) in consensus with Society of Abdominal Radiology (SAR) suggested immediate biopsy and repeat biopsy for a PI-RADS 4 or 5 lesion detected on mpMRI, and biopsy for a PI-RADS 3 lesion should not be routinely deferred [23]. PI-RADS 3 lesions corresponded to high-grade PCa in 16–21% [24].

Hsieh and al. in their series showed that the PPV (Positive Predictive Value) of a PI-RADS ≥ 3 lesion for csPC was 35.8%. They performed biopsy in all patients with PI-RADS 5 and added PHI ≥ 30 as selection criteria in patients with PI-RADS 3 or 4. And up to 50% of biopsy could be avoided with only one patient of csPC being missed. Therefore, the combination of PHI and mpMRI may be promising for pre-biopsy assessment to detect csPC and avoid unnecessary biopsy as much as possible [18]. A low number of csPCa cases remained undiagnosed by negative mpMRI. PI-RADS 1–2 lesions corresponded to about 1 in 10 probability of diagnosis of csPCa [25]. The value of obtaining mpMRI before a biopsy in biopsy-naive patients is a major topic of interest, as mpMRI is most often recommended in patients with previous negative biopsies. [23]

Three prospective multicenter trials have evaluated pre-biopsy mpMRI in biopsy-naive patients (PROMIS trial, PRECISION trial and MRI-FIRST trial) [20].

The PROMIS trial was designed to assess the utility of mpMRI as a triage test in biopsy-naive patients to avoid unnecessary TRUS-biopsy [26].

The results of the PROMIS trial indicated that mpMRI missed cancers of lower grade and often smaller disease compared to detected PCa [27].

In this study, all patients in the group with PI-RADS 1–2 had negative biopsy. Only one patient with PI-RADS 3 had a positive biopsy. That patient was subjected to RP and was diagnosed with PCa, according to previously reported mpMRI. The other goal of this study was to assess the association between PHI, mpMRI and Gleason score of PCa. The diagnostic accuracy of PHI for the identification of csPCa might be increased when combined with mpMRI. Many studies have reported the association between PHI and csPCa focusing on Gleason score. [28,29]. As the PHI increased, the ratio of high G/S also increased. PHI was higher in csPCa with Gleason score (GS) ≥ 7 than that in GS < 7 (79.43 vs 63.61, $p=0.0638$). and only 12.5% had GS < 7 with PI-RADS 3, vs 87.5 with GS ≥ 7 and PI-RADS 4-5.

This viewpoint may keep away a lot of unnecessary biopsies and definitive medical therapy if PHI and MRI would be included in the diagnostic algorithm for patients with suspected PCa to select patients for biopsy [30].

Furthermore, PHI has been proposed as a tool to select and monitor patients on active surveillance (AS), and the diagnostic validity of PHI when combined with mpMRI might be increased for the identification of csPCa [31].

Among other biomarkers, PHI was the cheapest, easier to perform and the only one FDA approved and CE-marked [32]. When combined with MRI spectroscopy may produce model able to reduce biopsies and to minimize over-diagnosis, without missing csPCa and overtreatment.

There would be several limitations to this study. The examined patients do not represent a screening population. It is done in a single secondary referral center and patients were enrolled due to the increased suspicion of csPCa. The number of examined patients is also limited.

This should be considered as a pilot study of combining PHI and MRI spectroscopy to detect csPC. We used the combination of trans-rectal target biopsy and standard biopsy as the pathological reference standard.

The diagnostic validity should be better using the trans-perineal template-guided mapping biopsy. A major limitation of this study is that we did not evaluate the results of the follow-up of patients with high PI-RADS score and negative biopsy because of the lack of time. This issue is clinically relevant.

Conclusion

In conclusion, the combination of PHI and mpMRI (MRI spectroscopy) had higher validity for detection and prediction of csPC compared with PHI or mpMRI alone. The application of PHI in addition to mpMRI in clinical practice may ensure a personalized therapeutic approach for patients with suspected PCa and may reduce up to 50% of prostate biopsies with PI-RADS 5 as well as PI-RADS 3 or 4 and PHI \geq 40. External validation studies are needed to confirm the integration of PHI and mpMRI in the detection of csPCa.

Informed Consent Statement:

All procedures were in accordance with the ethical standards of the institutional research committee and with the Helsinki Declaration and its later amendments or comparable ethical standards. Before participation, written informed consent was obtained from each patient.

Conflicts of Interest:

The authors declare no conflict of interest.

Abbreviations

PHI- prostate health index; fPSA-free PSA; PCa-prostate cancer; nonPCa-no significant prostate cancer; PSA-prostate-specific antigen, pPSA: proPSA; p2PSA: [-2]proPSA; DRE-digital rectal examination; CI-confidence interval; AUC-area under curve; PI-RADS- Prostate Imaging Reporting and Data System; mpMRI-multiparametric MRI; TRUS-trans-rectal ultrasound; Gleason score-GS; FDA Federal Drug Administration;

References

1. Rawla P. Epidemiology of prostate cancer. *World J Oncol.* 2019;10: 63–89.
2. Tompson, I. M. et al. Prevalence of prostate cancer among men with a prostate-specific antigen level \leq 4.0 ng per milliliter. *N. Engl. J. Med.* 2004; 350, 2239–2246
3. Hori, S., Blanchet, J. S. & McLoughlin, J. From prostate-specific antigen (PSA) to precursor PSA (proPSA) isoforms: a review of the emerging role of proPSAs in the detection and management of early prostate cancer. *BJU Int.* 2013;112, 717–728
4. Visser, W.C.H.; de Jong, H.; Melchers, W.J.G.; Mulders, P.F.A.; Schalken, J.A. Commercialized Blood-, Urinary- and Tissue-Based Biomarker Tests for Prostate Cancer Diagnosis and Prognosis. *Cancers* 2020, 12, 3790. [CrossRef] [PubMed]
5. Jansen FH, van Schaik RHN, Kurstjens J, Horninger W, Klocker H, Bektic J, Wildhagen MF, Roobol MJ, Bangma CH, Bartsch G. Prostate-Specific Antigen (PSA) Isoform p2PSA in Combination with Total PSA and Free PSA Improves Diagnostic Accuracy in Prostate Cancer Detection. *European Urology.* 2010;57(6):921-7
6. Lazzeri M, Lughezzani G, Haese A, McNicholas T, de la Taille A, Buffi NM, Cardone P, Hurle R, Casale P, Bini V, Redorta JP, Graefen M, Guazzoni G. Clinical performance of prostate health index in men with tPSA $>$ 10ng/ml: Results from a multicentric European study. *Urologic Oncology: Seminars and Original Investigations.* 2016;34 (9):415.e13-. e19
7. Wei J.T., Barocas D., Carlsson S., Coakley F, Eggener S, Etzioni R, et al. Early detection of prostate cancer: AUA/SUO guideline part II: considerations for a prostate biopsy. *J Urol.* 2023 [PubMed] [Google Scholar]
8. Kasivisvanathan, V.; Rannikko, A.S.; Borghi, M.; Panebianco, V.; Mynderse, L.A.; Vaarala, M.H.; Briganti, A.; Budaus, L.; Hellawell, G.; Hindley, R.G.; et al. MRI-Targeted or Standard Biopsy for Prostate-Cancer Diagnosis. *N. Engl. J. Med.* 2018, 378, 1767–1777. [CrossRef]

9. Mottet, N.; van den Bergh, R.C.N.; Briers, E.; Van den Broeck, T.; Cumberbatch, M.G.; De Santis, M.; Fanti, S.; Fossati, N.; Gandaglia, G.; Gillessen, S.; et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. *Eur. Urol.* 2021, 79, 243–262. [CrossRef] [PubMed]
10. Grey, A.D.; Chana, M.S.; Popert, R.; Wolfe, K.; Liyanage, S.H.; Acher, P.L. Diagnostic accuracy of magnetic resonance imaging (MRI) prostate imaging reporting and data system (PI-RADS) scoring in a transperineal prostate biopsy setting. *BJU Int.* 2015, 115, 728–735. [CrossRef] [PubMed]
11. Ferro M, Crocetto F, Bruzzese D, Imbriaco M, Fusco F, Longo N, et al Prostate health index and multiparametric MRI: partners in crime fighting over-diagnosis and overtreatment in prostate cancer, *Cancers (Basel)* 2021:13
12. McDonald ML, Parsons JK. The case for tailored prostate cancer screening: An NCCN perspective. *J Natl Compr Canc Netw* (2015) 13:1576–83. doi: 10.6004/ jnccn.2015.0183
13. Fütterer JJ, Briganti A, De Visschere P, Emberton M, Giannarini G, Kirkham A, Taneja SS, Thoeny H, Villeirs G, Villers A (2015) Can clinically significant prostate cancer be detected with multiparametric magnetic resonance imaging? A systematic review of the literature. *Eur Urol* 68(6):1045–1053. <https://doi.org/10.1016/j.eururo.2015.01.013>
14. Loeb S, Shin SS, Broyles DL, Wei JT, Sanda M, Klee G, Partin AW, Sokoll L, Chan DW, Bangma CH, van Schaik RHN, Slawin KM, Marks LS, Catalona WJ (2017) Prostate health index improves multivariable risk prediction of aggressive prostate cancer. *BJU Int* 120(1):61–68. <https://doi.org/10.1111/bju.13676>
15. Network NCC (2018) NCCN guideline prostate cancer early detection. version 2. 2018. https://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf. Accessed Dec 09 2018
16. Chiu PK, Ng CF, Semjonow A, Zhu Y, Vincendeau S, Houlgatte A, Lazzeri M, Guazzoni G, Stephan C, Haese A, Bruijne I, Teoh JY, Leung CH, Casale P, Chiang CH, Tan LG, Chiong E, Huang CY, Wu HC, Nieboer D, Ye DW, Bangma CH, Roobol MJ (2019) A multicentre evaluation of the role of the prostate health index (PHI) in regions with differing prevalence of prostate cancer: adjustment of PHI reference ranges is needed for European and Asian settings. *Eur Urol* 75(4):558–561. <https://doi.org/10.1016/j.eururo.2018.10.047>
17. Gnanapragasam VJ, Burling K, George A, Stearn S, Warren A, Barrett T, Koo B, Gallagher FA, Doble A, Kastner C, Parker RA (2016) The prostate health index adds predictive value to multiparametric MRI in detecting significant prostate cancers in a repeat biopsy population. *Sci Rep* 6:35364
18. Hsieh, P.F.; Li, W.J.; Lin, W.C.; Chang, H.; Chang, C.H.; Huang, C.P.; Yang, C.R.; Chen, W.C.; Chang, Y.H.; Wu, H.C. Combining prostate health index and multiparametric magnetic resonance imaging in the diagnosis of clinically significant prostate cancer in an Asian population. *World J. Urol.* 2020, 38, 1207–1214. [CrossRef]
19. Tosoian, J.J.; Druskin, S.C.; Andreas, D.; Mullane, P.; Chappidi, M.; Joo, S.; Ghabili, K.; Agostino, J.; Macura, K.J.; Carter, H.B.; et al. Use of the Prostate Health Index for detection of prostate cancer: Results from a large academic practice. *Prostate Cancer Prostatic Dis.* 2017, 20, 228–233. [CrossRef] [PubMed].
20. Fan, Y.H.; Pan, P.H.; Cheng, W.M.; Wang, H.K.; Shen, S.H.; Liu, H.T.; Cheng, H.M.; Chen, W.R.; Huang, T.H.; Wei, T.C.; et al. The Prostate Health Index aids multi-parametric MRI in diagnosing significant prostate cancer. *Sci. Rep.* 2021, 11, 1286. [CrossRef] [PubMed]
21. Stejskal, J.; Adamcova, V.; Zalesky, M.; Novak, V.; Capoun, O.; Fiala, V.; Dolejsova, O.; Sedlackova, H.; Vesely, S.; Zachoval, R. The predictive value of the prostate health index vs. multiparametric magnetic resonance imaging for prostate cancer diagnosis in prostate biopsy. *World J. Urol.* 2021, 39, 1889–1895. [CrossRef]
22. Tan, T.W.; Png, K.S.; Lee, C.H.; Yuwono, A.; Yeow, Y.; Chong, K.T.; Lee, Y.M.; Tan, C.H.; Tan, Y.K. MRI Fusion-Targeted Transrectal Prostate Biopsy and the Role of Prostate-Specific Antigen

- Density and Prostate Health Index for the Detection of Clinically Significant Prostate Cancer in Southeast Asian Men. *J. Endourol.* 2017, 31, 1111–1116. [CrossRef] [PubMed]
23. Rosenkrantz AB, Verma S, Choyke P, Eberhardt SC, Eggener SE, Gaitonde K, Haider MA, Margolis DJ, Marks LS, Pinto P, Sonn GA, Taneja SS: Prostate magnetic resonance imaging and magnetic resonance imaging targeted biopsy in patients with a prior negative biopsy: a consensus statement by AUA and SAR. 2016: *J Urol* 196(6):1613–1618. <https://doi.org/10.1016/j.juro.2016.06.079>
 24. Schoots, I.G. MRI in early prostate cancer detection: How to manage indeterminate or equivocal PI-RADS 3 lesions? *Transl. Androl. Urol.* 2018, 7, 70–82. [CrossRef] [PubMed]
 25. Sathianathan, N.J.; Omer, A.; Harriss, E.; Davies, L.; Kasivisvanathan, V.; Punwani, S.; Moore, C.M.; Kastner, C.; Barrett, T.; Van Den Bergh, R.C.; et al. Negative Predictive Value of Multiparametric Magnetic Resonance Imaging in the Detection of Clinically Significant Prostate Cancer in the Prostate Imaging Reporting and Data System Era: A Systematic Review and Metaanalysis. *Eur. Urol.* 2020, 78, 402–414. [CrossRef] [PubMed]
 26. Ahmed, H. U. et al. Diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PROMIS): a paired validating confirmatory study. *Lancet* 2017; 389, 815–822
 27. Norris, J.M.; Carmona Echeverria, L.M.; Bott, S.R.J.; Brown, L.C.; Burns-Cox, N.; Dudderidge, T.; El-Shater Bosaily, A.; Frangou, E.; Freeman, A.; Ghei, M.; et al. What Type of Prostate Cancer Is Systematically Overlooked by Multiparametric Magnetic Resonance Imaging? An Analysis from the PROMIS Cohort. *Eur. Urol.* 2020, 78, 163–170. [CrossRef] [PubMed]
 28. Stephan C, Vincendeau S, Houlgatte A, Cammann H, Jung K, Semjonow A Multicenter evaluation of [-2] prostatespecific antigen and the prostate health index for detecting prostate cancer. *Clin Chem* 2013; 59(1):306–314
 29. Loeb S, Sanda MG, Broyles DL, Shin SS, Bangma CH, Wei JT, Partin AW, Klee GG, Slawin KM, Marks LS The prostate health index selectively identifies clinically significant prostate cancer. *J Urol* 2015; 193(4):1163–1169
 30. Sedlackova, H.; Dolejsova, O.; Hora, M.; Ferda, J.; Hes, O.; Topolcan, O.; Fuchsova, R.; Kucera, R. Prostate Cancer Diagnostic Algorithm as a "Road Map" from the First Stratification of the Patient to the Final Treatment Decision. *Life* 2021, 11, 324. [CrossRef]
 31. Pastor-Navarro, B.; Rubio-Briones, J.; Borque-Fernando, A.; Esteban, L.M.; Dominguez-Escrig, J.L.; Lopez-Guerrero, J.A. Active Surveillance in Prostate Cancer: Role of Available Biomarkers in Daily Practice. *Int. J. Mol. Sci.* 2021, 22, 6266. [CrossRef] [PubMed]
 32. Ferro, M.; De Cobelli, O.; Lucarelli, G.; Porreca, A.; Busetto, G.M.; Cantiello, F.; Damiano, R.; Autorino, R.; Musi, G.; Vartolomei, M.D.; et al. Beyond PSA: The Role of Prostate Health Index (phi). *Int. J. Mol. Sci.* 2020, 21, 1184. [CrossRef]