Fast-Track for Prostate Cancer and the Protective Factor of IPSS-score on Deviating MRI Results.

S. Gravendeel, Medical Student UMC, Utrecht University, the Netherlands
Student number: 583010

Supervisors: L. Paulino Pereira (pHD candidate), R. van den Bergh (Urologist, St.-Antonius Hospital Nieuwegein), R. Meijer (Urologist, UMC Utrecht)

Department: Urology, St.-Antonius Hospital Nieuwegein
Duration: 22-05-2023 - 18-08-2023

Abbreviations

PCa = prostate cancer
GP = general practitioner
PSA = prostate-specific antigen
DRE = digital rectal exam
BPH = benign prostate hyperplasia
MRI = magnetic resonance imaging
LUTS = lower urinary tract symptoms
PI-RADS = Prostate Imaging-Reporting and Data System
IPSS = International Prostate Symptom Score
IQR = interquartile range
BMI = body mass index
NA = not applicable

Abstract

Introduction. Prostate cancer requires a faster diagnostic pathway due to the long time to diagnosis and patient anxiety. To address this issue, a quick diagnostic route <36 hours was implemented. Previous research highlighted lower urinary tract symptoms as a protective factor for prostate biopsies. Therefore, our study aims to individualize the fast-track by exploring the association between the International Prostate Symptom Score and deviant magnetic resonance imaging scans.

Methods. Retrospective single-center cohort study, aiming to associate the International Prostate Symptom Score with abnormal magnetic resonance scans in men who had undergone the prostate cancer fast-track. Male patients participated from July 2022 to March 2023 at St. Antonius Hospital Nieuwegein. Primary outcome: abnormal magnetic resonance imaging scan, secondary outcomes: biopsy rates, prostate cancer diagnosis. Group 1: PI-RADS score 1-2 scans, group 2: PI-RADS score 3-5 scans. Univariate and multivariate logistic regression analyses were used.

Results. 268 men were enrolled. Multivariate analysis showed significant associations between magnetic resonance imaging scan abnormalities and International Prostate Symptom Score (OR 0.952 [0.908-0.997]; *p* 0.036), IPSS mild vs. severe (OR 3.844 [1.236-11.952], *p* 0.020), IPSS severe vs. mild (OR 0.260 [0.084-0.809]; *p* 0.020, irritative LUTS at referral (OR 0.420 [0.186-0.946]; p 0.036) and LUTS presence (OR 0.549 [0.304-0.989]; p 0.046).

Discussion. Based on our findings, upon confirmation though a prospective study, it appears that in the future, men with a mild IPSS score should consistently be placed in the fast-track, while men exhibiting irritative lower urinary tract symptoms should not.

Introduction

Prostate cancer (PCa) is a widespread disease, with 1.41 million new cases worldwide each year. In Europe, it ranks as the most commonly diagnosed cancer in men which may further increase even due to demographical trends [1-3]. The period leading to the final diagnosis of prostate cancer is a time characterized by substantial uncertainty and anxiety for patients [4]. Considering that, in the Netherlands in 2017, the average time between general practitioner (GP) referral and final diagnosis for prostate cancer was still 137 days, compared to 7 and 21 days for breast cancer and melanoma, respectively, highlights the need for a faster diagnostic process [5]. To address this, one such quick diagnostic route was implemented at our center last year, as described in the study conducted by Pereira et al.

Within this fast-track for prostate cancer, men with elevated prostate-specific antigen (PSA) levels or abnormal digital rectal exam (DRE) findings were referred to the hospital by their GP, where they underwent a repeat PSA blood test and magnetic resonance imaging (MRI) of the prostate. Subsequent to these tests, a consultation with a urologist followed, during which biopsies were taken in the event of an abnormal MRI scan. Histology results were known the next day, followed by a telephone consultation, resulting in a full assessment <36 hours [6].

Due to limited capacity, the fast-track cannot accommodate all patients with suspected prostate cancer. Men at the highest risk of having an abnormal MRI scan benefit most from the fast-track, because it enables MRI scans to be evaluated and biopsies to be performed immediately. Considering that our group of interest is already a high-risk subgroup for PCa due to elevated PSA or abnormal DRE results, we must identify a factor that accentuates this risk even further.

Earlier research into the fast-track detected that lower urinary tract symptoms (LUTS) would be protective of prostate biopsies but did not consider the severity of these complaints and introduced possible bias by combining ‘no’ and ‘unknown’ LUTS together [7].

One plausible explanation is that LUTS are often caused by benign conditions, such as benign prostate hyperplasia (BPH) or prostatic infection, which can result in elevated PSA values. [8,9]. Conversely, PCa is also recognized to cause elevated PSA levels [10]. Due to a lack of a definitive association between BPH or prostatic infection and PCa, elevated PSA levels do not necessarily indicate prostate cancer. They could be reasonably attributed to another cause of the heightened PSA [9,11,12].

Therefore, the study’s objective is to individualize the fast-track by exploring the association between LUTS, stratified by severity using IPSS scores, and deviating MRI scans. Additionally, we will investigate other potential risk factors and compare the predicting value of IPSS with LUTS as mentioned during consultations. In the event of finding an association, our aim is to use the most relevant factor in streamlining triage for rapid diagnosis, thereby improving efficiency and patient satisfaction.

Methods

Participants
From July 2022 to March 2023, men who underwent the fast-track for prostate cancer at St. Antonius Hospital Nieuwegein, The Netherlands, were enrolled in this retrospective single-center cohort study. Patients were included when they completed to fast-track after being referred to the urologist by their GP or other healthcare professional due to elevated PSA levels (three-50 mg/ml) or an abnormal DRE. Exclusion criteria included a medical history of prostate carcinoma, previous prostate analysis or unavailable MRI results.

Approval from the hospital's ethics committee (registration number: W23.076) was received before initiation.

Process
At the hospital, eligible patients underwent a series of assessments, including a repeat blood test for PSA value, an MRI-scan of the prostate, and a consultation with a urologist. Prostate biopsies were performed if indicated. For patients with an MRI-scan showing a Prostate Imaging-Reporting and Data System (PI-RADS) score of four or higher, a prostate biopsy was deemed necessary. In the case of a PI-RADS score of three, the decision for biopsy was based on additional factors, such as PSA density and patient characteristics, including family history. Biopsies were not necessary for PI-RADS scores of two or lower. The taken biopsies underwent histological examination, and the Gleason score was assigned, categorizing prostate cancer into International Society of Urological Pathology (ISUP) groups. Clinically significant prostate cancer (csPCa) is defined as Gleason seven or greater, corresponding to ISUP group two or higher.

Patients were requested to complete the International Prostate Symptom Score (IPSS) questionnaire before their appointment with the urologist [13]. The IPSS questionnaire scores LUTS severity from zero to 35, stratifying scores from zero to seven as mild, eight to 19 as moderate and 20 to 35 as severe. During the consultation, the urologist also inquires about LUTS symptoms. Additional information regarding LUTS, family history, medication use for LUTS, DRE, and PSA results were gained from the referral letter if provided. Demographic characteristics were also collected for analysis.

The study's primary outcome is the detection of an abnormal MRI scan of the prostate gland, which is assessed by the PI-RADS score. PI-RADS scores 1-2 indicate normal MRI results, while PI-RADS scores 3-5 indicate abnormalities. Secondary outcomes include biopsy rate and prostate cancer diagnosis.

Statistics
Patient data was retrieved from electronic medical files using the Epic system [14]. The RedCap platform was utilized for obtaining the necessary data [15]. Data analysis was carried out using IBM Statistics SPSS Version 26.0 [16].

The study participants were male individuals categorized into two groups: Group 1 consisted of men with a normal MRI of the prostate gland (PI-RADS 1-2), while Group 2 included men with an abnormal MRI (PI-RADS 3-5). Characteristics of both groups, as well as the overall study population, were described using the median and interquartile range (IQR), since the variables were non-normally distributed. Categorical variables were presented using frequencies and percentages. Assessed characteristics included age, body mass index (BMI), drug use for LUTS, family history of PCa or other hereditary cancer, PSA values at referral and during hospitalization, LUTS mentioned during consultations with the GP and/or urologist, IPSS questionnaire scores, presence of suspicious DRE findings at the GP or urologist, prostate volume on MRI, and pathological results. LUTS mentioned during consultations was categorized by the researcher into irritative, obstructive, irritative and obstructive, and unspecified, based on the information in the referral letter and data from Epic.

The two groups were compared through chi-square tests for categorical variables and Mann-Whitney U tests for numerical variables, with a predefined significance level of $p < 0.05$. In certain variables, there were instances of missing data or data that was marked as 'unknown', both of which were handled as missing data. Results were summarized in a baseline table that reflects the number of patients for whom the data was available in each case.

Univariate logistic regression was conducted to determine whether LUTS could serve as a predictive factor. Abnormal MRI (PI-RADS 3-5) was used as the dependent variable. The individually tested independent variables included: LUTS reported at urologist and/or GP, LUTS reported solely at the urologist, LUTS reported solely at the GP, total IPSS score, IPSS severity subgroups (mild vs moderate and severe, moderate vs mild, moderate vs severe, and severe vs mild and moderate) and LUTS divided into subgroups (irritative, obstructive, irritative and obstructive, unspecified) at urologist and GP.

Additional univariate logistic regression was employed to identify risk factors for abnormalities on MRI. The selection of risk factors was based on prior knowledge of risk factors for prostate cancer. Independent variables included: age, BMI, drug use for LUTS, family history of prostate cancer, family history of hereditary cancer types linked to PCa as ovarium and breast cancer under 50 years of age, DRE at GP and urologist and PSA at referral and hospital [1, 9, 10, 17].

Multiple multivariate analyses were conducted to assess the relationship between MRI-detected abnormalities and IPSS and LUTS. Potential predictive or risk factors identified from the univariate analysis with a significance level of $p < 0.2$ were used. The goodness of fit of the model was assessed using the Nagelkerke R-squared statistic. Odds ratios (OR) and confidence intervals (CI) were used to describe the data and assess the strength of associations. Variables with a significance level of $p < 0.05$ were considered statistically significant in the multivariate analysis.

DRE at urologist and PSA at the hospital were excluded from the multivariate models. This ensured the development of a model applicable for triage before entering the fast-track, as this information is logically not available beforehand. To compare the predictive value of LUTS with IPSS, information that emerges during consultation will be used, such as LUTS at urologist or combined with the GP. Thus, this is solely used for the purpose of comparison and not for a constructing a predictive model.

Results

A total of 330 patients were initially enrolled, but 60 patients were excluded due to a medical history of PCa or previous PCa diagnostics. Subsequently, two patients were excluded as MRI scans were not available. As a result, a final cohort of 268 patients was included, with Group 1 consisting of 161 patients and Group 2 comprising 107 patients.
Notably, of the overall study population, 209 patients (78%) completed the IPSS questionnaire, providing valuable data for further analysis.

Baseline characteristics
Table 1 presents the patient characteristics of the study population. The two groups showed statistically significant differences in several variables. Men with abnormal MRI results were significantly older (70 vs 66, $p = 0.001$) and had higher PSA values at referral (7.18 vs 5.28, $p < 0.000$) and at repeat PSA in the hospital (6.64 vs 5.28, $p < 0.000$). Additionally, the incidence of irritative LUTS was significantly higher among men with normal MRI results compared to those with abnormal MRI results (19.9% vs 10.3%, $p = 0.031$). Moreover, men with only mild LUTS complaints had abnormal MRI findings more frequent (30.8% vs 20.5%, $p = 0.049$).

Table 1: Patient characteristics

	Overall N = 268	PIRADS 1-2 (n=161)	PIRADS 3-5 (n=107)	*p*-value
Descriptives				
Age at first visit, median [IQR]	67 [61-72]	66 [60-71]	70 [64-73]	**0.001***
BMI, median [IQR]	25.8 [24.5-28.4]	26.2 [24.6-29.1]	25.5 [24.2-27.9]	0.185*
Family history of PCa, n (%)	n = 121 (%), 46 (17.0)	n=71, 30 (18.6)	n=50, 16 (15.0)	0.472**
Family history of hereditary cancer	n=48, 5 (10.3)	n =28,11 (6.8)	n=20, 5 (4.7)	0.560**
Drug use for LUTS	n = 241 (%), 24 (10.0)	n=145, 14 (8.7)	n=96, 10 (9.3)	0.977**
PSA at referral, median [IQR]	5.85 [4.68-8.30]	n=160, 5.28 [4.20-6.62]	n=106, 7.18 [5.28-10.33]	**<0.000***
PSA at first visit, median [IQR]	5.65 [4.20-7.50]	n=129, 5.06 [3.68-6.26]	n=85, 6.64 [5.12-11.90]	**<0.000***
Information on LUTS and IPSS				
History of LUTS reported at referral	n = 203 (%), 138 (67.8)	87 (71.3)	51 (62.9)	0.212**
Irritative	43 (21.2)	32 (36.8)	11 (21.6)	**0.031****
Obstructive	35 (17.2)	18 (20.7)	17 (33.3)	0.250**
Irritative and obstructive	45 (22.2)	26 (29.9)	19 (37.3)	0.719**
Unspecified	15 (7.4)	11 (12.6)	4 (7.8)	0.277**
History of LUTS reported by Urologist	183 (68.3)	116 (72.0)	67 (62.6)	0.104**
Irritative	30 (11.2)	21 (18.1)	9 (13.4)	0.239**
Obstructive	46 (17.2)	29 (25.0)	17 (25.4)	0.651**
Irritative and obstructive	106 (39.6)	66 (56.9)	40 (59.7)	0.554**
Unspecified	1 (0.4)	0 (0)	1 (1.5)	0.219**
LUTS reported by GP or urologist	196 (73.1)	124 (77.0)	72 (67.3)	0.078**
IPSS questonnaire filled out	209 (78.0)	125 (77.6)	84 (78.5)	0.867**
IPSS-scores, median [IQR]	10 [6-15.5]	11 [7-17]	10 [5.25-14]	0.076*
IPSS-score 0-7 'mild', n, (%)	66 (24.6)	33 (20.5)	33 (30.8)	**0.049****
IPSS score 8-19 'moderate'	115 (42.9)	73 (45.3)	42 (39.3)	0.231**
IPSS score 20-35 'severe'	28 (10.4)	19 (11.8)	9 (8.4)	0.351**

Abbreviations: IQR (interquartile range) BMI (body mass index), PSA (prostate specific antigen), PCa (prostate cancer), LUTS (lower urinary tract symptoms), IPSS (International Prostate Symptom Score)

Clinical outcomes

Table 2 displays the clinical outcomes, including an overview of the highest PI-RADS scores. Differences between the two groups are observed in terms of DRE results at the urologist. In Group 2, 42.7% of men had a suspicous DRE, while only 1.9% in Group 1, with a *p*-value of <0.000. Furthermore, a significant disparity in prostate volume is observed, where men in Group 2 exhibited a smaller mean prostate volume (45 cc) compared to those in Group 1 (53 cc), with a *p*-value of 0.003. PSA density at referral and at first visit also differed significantly, with values of 0.102 vs. 0.173 and 0.075 vs. 0.118, both having a *p*-value <0.000.

Table 2: Clinical outcomes

	Overall N = 268	PIRADS 1-2 (n=161)	PIRADS 3-5 (n=107)	p value
Suspect DRE referral, n (%)	n = 130, 29 (22.1)	n=81, 17 (21.0)	n=50, 12 (24.0)	0.642**
Suspect DRE urologist	n = 155, 39 (25.2)	n=66, 1 (1.9)	n=89, 38 (42.7)	**<0.000****
Prostate volume (cc), median [IQR]	50 [37-66]	53 [40-70]	45 [30-60]	**0.003***
PSA density referral, median [IQR]	0.117 [0.083-0.181]	0.102 [0.075-0.135]	0.173 [0.107-0.292]	**<0.000***
PSA density at first visit, median [IQR]	0.089 [0.051-0.150]	0.075 [0.048-0.113]	0.118 [0.069-0.234]	**<0.000***
Highest PI-RADS (n=268)				
1	84 (31.3)	84 (52.2)	0	NA
2	77 (28.7)	77 (47.8)	0	NA
3	19 (7.1)	0	19 (17.8)	NA
4	50 (18.7)	0	50 (46.7)	NA
5	38 (14.2)	0	38 (35.5)	NA

Abbreviations: DRE (digital rectal examination), IQR (interquartile range) PI-RADS (Prostate Imaging Reporting and Data System), NA (Not applicable)

Biopsy outcomes

Table 3 presents the data on biopsy outcomes. A much higher proportion of biopsies were performed in Group 2 compared to Group 1 (85% vs 1.9%, p-value < 0.000). Additionally, there was a greater occurrence of prostate cancer (PCa) and clinically significant prostate cancer (csPCa) in Group 2 compared to Group 1.

Table 3: Biopsy outcomes

	Overall N = 268	PIRADS 1-2 (n=161)	PIRADS 3-5 (n=107)	p value
Biopsy performed n, (%)	94 (35.1)	3 (1.9)	91 (85.0)	**<0.000****
Highest ISUP & Gleason				
benign	16 (17.0)	1 (33.3)	15 (16.5)	0.445**
group 1 (gleason 6)	17 (18.1)	1 (33.3)	16 (17.6)	0.486**
group 2 (gleason 3+4)	22 (23.4)	0	22 (24.2)	0.331**
group 3 (gleason 4+3)	19 (20.2)	1 (33.3)	18 (19.8)	0.565**
group 4 (gleason 8)	13 (13.8)	0	13 (14.3)	0.481**
group 5 (gleason 9-10)	7 (7.4)	0	7 (7.7)	0.618**
PCa, rate	79 (29.5)	2 (1.2)	77 (72.0)	**<0.000****
csPCa	64 (23.9)	1 (0.6)	63 (58.9)	**<0.000****

Biopsy outcomes. Abbreviations: ISUP (nternational Society of Urological Pathology), PCa (Prostate cancer), csPCa (clinically significant prostate cancer)

Univariate analysis

The results of univariate logistic regression, which examine the relationship between MRI abnormalities and LUTS or IPSS, are reflected in **Table 4.**

Significant results were discovered for LUTS reported at GP and/or urologist, LUTS as assessed by a urologist and irritative LUTS at referral.

Additionally, the numerical IPSS score was found to be a possible predictor, as was found for IPSS category mild versus moderate or severe, IPSS category moderate vs mild, IPSS category mild vs moderate, IPSS category severe vs mild and IPSS mild vs severe.

Table 4: Univariate analysis of LUTS and IPSS

	OR [95% CI]	*p*-value
LUTS reported at GP and/or urologist	0.614 [0.356-1.059]	**0.080**
LUTS mentioned at urologist	0.650 [0.386-1.094]	**0.105**
Irritative	0.612 [0.269-1.393]	0.242
obstructive	0.860 [0.446-1.657]	0.652
obstructive and irritative	0.859 [-0.520-1.420]	0.554
LUTS mentioned at referral	0.684 [0.376-1.243]	0.213
Irritative	0.442 [0.208 - 0.938]	**0.034**
obstructive	1.535 [0.738-3.192]	0.252
obstructive and irritative	1.132 [0.578-2.216]	0.719
IPSS score	0.971 [0.933-1.012]	**0.161**
IPSS mild vs moderate or severe	1.804 [0.998-3.259]	**0.051**
IPSS moderate vs. mild	0.575 [0.311-1.063]	**0.078**
IPSS severe vs. mild	0.474 [0.187-1.199]	**0.115**
IPSS severe vs. mild or moderate	0.669 [0.287-1.561]	0.353
IPSS moderate vs. severe	1.215 [0.504-2.926]	0.665
IPSS mild vs. severe	2.111 [0.834-5.342]	**0.115**
IPSS mild vs. moderate	1.738 [0.941-3.211]	**0.078**
IPSS severe vs. moderate	0.823 [0.342-1.983]	0.665

Abbreviations: LUTS (lower urinary tract symptoms), IPSS (International Prostate Symptom Score), OR (odds ratio).

The univariate analysis of various baseline characteristics and abnormal MRI results (**Table 5**) revealed a significant association for age. Similarly, PSA value at referral and PSA value at the hospital were both associated with abnormal MRI findings.
An abnormal DRE by a urologist showed a particularly strong association, with an OR of 48.431 and a 95% CI of [6.430-364.782], and a significant p-value of <0.000.

Table 5: Univariate analysis of potential risk factors for MRI PI-RADS 3-5

	OR [95% CI]	*p*-value
Age	1.044 [1.007-1.082]	**0.018**
Drug use for LUTS	1.088 [0.462-2.561]	0.847
Family history of PCa	1 [0.999-1.000]	0.671
Family history hereditary cancer	1 [0.999-1.001]	0.785
PSA value at referral	1.145 [1.075-1.221]	**<0.000**
PSA value at hospital	1.243 [1.122-1.276]	**<0.000**
Abnormal DRE urologist	48.431 [6.430-364.782]	**<0.000**
Abnormal DRE GP	1.221 [0.526-2.836]	0.642

Abbreviations: LUTS (lower urinary tract symptoms), PCa (Prostate cancer), PSA (prostate specific antigen), DRE (digital rectal examination), OR (odds ratio).

Multivariate analysis
The multivariate analysis, examining the link between risk factors and LUTS or IPSS, resulted in five distinct models. One variable concerning IPSS or LUTS was utilized in each model, given the overlapping nature of these variables. **Table 6** indicates that a higher IPSS score was associated with a decreased chance of abnormalities. Additionally, the presence of an elevated PSA value at referral showed a positive association with abnormal MRI. Age was

not significantly associated in this model. The Nagelkerke test yielded a predictive capacity of 0.177.

Tabel 6: Multivariate analysis of baseline risk factors and IPSS-score value.

	OR [95% CI]	*p*-value
Age	1.025 [0.985-1.067]	0.216
PSA value referral	1.173 [1.075-1.281]	**<0.000**
IPSS-score	0.952 [0.908-0.997]	**0.036**

Abbreviations: PSA (prostate specific antigen), IPSS (International Prostate Symptom Score, OR (odds ratio)

In **Table 7** is reflected that mild category IPSS-score gives a higher chance of MRI abnormalities then severe category does (OR 3.844 [1.236-11.952] vs. OR 0.260 [0.084-0.809]). PSA value upon referral is a significant predictor, while age is not. The Nagelkerke test showed a value of 0.196.

Tabel 7: Multivariate analysis of baseline risk factors and IPSS-score value.

	OR [95% CI]	*p*-value	OR [95% CI]	*p*-value
Age	1.022 [0.982-1.063]	0.288	1.022 [0.982-1.063]	0.288
PSA value referral	1.182 [1.077-1.298]	**0.000**	1.182 [1.077-1.298]	**0.000**
Mild vs. severe	3.844 [1.236-11.952]	**0.020**	NA	NA
Severe vs. mild	NA	NA	0.260 [0.084-0.809]	**0.020**

Abbreviations: PSA (prostate specific antigen), NA (non-applicable), OR (odds ratio)

Table 8 displays that irritative LUTS at referral shows a negative association with MRI abnormalities, while PSA value at referral and age at enrollment demonstrated a positive association. The Nagelkerke test for this model indicated the highest predictive capacity with a value of 0.208.

Table 8: Multivariate analysis of baseline risk factors and irritative LUTS at referral.

	OR (95% CI)	*p*-value
Age	1.051 [1.004-1.099]	**0.031**
PSA value referral	1.127 [1.057-1.201]	**<0.000**
Irritative LUTS at referral	0.420 [0.186-0.946]	**0.036**

Abbreviations: PSA (prostate specific antigen), LUTS (lower urinary tract symptoms), OR (odds ratio)

Lastly, **Table 9** illustrates significant associations for LUTS at GP and/or urologist, PSA at referral, and age. The Nagelkerke test value was 0.191.

Table 9: Multivariate analysis of baseline risk factors and LUTS reported.

	OR (95% CI)	p-value
Age	1.046 [1.007-1.088]	**0.022**
PSA value referral	1.144 [1.074-1.219]	**<0.000**
LUTS reported by GP or urologist	0.549 [0.304-0.989]	**0.046**

Abbreviations: PSA (prostate specific antigen), LUTS (lower urinary tract symptoms), OR (odds ratio)

PP-plot

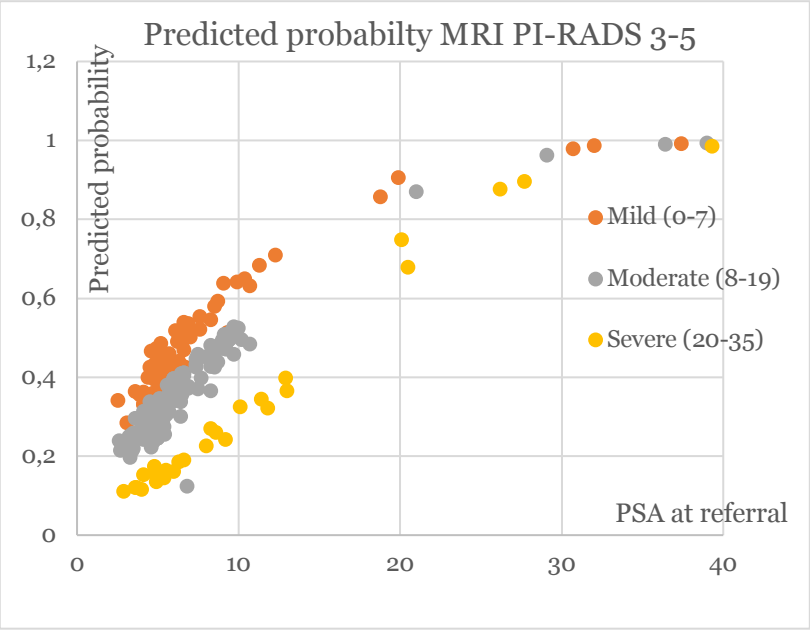

Figure 1: Predicted probability of MRI scans with PI-RADS score 3-5, using model 2. IPSS scores are displayed per category. Y-axis: predicted probability, x-axis PSA value at referral.

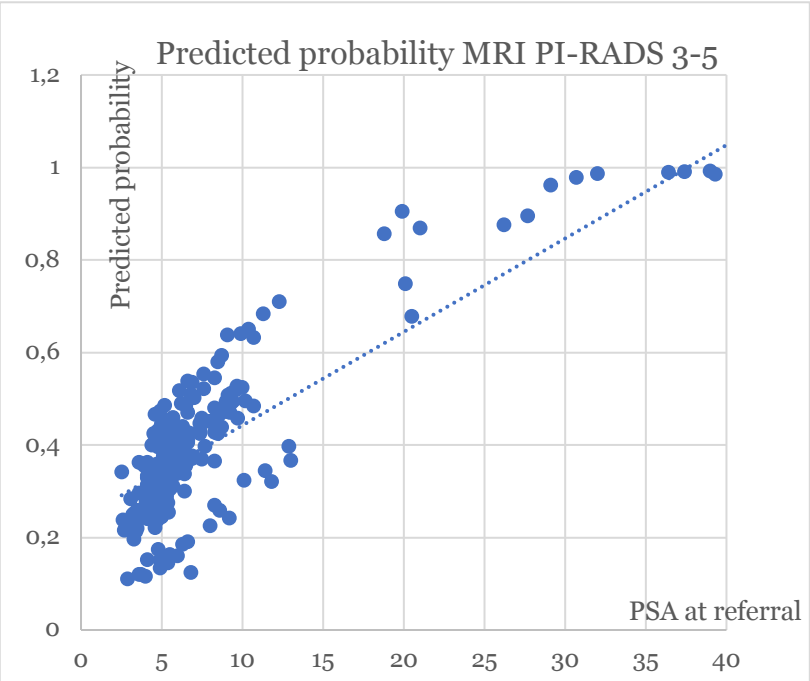

Figure 2: Predicted probability of MRI scans with PI-RADS score 3-5, using model 2. A best line of fit is displayed. Y-axis: predicted probability, X-axis PSA value at referral.

Focusing on using IPSS score for triage, a plot of the predicted probability was created using the data from **Table 7.** Due to the higher Nagelkerke for IPSS category mild vs. severe than for IPSS numerical score, that model was used. As illustrated in **Figure 1**, at equal PSA values, IPSS score categories clearly exhibit distinguishable probabilities of MRI deviations. The severe category presents a lower likelihood than the mild category. **Figure 2** highlights the best line of fit, showing that with increasing PSA values, the probability of abnormalities rises. Furthermore, for elevated PSA-values, the likelihood of having an abnormal MRI is high, irrespective of IPSS severity.

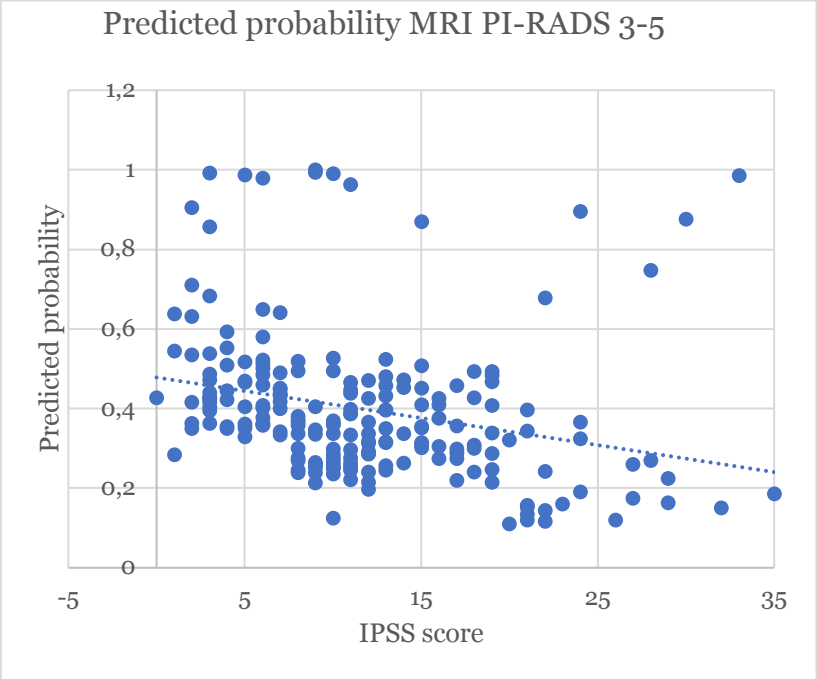

Figure 3: Predicted probability of MRI scans with PI-RADS score 3-5, using model 1. A best line of fit is displayed. Y-axis: predicted probability, x-axis IPSS score as a numerical variable.

Graphically displayed in **Figure 3**, an increasing IPSS score correlates with a decreasing probability of an MRI with deviations.

Discussion

The study's objective was to individualize the rapid diagnostic pathway for prostate cancer by exploring the association between IPSS score and MRI scan abnormalities. Furthermore, the predictive values of reported LUTS and IPSS score were compared while also investigating into other risk factors.
Our findings reveal a significant reduction in the probability of detecting abnormal prostate MRI results among patients with high IPSS scores, when LUTS were reported during the consultation and when irritative LUTS at referral were present. These results provide indications that incorporating IPSS questionnaires can enhance triage.

First, a higher IPSS score demonstrated a statistically significant negative association with abnormalities on MRI (OR = 0.953, 95% CI [0.910-0.998], p-value = 0.040).
In the segregated models based on the severity of IPSS scores, we observed interesting associations as well. Patients with mild IPSS scores showed higher odds of MRI abnormalities (OR 3.844 [1.236-11.952], p=0.020), while patients with severe IPSS scores had substantially lower odds of abnormalities (OR 0.260 [0.084-0.809], p =0.020).

In these models, age was found not to be significant. This is remarkable since age is one of the most important risk factors for prostate cancer [9]. We selected a relatively elderly study population, which may have influenced the predictive power of age compared to a population with a broader age distribution. Besides, it should be noted that the likelihood of urinary symptoms also increases with advancing age and is therefore a contributing factor in experiencing urinary complaints [11,18,19].
PSA was significant, as expected, since it is the most important diagnostic marker available [8,10].

Previous research findings suggested that LUTS might act as a protective factor. This corresponds with our finding that higher IPSS scores, which reflect the presence of more LUTS, reduce the chances of MRI abnormalities [7].
LUTS is often associated with BPH, which is linked to an elevated PSA level; however, it does not increase the risk of prostate cancer but can still coexist [11, 20]. This supports the hypothesis that an elevated PSA level, when combined with LUTS, is more likely to be explained by BPH than by PCa [19].
The first model of the Rotterdam Prostate Cancer Risk Calculator (RPCRC) estimates an individual's risk of prostate cancer based on age, family history and IPSS score. A higher IPSS score is also considered to have a protective factor in this calculator. However, this calculator is designed for patients whose PSA value and DRE are not investigated, leading to a much lower prior probability than in our study cohort [21,22].
A study that aligns better with our study population, although using another endpoint, demonstrates similar results. Ito et al. observed a significant correlation between lower IPSS scores and an increased incidence of PCa in their study comprising men with elevated PSA levels who also completed the IPSS questionnaire [23].
Although Martin et al. reported an association between higher IPSS scores and a higher localized PCa risk, it is important to consider their diverse age group in the study population and randomly selected participants. The absence of measured PSA values or DRE results further contributes to a much lower prior probability within this cohort. Considering the independent increased risk of urinary complaints and PCa among older men, we can explain why our study with a different population yields dissimilar results [24].

Furthermore, the presence of LUTS, whether reported by the urologist or the general practitioner, showed a protective value (OR 0.549 with a 95% CI of [0.304-0.989], p-value 0.046). It is noteworthy that the categorized IPSS score provides a stronger predictive value than the presence of LUTS.
This could be explained by the standardized nature of the IPSS questionnaire, while assessment and documentation of LUTS are highly subjective and can be interpreted differently by different investigators.
Additionally, it seems reasonable to expect a correlation between symptom severity and underlying pathophysiology. While prostate cancer most often occurs in the peripheral zone of the prostate, the most important comorbidity, BPH, arises more centrally and therefore results in more complaints [25-27]. Therefore, pronounced LUTS symptoms could be attributed to a BPH diagnosis and explain heightened PSA values. For PCa, intense symptoms would be infrequent due to tumor's location, mild urinary symptoms remain understandable.

Specifically mentioning irritative LUTS in the referral letter also indicated a decreased likelihood of abnormal MRI scans (OR = 0.420, 95% CI [0.186-0.946], p-value = 0.036). This could again originate from prostatitis and BPH, frequently manifesting irritative LUTS like urgency and frequency. Symptoms of prostatitis can also resolve after antibiotics and possible cease by the time of the urologist consultation [28]. BPH and prostatitis do not confer a higher likelihood of prostate carcinoma, thereby reducing the probability of diagnosing prostate carcinoma in the presence of symptoms related to these conditions [29].

No significant association was found between LUTS mentioned at referral of other categories (obstructive, or in combination), and notably, no significant association was observed between LUTS mentioned at the urologist, as demonstrated in previous research [7].

Obstructive LUTS are not described as a specific symptom of prostate carcinoma or another common urological condition that results in elevated PSA levels or abnormal DRE [2]. As a result, it is not surprising that no association shows.
The second difference could be attributed to the different approach used in the previous study, where the absence of LUTS and unknown LUTS status were combined. In the current study we corrected for this bias by treating unknown LUTS as missing data, resulting in relatively more patients with LUTS as mentioned at the urologist (68.3% vs 58.3% compared to Verlinden) and the GP (67.8 % vs 45% compared to Verlinden). This may have biased the predictive value in that study, leading to a difference as compared to the results of the current study.

Combining LUTS reported by both GP and urologist provides a more comprehensive picture than LUTS presence solely from either. The lack of significance at the GP could arise from substantial missing data on LUTS and varied reporting, introducing subjectivity. Also, information is possibly not as extensively collected as it would be by a urologist. Results at the urologist could be explained by potential symptoms that resolve after GP visit. Furthermore, subjective interpretation regarding the presence and absence of LUTS and variations in determining the threshold for documenting LUTS complaints occur, even among urologists. These findings once again highlight that IPSS is a more reliable and quantified measure.

Consistent with previous research, the following risk factors were identified: older age (OR 1.044 CI [1.007-1.082], p-value of 0.018), PSA value at referral (OR 1.145 [95% CI [1.075-1.221], p-value <0.000), repeat PSA value at the hospital (OR 1.243 CI [1.122-1.276], p-value <0.000), and abnormal digital rectal examination (DRE) by a urologist (OR 48.431 CI [6.430-364.782], p-value <0.000). [9]

Furthermore, the analysis of the predicted probability (**Graph 1**) revealed that, for equivalent PSA values, patients with mild LUTS displayed a significantly higher likelihood of MRI abnormalities compared to those with moderate or severe LUTS. The influence of IPSS primarily applies to lower PSA values, for higher PSA values the risk of abnormalities will be substantially high irrespective of the LUTS circumstances. Notably, the odds demonstrated a progressive pattern, increasing from mild to moderate, and further to severe LUTS.

Strengths and limitations
The strengths of the study include the use of a validated and quantified questionnaire which was completed by a substantial proportion of the study population. Additionally, we examined a research population that almost precisely aligns with the group which we intend to implement measures for.
Several limitations must also be considered. The retrospective design resulted in a substantial amount of missing data, including family history, completed IPSS questionnaires, references to LUTS in referral letters and DRE results at GP. Additionally, the subjective interpretation of LUTS presence based on referral letter information, and the potential non-response bias, in which men without urinary complaints might not fill out the questionnaire as much as patients with urinary complaints, are notable restrictions. Furthermore, the exclusion of patients with a history of prostate cancer or previous analysis for prostate cancer led to the formation of an even higher-risk group, as previous biopsy or history lower the change of PCa diagnosis. [30]

A potential future direction would involve a prospective design, with all patients completing an IPSS questionnaire before their urologist visit. Categorization into fast-track or standard diagnostic pathway based on IPSS severity will then assess if anticipated outcomes are realized. A cutoff value for PSA value and influence of IPSS should be investigated. Also, the

influence of irritative LUTS at referral should be tested. Additionally, increasing the sample size would be beneficial to obtain more reliable findings.

Conclusion & impact
The study provides valuable insights into the link between IPSS score and prostate MRI abnormalities within this specific high-risk cohort, indicating that IPSS score predicts abnormalities better than reported LUTS complaints. Especially for lower PSA values, mild LUTS cause much higher probability of an abnormal MRI, underscoring the preference for placing patients in the fast-track pathway. Also, irritative LUTS at referral tend to act as protective factor, which may warrant considering placing the patient in the regular diagnostic pathway. This has the potential to improve selecting the fast-track patients and increase efficiency for this new pathway, though confirmation thought further research is needed.

References

1. Pernar CH, Ebot EM, Wilson KM, Mucci LA. The Epidemiology of Prostate Cancer. Cold Spring Harb Perspect Med. 2018 Dec 3;8(12):a030361. doi: 10.1101/cshperspect.a030361.
2. Gandaglia G, Leni R, Bray F, Fleshner N, Freedland SJ, Kibel A, Stattin P, Van Poppel H, La Vecchia C. Epidemiology and Prevention of Prostate Cancer. Eur Urol Oncol. 2021 Dec;4(6):877-892. doi: 10.1016/j.euo.2021.09.006.
3. Culp MB, Soerjomataram I, Efstathiou JA, Bray F, Jemal A. Recent Global Patterns in Prostate Cancer Incidence and Mortality Rates. Eur Urol. 2020 Jan;77(1):38-52. doi: 10.1016/j.eururo.2019.08.005.
4. De Sousa A, Sonavane S, Mehta J. Psychological aspects of prostate cancer: a clinical review. Prostate Cancer Prostatic Dis. 2012 Jun;15(2):120-7. doi: 10.1038/pcan.2011.66.
5. Helsper CCW, van Erp NNF, Peeters PPHM, de Wit NNJ. Time to diagnosis and treatment for cancer patients in the Netherlands: Room for improvement? Eur J Cancer. 2017 Dec;87:113-121. doi: 10.1016/j.ejca.2017.10.003.
6. Paulino Pereira LJ, Heetman JG, van den Bergh RCN, van Melick HHE. Superfast Magnetic Resonance Imaging-based Diagnostic Pathway for Prostate Cancer. Eur Urol Open Sci. 2022 Oct 25;46:30-32. doi: 10.1016/j.euros.2022.09.017.
7. S. Verlinden. (2023) Clinical Outcomes of The Diagnostic Fast Track for Prostate Cancer, a Process Analysis. 2023 Jan. (Medical student)
8. Taplin ME, Smith JA. Clinical presentation and diagnosis of prostate cancer. In: Lee WR, Richie JP, Sartor AO, editors. UpToDate. [updated Feb 06, 2023; cited Jul 2023]. Available from: https://www.uptodate.com/contents/clinical-presentation-and-diagnosis-of-prostate-cancer.
9. Sartor AO. Risk factors for prostate cancer. In: Lee WR, Richie JP, editors. UpToDate. [updated Oct 10, 2022; cited Jul 2023]. Available from: https://www.uptodate.com/contents/risk-factors-for-prostate-cancer
10. Merriel SWD, Pocock L, Gilbert E, Creavin S, Walter FM, Spencer A, Hamilton W. Systematic review and meta-analysis of the diagnostic accuracy of prostate-specific antigen (PSA) for the detection of prostate cancer in symptomatic patients. BMC Med. 2022 Feb 7;20(1):54. doi: 10.1186/s12916-021-02230-y.
11. McVary KT. Clinical manifestations and diagnostic evaluation of benign prostatic hyperplasia. In: O'Leary MP, editor. UpToDate. [updated Mar 22, 2023; cited Jul 2023]. Available from: https://www.uptodate.com/contents/clinical-manifestations-and-diagnostic-evaluation-of-benign-prostatic-hyperplasia
12. Kristal AR, Arnold KB, Schenk JM, Neuhouser ML, Weiss N, Goodman P, Antvelink CM, Penson DF, Thompson IM. Race/ethnicity, obesity, health related behaviors and the risk of symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. J Urol. 2007 Apr;177(4):1395-1400; quiz 1591. doi: 10.1016/j.juro.2006.11.065.
13. Barry MJ, Fowler FJ Jr, O'Leary MP, Bruskewitz RC, Holtgrewe HL, Mebust WK, Cockett AT. The American Urological Association symptom index for benign prostatic hyperplasia. The Measurement Committee of the American Urological Association. J Urol. 1992 Nov;148(5):1549-57; discussion 1564. doi: 10.1016/s0022-5347(17)36966-5.
14. Epic Systems. 2022. [Cited 2023 July]. Epic: https://www.epic.com/about.
15. PA Harris, R Taylor, R Thielke, J Payne, N Gonzalez, JG. Conde. (2009*)Research electronic data capture (REDCap)* – A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. *Apr;42(2):377-81.*
16. IBM Corp. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp; 2019.
17. Schröder FH, Roobol MJ, Bangma CH. Vroege opsporing van prostaatkanker--aanbevelingen na 13 jaar follow-up in de Europese gerandomiseerde studie [Early

detection of prostate cancer--recommendations after 13 years of follow-up in the European randomised study]. Ned Tijdschr Geneeskd. 2015;159:A8677.
18. Berry SJ, Coffey DS, Walsh PC, Ewing LL. The development of human benign prostatic hyperplasia with age. J Urol. 1984 Sep;132(3):474-9. doi: 10.1016/s0022-5347(17)49698-4.
19. Platz EA, Joshu CE, Mondul AM, Peskoe SB, Willett WC, Giovannucci E. Incidence and progression of lower urinary tract symptoms in a large prospective cohort of United States men. J Urol. 2012 Aug;188(2):496-501. doi: 10.1016/j.juro.2012.03.125.
20. Chang RT, Kirby R, Challacombe BJ. Is there a link between BPH and prostate cancer? Practitioner. 2012 Apr;256(1750):13-6, 2.
21. Schröder FH, Hugosson J, Roobol MJ, Tammela TL, Ciatto S, Nelen V, Kwiatkowski M, Lujan M, Lilja H, Zappa M, Denis LJ, Recker F, Berenguer A, Määttänen L, Bangma CH, Aus G, Villers A, Rebillard X, van der Kwast T, Blijenberg BG, Moss SM, de Koning HJ, Auvinen A; ERSPC Investigators. Screening and prostate-cancer mortality in a randomized European study. N Engl J Med. 2009 Mar 26;360(13):1320-8. doi: 10.1056/NEJMoa0810084.
22. Roobol MJ, Zhu X, Schröder FH, van Leenders GJ, van Schaik RH, Bangma CH, Steyerberg EW. A Calculator for Prostate Cancer Risk 4 Years After an Initially Negative Screen: Findings from ERSPC Rotterdam. Eur Urol. 2013 Apr;63(4):627-33. doi: 10.1016/j.eururo.2012.07.029.
23. Ito M, Masuda H, Kawakami S, Fujii Y, Koga F, Saito K, Yamamoto S, Yonese J, Fukui I, Kihara K. Impact of lower urinary tract symptoms on prostate cancer risk among Japanese men with prostate-specific antigen <10 ng/mL and non-suspicious digital rectal examination. Int J Urol. 2013 Dec;20(12):1163-8. doi: 10.1111/iju.12141.
24. Martin RM, Vatten L, Gunnell D, Romundstad P, Nilsen TI. Lower urinary tract symptoms and risk of prostate cancer: the HUNT 2 Cohort, Norway. Int J Cancer. 2008 Oct 15;123(8):1924-8. doi: 10.1002/ijc.23713.
25. Chandra Engel J, Palsdottir T, Aly M, Egevad L, Grönberg H, Eklund M, Nordström T. Lower urinary tract symptoms (LUTS) are not associated with an increased risk of prostate cancer in men 50-69 years with PSA ≥3 ng/ml. Scand J Urol. 2020 Feb;54(1):1-6. doi: 10.1080/21681805.2019.1703806.
26. Oh JJ, Jeong SJ, Jeong CW, Byun SS, Hong SK, Choe G, Lee SE. Is there any association between the severity of lower urinary tract symptoms and the risk of biopsy-detectable prostate cancer in patients with PSA level below 20 ng/ml in multi-core prostate biopsy? Prostate. 2013 Jan;73(1):42-7. doi: 10.1002/pros.22537.
27. Holtedahl K, Borgquist L, Donker GA, Buntinx F, Weller D, Campbell C, Månsson J, Hammersley V, Braaten T, Parajuli R. Symptoms and signs of urogenital cancer in primary care. BMC Prim Care. 2023 Apr 26;24(1):107. doi: 10.1186/s12875-023-02063-z.
28. Brehm TJ, Trautner BW, Kulkarni PA. Acute and Chronic Infectious Prostatitis in Older Adults. Infect Dis Clin North Am. 2023 Mar;37(1):175-194. doi: 10.1016/j.idc.2022.09.004.
29. Gnanapragasam VJ, Greenberg D, Burnet N. Urinary symptoms and prostate cancer-the misconception that may be preventing earlier presentation and better survival outcomes. BMC Med. 2022 Aug 4;20(1):264. doi: 10.1186/s12916-022-02453-7.
30. Zhu X, Albertsen PC, Andriole GL, Roobol MJ, Schröder FH, Vickers AJ. Risk-based prostate cancer screening. Eur Urol. 2012 Apr;61(4):652-61. doi: 10.1016/j.eururo.2011.11.029.