ORIGINAL SCIENTIFIC ARTICLE

PROGNOSTIC VALUE OF PROSTATA SPECIFIC ANTIGEN AND DIGITAL RECTAL EXAMINATION AT PROSTATE BIOPSY

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ABSTRACT

Prostate cancer is a worldwide health concern with an increasing global incidence. In the Republic of Serbia, it is the third most commonly diagnosed cancer in men. The research aims to determine the influence of PSA value and digital rectal examination on the pathohistological findings of prostate biopsy in men in Central Serbia. The study was designed as a retrospective, cross-sectional analytical study conducted in the period from December 2021 to December 2022 after receiving the confirmation of the Ethics Committee of the University of Applied Sciences Kragujevac. Among 151 respondents aged 49 to 88 who underwent consecutive biopsies during the study period, prostate cancer was detected in 65 (42%). Out of 65 positive biopsies, 33 subjects had a Gleason score of up to 7, while 32 subjects had a Gleason score over 7. Prostate biopsies significantly correlated with PSA levels ($p=0.02$), while DRE and prostate volume did not show statistical significance on the prostate biopsy result. PSA level testing leads to early detection of prostate disease in the elderly. PSA value was the only clinical variable associated with an increased rate of prostate cancer in men ≥ 70 and older ($p=0.02$). DRE, PSA, and prostate volume are important parameters associated with an increase in prostate cancer detection rate in men over 70 years of age.

Keywords: *Older patients, PSA screening, pathohistological findings, digital rectal examination, prostate biopsy.*

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INTRODUCTION

Prostate cancer remains a health concern worldwide with an increasing global incidence. It is the second most common cancer and the fifth leading cause of cancer deaths worldwide, with an estimated 1.1 million new cases and 300,000 deaths in 2012 (1). Prostate cancer incidence varies by race/ethnicity, with African-Americans experiencing a 73% higher incidence rate than whites (2). Prostate-specific antigen (PSA) is ranked among the most valuable tumor markers in early detection, staging, follow-up, and treatment evaluation of prostate cancer. Since its discovery in 1979, the PSA has evolved into an invaluable tool for detecting, staging, and monitoring prostate cancer in men (3).

Prostate-specific antigen (PSA) and digital rectal examination (DRE) are important screening tools, while imaging modalities are used for metastatic workup. The golden standard in prostate cancer diagnosis is prostate biopsy with a variable number of prostate cores taken.[4] Findings such as abnormal digital rectal examination (DRE) and/or elevated serum prostate-specific antigen (PSA) level are the main indications for biopsy (5,6,7). Digital rectal examination is the oldest, non-invasive screening procedure for prostate cancer with a high specificity and a high negative predictive value. However, its moderate sensitivity does not allow for conclusions.[8] Moreover, it is crucial for evaluating the prostate for size, nodularity, induration, lobar asymmetry and/or tenderness. Even though it is simple to perform, non-invasive and inexpensive, it is subjective and often detects advanced disease (9,10). On the other hand, PSA is organ-specific but not cancer-specific, so other prostatic diseases, such as benign prostatic hyperplasia and prostatitis, may influence its effectiveness for cancer detection. Nonetheless, it is objective and cost-effective (11,12). The advantage of PSA is that it detects more organ-confined cancers than digital rectal examination (DRE). Thus, when used together, PSA and DRE detect more cancers than DRE alone (13). The 2013 Prostate Cancer World Congress consensus concluded that "*For men aged 50-69, level 1 evidence demonstrates that PSA testing reduces prostate cancer-specific mortality and the incidence of metastatic prostate cancer*" (14). Although several guidelines consider PSA to be a major cancer screening test, the PSA alone is not a reliable parameter to predict the probability of cancer histopathology on TRUS-guided prostate biopsy (15,16). Many parameters other than PSA, like f PSA, PSA velocity, PSA density, age-adjusted PSA values, DRE, and prostate volume, have been used to predict more precise results of prostate biopsies (17,18) Furthermore, Nomikos et al. reported that abnormal DRE significantly helped diagnose prostate cancer in older men with PSA<20 ng/ml (19).

For the above reasons, this study aims to evaluate the use of prostate-specific antigen (PSA) and digital rectal examination (DRE) prior to prostatic biopsy to predict prostate cancer diagnosis and determine which modality is more helpful for diagnosing prostate cancer.

MATERIAL AND METHODS

Study design

The study was designed as a retrospective, cross-sectional analytical study conducted by extracting data from the medical history of patients treated at the Clinic for Urology, UCC Kragujevac. Data extraction was performed using a semi-structured questionnaire intended for research purposes, which included data on the patient's age, TPSA values, DRE findings, prostate volume, and PH findings. The research was conducted according to the principles of Good Clinical Practice and the Declaration of Helsinki after receiving the confirmation of the Ethics Committee of the University Clinical Center Kragujevac.

Study population

The study population consisted of 151 patients who underwent a TRUS prostate biopsy at the Urology Clinic of the University Clinical Center Kragujevac from December 2021 to December 2022. TRUS biopsy was performed on an ultrasound machine (Toshiba). During each examination, 10 to 12 targeted samples were taken from the patient, and 5-6 samples each from the peripheral zone of both prostate lobes. DRE findings are classified as suspicious based on the presence of nodules, changes in prostate consistency (increased hardness), and loss of sulcus. Prostate volume was measured during the TRUS examination. After taking the material, the tissue samples were placed in formalin and sent to the Service for Pathological Diagnostics, UCC Kragujevac, for further PH verification. The tissue samples were fixed in a buffered formaldehyde solution, after which they were routinely processed in an autotechnicon and molded in paraffin blocks. From paraffin blocks, 4 μm thick sections were made, on which the H&E staining method and the immunohistochemical ABC staining method were applied.

Inclusion and exclusion criteria

Patient inclusion criteria in this study included:

- elevated PSA values and/or suspicious DRE findings,
- patients older than 49 years,
- PSA values > 4 ng/ml and/or abnormal DRE findings.

Patient exclusion criteria were:

- previous history of PCa or metastatic prostate disease,
- results of previous biopsies,
- patients on specific antitumor therapy for prostate cancer,
- any malignancy of the urogenital region.

Sample size calculation

The required sample size was calculated using G*Power software (20), based on the expected correlation of DRE and PSA values with prostate biopsy PH findings. Taking into account recently published studies (21) in this field in Europe and the world, 151 subjects were needed to conduct the research in terms of the minimum number of subjects for this cross-sectional study.

Statistical data processing

All statistical data were processed and obtained in the IBM SPSS Statistics 24. Descriptive statistics explained the mean value, minimum, maximum, median, standard deviation and variance for age, prostate volume, and PSA values. The absolute and relative frequency of suspicious/non-suspicious DRE, men under and over 70 years of age, as well as malignant and benign PH findings, were determined. The normality of the distribution for the analyzed parameters was tested using the Kolmogorov-Smirnov test. Statistical significance between groups was determined using the Mann-Whitney non-parametric test. χ^2 test was used to determine the dependence of DRE values and PH findings. A statistical significance of $p<0.05$ was considered statistically significant. The results are shown in the table.

RESULTS

During the research period at the Urology Clinic, 180 prostate biopsies were performed. Due to the extreme PSA level values, the results of 29 subjects were not considered further, so the research analyzed 151 respondents. Sixty-seven respondents were over 70 years old, of which 32 (47.8%) had prostate cancer, and 84 respondents were aged up to 70 years, of which 32 (38%) had prostate cancer confirmed. The average age of the respondents was about 69, with the youngest and the oldest respondent being 49 and 88 years old, respectively. Except for age, where the data follow a normal distribution (Kolmogorov-Smirnov test, 0.20>0.05), other data do not follow a normal distribution (0.00<0.05). Table 1 shows the demographic characteristics of the respondents depending on their age.

Prostate biopsy was performed only in 3 (4%) patients with PSA below 4mg/ml and abnormal DRE results. Four groups of PSA values were determined: 2 (2.4%) respondents under 70 years of age, 1 (1.5%) respondent over 70 years had a value below 4 ng/ml, 71 respondents (84.5%) up to 70 years of age had a PSA value of 4.1 to 15 ng/ml, and 42 respondents (62.7%) over 70 years of age. A PSA value of 15.1 to 30 ng/ml was found in 9 respondents (10.7%) under 70 years of age and 19 respondents over 70 years of age (28.4%). Two respondents (2.4%) under 70 years of age and 5 respondents (7.5%) over 70 years had a PSA value over 30ng/ml. (Table 1). Twenty-eight patients under the age of 70 (33.7%) and 17 respondents over the age of 70 (25.4%) had a negative DRE result. Suspicious DRE findings were found in 55 respondents (66.3%) under the age of 70 and in 50 respondents (74.6%) over the age of 70. DRE findings did not show a statistically significant impact on pathohistological prostate biopsy findings (p=0.09).

Older patients had a larger prostate volume (54.17±33.69), which is shown in Table 2. Gleason score > 7 was more common in the older group of patients. The size of the effect between the studied groups is shown in Table 2, which for PSA values (Phi=0.26) and Gleason score (Phi=0.30) is characterized as medium size of the effect between the studied groups, with a statistical significance of p=0, 01 for both investigated parameters.

DISCUSSION

PCa is the second most common cancer in men, and prostate cancer mortality is the sixth leading cause of death in the world[13]. According to 2021 data from the Institute for Public Health of the Republic of Serbia "Dr. Milan Jovanovic - Batut," prostate cancer ranks third with 10.5% of patients, right after lung cancer with 21.3% and colon and rectal cancer with 12.8% of patients. In Central Serbia, the standardized incidence rate includes men aged 40 to 75, while the standardized mortality rate includes men over 55, which indicates a mortality rate of 18.5% in this part of Serbia (22). It is important to note that men under the age of 60 may also be at risk, even if they do not have symptoms. Therefore, prevention through early PSA screening is recommended, and whether PSA screening reduces prostate cancer mortality remains controversial due to the inconsistency of the results of randomized clinical studies in the country and the world (23,24).

In this study, we analyzed age, PSA, prostate volume, DRE, and Gleason score as predictors for positive biopsy findings, which were also recognized as such in the study by *Mbaeri TU et al.,* conducted in Nigeria (25). The results of our study showed that total PSA is a predictor of a positive biopsy result in men older than 70 years (p=0.02), as in the study by *Ferlay et al.*[26] The reason for this result may be that the prostate biopsy in the older population had higher PSA values than in the younger patients. Prostate volume was analyzed to examine the direct influence of prostate volume on the prediction of histopathological findings. According to a study by *Sakaguchi K et al*. (27), in Japanese men with a PSA level over ng/ml, prostate volume was a significant predictor for a positive biopsy finding. Based on the results of our study, prostate volume should not be considered a predictive factor for a positive prostate biopsy (p=0.783). This result can be explained by the fact from the study by *Gordana Dj. et al.* (28) that the possibility of detecting cancer decreases with an increase in prostate volume.

When it comes to DRE as a predictive factor, according to the study *by Ojewola RW et al.* (29), it was shown that in a group of Nigerian men, it was a sufficiently accurate method for prostate disease screening. *Nomikos M. et al.* (30), believe that an abnormal DRE significantly helps diagnose prostate cancer in elderly men with PSA values below

20ng/ml. However, in our study, there was no statistical significance (p=3.04) between age groups and DRE in suspected DRE. This can be explained by the fact that patients over 75 years of age have a higher probability of prostate cancer in advanced clinical stages (31). During the study period, we had only 44.37% of respondents over 70 years of age, which is insufficient for possible statistical significance.

The limitations of this study are reflected in the retrospective design, which can sometimes limit the number of respondents that the research can cover. For a more realistic assessment of the problem of early detection of prostate cancer, a multicenter study in the Serbian population with a larger number of respondents and centers similar to African countries is necessary, as in the study *by Louisa K. Makau-Baras et al.* (32) Apart from diagnostic procedures, future research may include pharmacoeconomic studies of healthcare costs and the quality of life of these patients.

Table 1. Data of interest of respondents depending on age

Characteristics of the respondents		< 70	≥ 70	p
DRE	negative	28 (33.7%)	17 (25.4%)	
	suspicious	55 (66.3%)	50 (74.6%)	p=0,351

Characteristics of the respondents		< 70	≥ 70	p
PSA* (ng/ml)	<4	2 (2,4%)	1 (1,5%)	
	4,1 - 15	71 (84,5%)	42 (62,6%)	
	15,1 - 30	9 (10,7%)	19 (28,4%)	**p=0,013***
	>30	2 (2,4%)	5 (7,5%)	

*before biopsy

Characteristics of the respondents		< 70	≥ 70	p
Prostate volumen	<50ml	42 (50,6%)	39 (58,2%)	p=0,445
	>50 ml	41 (49,4%)	28 (41,8%)	

Characteristics of the respondents		< 70		p
Diagnosis	BPH	51 (61%)	35 (52.2%)	p=0,304
	Prostate cancer	33 (39%)	32 (47.8%)	

Characteristics of the respondents		< 70	≥ 70	p
Gleason score	5-7	30 (90,9%)	21 (65,6%)	
	8-10	3 (9,1%)	11 (34,4%)	**p=0,029***

*statistical significance

*for one patient there was the biopsy performed, without measuring the volume of prostate

Table 2. Mean value of PSA level and prostate volume depending on age

	< 70	≥ 70
PSA	10,29±6,46	13,68±8,64
Prostate volumen	53,11±25,92	54,17±33,69

CONCLUSION

PSA level testing leads to early detection of prostate disease in the elderly. PSA value was the only clinical variable associated with an increased rate of prostate cancer in men ≥ 70 and older (p=0.02). DRE and prostate volume are important parameters associated with an increase in prostate cancer detection rate, which did not show statistical significance in this study. The obtained results are useful in counselling men over 70 years of age for early prostate cancer detection. PSA and DRE are the basics in prostate cancer screening. With PSA value increase, the specificity and sensitivity increases as well - while DRE has specificity and sensitivity of 50-60% in prostate cancer screening and is impacted by urologists expertise. However, the decision to screen for prostate cancer is often made based on a urologist's assessment. Screening PSA levels and detecting latent asymptomatic disease can often increase healthcare costs and compromise the quality of life. On the other hand, the strict age limit of 50 years also limits screening in healthy younger men. In addition to multicenter domestic and foreign studies, for adequate observation and treatment of this problem, it is necessary to improve the pharmacist - sGP - urologist cooperation.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study protocol was approved by the Ethics Committee of the institution and was conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained from all patients.

CONFLICT OF INTEREST

There is no conflict of interest among the signed authors.

FUNDING

No funding.

List of abbreviations

TRUS - Transrectal ultrasound scan of the prostate;
BPH - Benign prostatic hyperplasia;
PSA - Prostata specific antigen;
DRE - Digital rectal examination of the prostate;
PH - Pathohistological findings;
HE - Hematoxylin-eosin staining method;
ABC - Avidin-Biotin Complex staining method;
sGP - Selected general practinioner;
PCa - Prostate Cancer.

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