

The role of prostate size in determining sermic PSA values in patients in grey zone patients

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ABSTRACT

Objective: To determine the relationship between the prostate volume and the serum values of prostate specific antigen among patients in the "grey zone", classified according to their age group. Gray zone represents serum prostate specific antigen values between 4.1 ng/ml to 10 ng/ml.

Material and Methods: Prospective and retrospective 1420 patients classified in four age-groups with LUTS (Lower Urinary Tract Symptoms) were analyzed. Patients were treated for Benign Prostate Hyperplasia (BPH) in the urology clinical at the University Clinical Center of Kosovo during the period of January 2010-October 2020. Data were recorded from patients according to age, prostate size estimated by trans abdominal ultrasound using 3.5 MHz ultrasonography, according to the ellipsoid formula, $V = D1 \times D2 \times D3/2.5$, Volume of prostate (V)= $T \times AP \times CC \times \pi/6$ where T=Transverse diameter, AP=Antero Posterior diameter, CC=Cranial Caudal diameter. Patients with confirmed prostate cancer were excluded from the study. Statistical analyses used t-test and ANOVA (Analysis of Variance) with 95% and 99% confidence intervals.

Results: For the grey zone patients, these mean values were 44.6 cm³ and 5.9 ng/mL.

Conclusions: The data provide evidence to support that prostate volume and serum Prostate Specific Antigen (PSA) concentration significantly correlate with aging and within the grey zone patients.

Keywords: grey zone, benign prostate hypertrophy, Prostate Specific Antigen (PSA), volume of prostate

INTRODUCTION

Benign Prostate Hyperplasia (BPH) disease is rare before the age of 30 years old in men. After the age of 50 years, the disease appears more often, and the obstructive symptoms are present in around 50% of men at the age of 75 years and in 30% of men at the age of 80 years at which prostatectomy intervention is required. The presence of testicular androgens and estrogens hormones are necessary in the development of the prostate in the embryo and its intensive growth until puberty.

All markers used in for prostate cancer screening the most important is the Prostate Specific Antigen (PSA). As tumor markers may serve specific products of tumor cells, their metabolites including also molecular markers. Since PSA is produced by benign cells and is also found in malignant prostate cells, they certainly do not represent an ideal tumor marker. An ideal tumor marker should be strongly specific and positive only in the presence of prostate cancer and adverse to other diseases. PSA is not quite sensitive which comes from the fact that 38% to 48% of patients with intra-prostatic carcinoma have normal PSA levels.

If the upper limit of normal PSA serum levels is considered to be 4 ng/ml, PSA as a prostate cancer tumor marker compared to BPH has a specificity of 49% and sensitivity of 71%. Despite these shortcomings in clinical practice, PSA currently represents the best tumor marker for prostate cancer detection. It is observed that PSA levels increases with age even without cancer existence. The reason for this occurrence is that the prostate volume growth is due to the development of BPH, but also contribute to the sub-clinical prostatitis, ischemia, infarct of the prostate and "leakage" of PSA, which is higher in old age man.

Starting from the 5th decade of life, PSA levels rise even in the absence of prostate cancer. Its level will increase also in the next decade. Older men have higher PSA values compared to younger males [1-7].

Today, there is a large number of tests for the PSA assessment, among them of which the most common is the Tandem R, where 100% of healthy people younger than 40 years and 97% of healthy people older than 40 years having PSA values up to 4.0 ng/ml. The examined persons older than 40 years do not have the PSA value above 10 ng/ml [8].

Similar to this test, there is the tandem E test which differs from the previous one where, instead of radioactive antibodies, alkaline

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phosphatase enzyme associated with the antibody is used, even when normal values for this test are 0 to 4 ng/ml [7].

PSA "gray zone" represents serum PSA values between 4.1 ng/ml to 10 ng/ml. It is named gray zone because the cause of serum PSA levels to increase may be due to different clinical conditions such as prostate cancer, BPH, prostatitis, ischemia and prostate infarct as well as various changes caused by age. To distinguish the causes of high serum PSA levels from prostate cancer, in clinical practice, prostate biopsy is necessary [7].

MATERIAL AND METHOD

Prospectively and retrospectively 1420 patients with LUTS (Lower Urinary Tract Symptoms) were analyzed. Patients were treated for BPH in the University Clinical Center of Kosovo Urology Clinic, during the period of time: January 2010-October 2020.

Research involving human subjects that is reported in the manuscript have been approved by the local ethical commission board from the University of Prishtina. Research carried out on humans was in compliance with the Helsinki Declaration.

Consent for participation in the study was obtained from participants. Data recorded from patients: age, prostate size estimated by transabdominal ultrasound using 3.5 MHz sonde, according to the ellipsoid formula, where $V = D1 \times D2 \times D3 / 2.5$ or Volume of prostate formula, $T \times AP \times CC \times \pi / 6$ where T=Transverse diameter, AP=Antero-Posterior diameter, CC=Cranial Caudal diameter. Also a Digital Rectal Exam (DRE) examination of prostate was performed. In cases suspected for prostate malignity ultrasound guided biopsy was performed.

Patients in which prostate cancer was confirmed were excluded from the study.

PSA values were calculated using IRMA method (Immunoradiometric Assay) monoclonal antibodies were obtained by a manufacturing company. The manufactured product is Immunotech-manufacturing company (Czech Republic). Laboratory analysis was conducted at the

Institute of Physiology and Immunology in UCCK in Pristina. Determination of PSA levels was based on the use of two different types of mouse monoclonal antibodies. Samples of serum or plasma were placed in test tubes incubated with monoclonal antibodies, which were present in the inner wall of the tube, in the presence of a second monoclonal antibody, which was marked with J125. After incubation the content of the test tube was washed so that antibodies tagged with J125 are left and not connected. Afterwards radioactivity was detected with gamma meters. These values are determined by a standard curve. Total PSA concentration in sample is proportional to the radioactivity. Radioactivity was measured by gamma radiation meter type DPC (Detector Positioned Coaxially).

The concentration of total PSA in the range of 146 healthy people is determined by this method. PSA average concentration was 0.77 ng/ml with a standard deviation of 0.76 ng/ml. 95% of the samples had total PSA below 1.8 ng/ml, and 99% of samples below 4.2 ng/ml.

Statistical parameters were calculated for the index of structure, the arithmetic average, standard deviation, minimum and maximum values, as well as linear correlation. Statistical analyses used t-test and Analysis of variance (ANOVA) with 95% and 99% confidence intervals.

RESULTS

The research included 1420 patients with benign prostate hyperplasia.

The average age of the patients involved in the research was 67.33 years old (Standard Deviation ± 8.07 years). The youngest patient with benign prostate hyperplasia was 50 years old and the oldest 87 years old. Divided by age group, the largest number of patients 670, or 47.2% belonged to the age group 60 years-69 years old and 420 patients, or 29.6% to the age group 70 years-79 years old, 210 of them, or 14.8% to the age group 50 years-59 years and 120 patients, or 8.5% of the age group 80 years - 89 years (Table 1 and Figure 1).

Tab. 1. Patients included in the survey classified by age group

Age group	N	%
50 years-59 years	210	14.8
60 years-69 years	670	47.2
70 years-79 years	420	29.6
80 years-89 years	120	8.5
Total	1420	100
Mean ± SD (vjet)	67.33 ± 8.07	
Range	50 years-87 years	

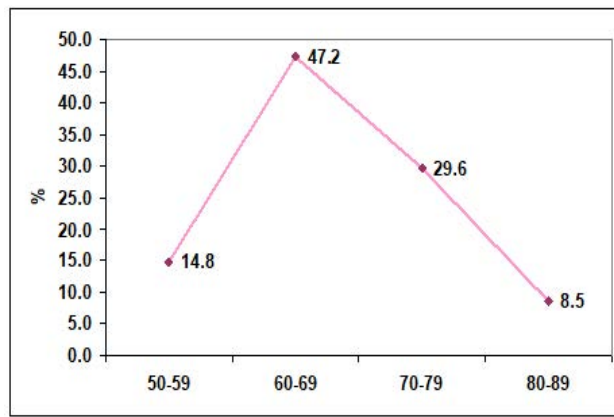


Fig. 1. Structure of patients according to the age group

In our clinical material, most 1030 patients of them, or 72.5% had ng/ml-10 ng/ml ie belong gray zone (Table 2 and Figure 2). serum PSA concentration below 4.1 ng/ml, 360 or 25.4% of 4.1

Tab. 2. Patients according to the concentration of PSA values

PSA values	N	%
<4.1 ng/ml	1030	72.5
4.1 ng/ml-10 ng/ml	360	25.4
>10 ng/ml	30	2.1
Total	1420	100

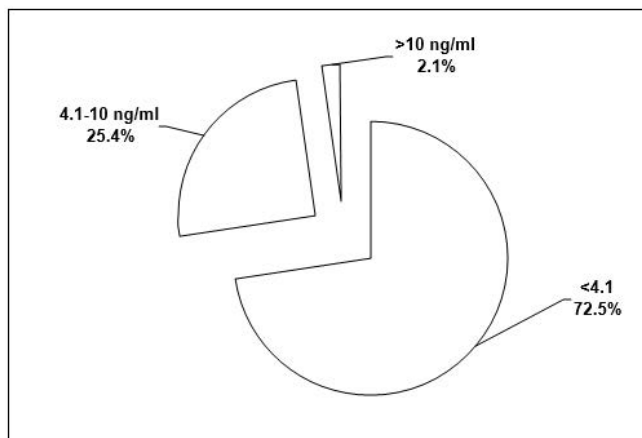


Fig. 2. Structure of patients belonging to the "gray zone"

Table 3 in the average prostate volume of gray zone patients and patients with PSA concentration <4.1 ng/ml. The average prostate volume for gray zone patients was 44.6 cm³ (Standard Deviation (SD) ± 11.6 cm³), while the average prostate volume patients with PSA values <4.1 ng/ml was 36.9 cm³ (Standard Deviation ± 8.2 cm³). T-test obtained a distinction with a high statistical significance between prostate volume of the two groups (t=4.328, p<0.0001).

Tab. 3. Values of PSA and prostate volume in "gray zone" patients

PSA Values	Volume of prostate cm ³		T-test
	Mean	SD	p-value
<4.1 ng/ml n=1030	36.9	8.2	t=4.328 p<0.0001
4.1 ng/ml-10 ng/ml n=360	44.6	11.6	

Table 4 Shows the average age of gray zone patients and patients with PSA concentration <4.1 ng/ml. The average age of gray zone patients was 71.00 years (± standard deviation 7.00 years), whereas the average age of patients with PSA values <4.1ng/ml was 66.00 years (standard deviation ± 8.00 years). With T-test it is shown a distinction with high statistical age significance between patients in both groups (t=3.329, p<0.001).

Tab. 4. PSA values and age in "gray zone" patients

PSA Values	Age Years		T-test
	Mean	SD	p-value
<4.1 ng/ml n=1030	66	8.00	t=3.329 p=0.001
4.1 ng/ml-10 ng/ml n=360	71	7.00	

In "gray zone" patients using a MULTIPLE correlation a positive correlation of a low level ($R=0.293$) between age, prostate volume and serum PSA values was gained. I.e. by aging–prostate and serum PSA levels increase (Table 5 and Figure 3).

Tab. 5. Average prostate volumes and average values of serum PSA of gray zone patients

Age group	N	%	Volume of prostate (cm ³)	PSA (ng/ml)
50 years-59 years	20	5.6	40.5	4.8
60 years-69 years	100	27.8	40.5	5.6
70 years-79 years	200	55.6	45.6	6.2
80 years-89 years	40	11.1	51.3	7.2
Total	360	100	44.6	5.9

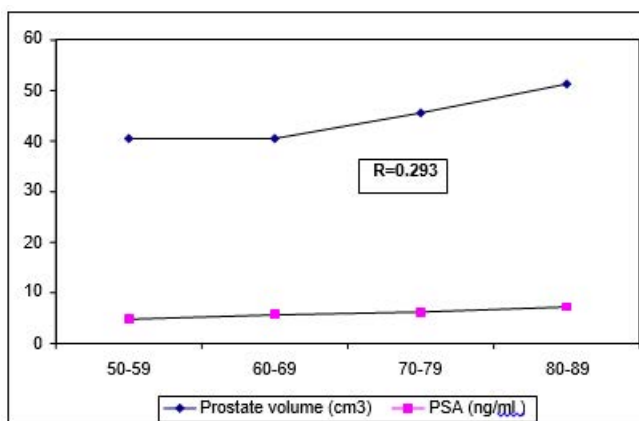


Fig. 3. Correlation between age, prostate volume and PSA value to gray zone patients

DISCUSSION

Despite the fact that PSA today is considered the leading tumor marker in prostate cancer detection, it is still far away as being an ideal tumor marker. Ideal tumor markers should be strongly specific to prostate cancer and negative to other diseases in the present study, PSA does not fulfill this condition. PSA also is not very sensitive, from the fact that 38% to 48% of patients with intraprostatic cancer have normal PSA values. Despite these shortcomings PSA is still considered the main tumor marker tool in prostate carcinoma detection [7-35].

PSA is strongly correlated with prostate volume and age in patients with BPH. It is proven that at the age of 60 years, the incidence of BPH is around 60%, whereas in the eighth decade approximately in 95.5% of men BPH is present [7, 11].

Increased serum PSA values except BPH and prostate cancer also affects many other factors such as urethral catheterization, acute prostate inflammation, AUR (Acute Urinary Retention), then endourologic interventions such as cystoscopy, Transurethral Resection of The Prostate (TURP) and prostate biopsy [4]. A correlation between AUR and PSA was determined in patients with chronic prostate inflammation [4].

PSA level above 4 ng/ml were detected in 64% of AUR patients and 38% in patients without AUR. Mean PSA levels in patients with chronic prostate inflammation in AUR was 7.75 ng/ml while in patients without AUR was 5.32 ng/ml [4].

Nadler and colleagues also suggested that prostate chronic inflammation increased PSA levels and these data were more compatible with other authors results such as Iran and colleagues who also demonstrated that inflammation in the prostate biopsy has significantly increased PSA levels as a result of damaged glandular epithelium [4].

Damage to the integrity of the prostate gland from inflammation may be the main cause of increased PSA values in the group with AUR (Acute Urinary Retention).

Every pathology that damages the prostate glands leads to distribution of prostate intraluminal secretion through stromal vascular structures and thus increases serum PSA levels. For that particular reason we suggest that prostate chronic inflammation seems to play a very important role in patients with AUR as a result of BPH and consequently increases PSA serum levels [35-40].

CONCLUSION

The data confirms that prostate volume and PSA concentration of sermic PSA have significant correlation and rises with aging among the "grey zone" patients .

AUTHORS CONTRIBUTION

A E.N made substantial contribution to conception and study design and data collection. AE.N , I,M, LS, XhC were involved in refining the study design ,statistical analysis and drafting manu-script. All authors read and approved the final manuscript .

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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