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Two-year profile of the records of patients referred to Adana city hospital urology clinic due to PSA high in primary care: a retrospective review

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ABSTRACT

Objective: To retrospectively evaluate the two-year records of patients referred to Adana City Training and Research Hospital by family physicians because of high prostate specific antigen (PSA), and to reveal the profile and related outcomes for clinical practices of family physicians about prostate cancer screening.

Material and Method: The files of 102 patients, who were referred to our clinic by their family physicians due to high PSA between April 2019 and May 2021, were retrospectively evaluated. Demographic data of patients, presence of additional disease, family history, control serum PSA value examined in family medicine centers and in our hospital at time of first admission, complete urinalysis (TIT), ultrasonography (USG) and multiparametric magnetic resonance (mpMR) findings, transrectal ultrasonographic biopsy (TRUS-BX) results and biopsy were noted. The treatments administered according to the results (radical prostatectomy, radiotherapy, hormone therapy, chemotherapy) were recorded.

Results: The mean age of the patients was 52.8±8.9 years. The PSA value of the patients at time of admission was 8.0±3.8 ng/ml. The mean PSA values measured at the time of admission to primary care and at the time of admission to Adana clinic after referral were 8.0±3.8 ng/ml and 8.0±3.0 ng/ml, respectively. There was no statistically significant difference between these values (p=0.2). Among all the patients presenting with elevated PSA, 36 (35%) patients underwent TRUS Bx, had prostate cancer as a result of pathology and underwent radical prostatectomy, which was the most common definitive treatment method with statistical significance (p<.001). The sensitivity value obtained from the ROC curve calculated based on the initial PSA value of the patients was 68.09 years and the specificity value was 48.15 years. At the same time, the cut-off PSA value calculated by examining the area under the ROC curve was determined to be <7.5 ng/ml.

Conclusion: An individualized, risk-adjusted strategy for screening should be determined. A shared decision-making process with the patient should be adopted, along with explaining the reasons for and consequences of PSA screening.

Keywords: Family medicine, cancer screening, prostate cancer, prostate specific antigen

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer diagnosed in men worldwide, accounting for 15% of all cancers (1). The prevalence of PCa under the age of 30 years is 5%, while it is 59% over the age of 79 years (2). While digital rectal examination (DRE), serum prostate specific antigen (PSA), transrectal ultrasonography (TRUS) and prostate biopsy (TRUS Bx) are included in the diagnostic evaluation, the introduction of PSA especially has led to serious advances in the diagnosis and treatment of PCa (3). Cancer screening is defined as the systematic examination of asymptomatic people (at risk). Screening for PCa with serum PSA aims to detect PCa at an early and manageable stage, thus directing curative treatment, and ultimately reducing overall and disease-specific mortality (4). Early diagnosis and treatment of PCa was reported to increase cancer-specific survival, and the first widespread screening results, especially in the USA, were associated with a decrease in PCa mortality (5,6). However, clinically insignificant PCa can also be detected as a result of screening, and the number of associated prostate biopsies that may cause sepsis increases in patients who undergo TRUS Bx (7). Therefore, it is useful to develop an individualized, risk-adapted strategy for early detection. People especially at risk including those over the age of

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50 years, with a family history, over the age of 45 years, of African origin, and with familial BRCA1 mutations should be prioritized for early diagnosis (8-10).

As can be seen from the literature above, PCa screening continues to be one of the most controversial issues in urology practice (11). The current situation also affects the decisions of family physicians. However, it is very important for family physicians to inform their patients about cancer screening. In addition, it is important to apply the necessary screening tests or to refer the patients to the relevant branches. Studies in the literature generally analyzed the attitudes of family physicians towards prostate cancer screening by assessing their attitudes towards PCa with questionnaire-based questions (12). In our study, we aimed to reveal the profile and related results about clinical practices of family physicians about prostate cancer screening by retrospectively evaluating the two-year records of patients referred to Adana City Training and Research Hospital (Adana) because of elevated PSA.

MATERIAL AND METHOD

Study Design

Our study retrospectively evaluated the files of 102 patients who were referred to our clinic by primary care family medicine centers between April 2019 and May 2021, after being approved by the Adana City Training and Research Hospital Clinical Researches Ethics Committee (Date: 2021, Decision No: 1595). All procedures adhered to the ethical rules and principles of the Helsinki Declaration. Data recorded included the demographic data of the patients, presence of additional disease, family history, control serum total PSA value examined in family medicine centers and in our hospital at time of first admission, complete urinalysis (TIT), ultrasonography (USG) and multiparametric magnetic resonance (mpMR) findings, transrectal ultrasonographic biopsy (TRUS) -BX) results, the treatments applied (radical prostatectomy, radiotherapy, hormone therapy, chemotherapy) and urinary tract infection according to the biopsy results, and serum total PSA value after antibiotic treatment. Serum total PSA level was measured using an electrochemiluminescence immunoassay (normal range; 0-2.5 ng/ml for age 40-49, 0-3.5 ng/ml for age 50-59, 0-4.5 for age 60-69, 70-79 0-6.5 ng/ml for age) (13).

Data Collection

The principles set out in the Declaration of Helsinki were followed. All methods were carried out in accordance with the relevant guidelines and regulations. Adana electronic hospital information system was used to obtain epidemiological data including demographic, clinical and laboratory findings. The serum total PSA value measured in venous blood samples was recorded. Peripheral venous blood samples were evaluated using standard procedures in the central laboratory of Adana City Training and Research Hospital. Biochemical hormonal parameters were measured with a Siemens ADVIA 1800 automated biochemistry analyzer (Siemens Healthcare Diagnostics Inc, Laboratory Diagnostics, Advia Centaur XPT, manufactured in Erlangen, Germany, Ireland).

Statistical Analysis

SPSS 23.0 package program (IBM, Armonk, NY) was used for statistical analysis of the data. Categorical measurements are summarized as numbers and percentages, and continuous measurements as mean and standard deviation (median and minimum-maximum where necessary). Chi-square and Fisher's exact tests were used to compare categorical variables. Shapiro-Wilk test was used to determine whether the parameters in the study showed normal distribution. In the comparison of continuous measurements between the groups, the distributions were checked and the Mann Whitney test was used for the parameters that did not show normal distribution in the double group analysis, and the Kruskal Wallis test was used for the analysis of more than two groups. In the study, the cut-off value was determined by calculating the sensitivity (sensitivity) and specificity (specificity) values based on the initial PSA value of the patients and examining the area under the ROC curve. Statistical significance level was taken as 0.05 in all tests.

RESULTS

The mean age of the patients was 52.8±8.9 years. Of patients, 8.8% had a family history of prostate cancer. The mean PSA value of the patients at the time of admission was 8.0±3.8 ng/ml. Only 50 patients had TRUS bx (**Table 1**).

The mean PSA values measured at the time of admission to primary care and at the time of admission to the ASEAH clinic after referral were 8.0±3.8 ng/ml and 8.0±3.0 ng/ml, respectively. There was no statistically significant difference between these values (p=0.2) (**Table 2**).

When the data of patients aged 40-45 years, 46-50 years and over 50 years of age were compared, the definitive treatments (RP, RT, HT) and Gleason score values in patients over 50 years old were relatively high, but only the presence of additional disease was statistically significantly higher (p<.001) (**Table 3**).

Among all the patients presenting with elevated PSA, 36 (35%) patients who underwent TRUS Bx, had prostate cancer as a result of pathology and underwent radical prostatectomy, which was the most common definitive treatment method with statistical significance (p<.001). There were 19 (18%) patients who received radiotherapy/hormonotherapy (**Table 4**).

Table 1. Demographic data in the study

	Frequency (n)	Percent (%)
Family history		
No	93	91.2
Yes	9	8.8
Additional illness		
No	50	49.0
Yes	52	51.0
Urinary tract infection		
No	68	66.7
Yes	34	33.3
TRUS Bx		
No	50	49.0
Yes	52	51.0
Radical Prostatectomy		
No	66	64.7
Yes	36	35.3
Radiotherapy / Hormonotherapy		
No	83	81.
Yes	19	18.6
Chemotherapy		
No	100	98.0
Yes	2	2.0
Gleason score		
3+3	24	23.5
3+4	4	3.9
4+3	7	6.9
4+4	9	8.8
4+5	1	1.0
None	57	55.9
	Mean±SD	Med (Min-Max)
Age	52.8±8.9	52 (40-75)
Initial PSA ng/ml	8.0±3.8	7 (3.9-20)
Control PSA ng/ml	8.0±3.0	7.5 (3.8-19)
PSA after antibiotics	4.6±4	3 (1-13)
mpMR PIRADs value	3.25±1.0	3 (1-5)

PSA: Prostate specific antigen, mpMR: Multiparametric magnetic resonance, TRUS-BX: Transrectal ultrasonographic biopsy

Table 2. Comparison of PSA at the time of admission in primary care and the control PSA value measured at first admission to ASEAH

	Mean±SD	Med (Min-Max)	p
Initial PSA ng/ml	8.0±3.8	7 (3.9-20)	0.2
Control PSA ng/ml	8.0±3.0	7.5 (3.8-19)	

PSA: Prostate specific antigen

Table 4. Definitive treatments applied to patients diagnosed with prostate cancer as a result of TRUS Bx

	Radical Prostatectomy		p
	No (n=66)	Yes (n=36)	
Radiotherapy /Hormonotherapy			
No	47 (71.2)	36 (100)	<.001
Yes	19 (28.8)	0 (0)	

TRUS Bx was applied to only 52 (51%) patients with elevated PSA. Gleason score 3+3 pathology was present in 24 (46%) patients, which was statistically significantly higher than other Gleason scores (p<.001) (**Table 5**).

Table 3. Comparison of the data for 40-45 year old, 46-50 year old and over 50 year old patients

	40-45 years	46-50 years	>50 years	p
Family history				
No	24 (88.9)	20 (95.2)	49 (90.7)	0.734
Yes	3 (11.1)	1 (4.8)	5 (9.3)	
Additional illness				
No	21 (77.8)	10 (47.6)	19 (35.2)	0.001
Yes	6 (22.2)	11 (52.4)	35 (64.8)	
Urinary tract infection				
No	20 (74.1)	15 (71.4)	33 (61.1)	0.442
Yes	7 (25.9)	6 (28.6)	21 (38.9)	
TRUS Bx				
No	15 (55.6)	11 (52.4)	24 (44.4)	0.604
Yes	12 (44.4)	10 (47.6)	30 (55.6)	
Radical Prostatectomy				
No	19 (70.4)	13 (61.9)	34 (63)	0.770
Yes	8 (29.6)	8 (38.1)	20 (37)	
Radiotherapy /Hormonotherapy				
No	22 (81.5)	17 (81)	44 (81.5)	0.998
Yes	5 (18.5)	4 (19)	10 (18.5)	
Chemotherapy				
No	26 (96.3)	21 (100)	53 (98.1)	0.654
Yes	1 (3.7)	0 (0)	1 (1.9)	
Gleason score				
3+3	8 (29.6)	5 (23.8)	11 (20.4)	0.753
3+4	0 (0)	0 (0)	4 (7.4)	
4+3	2 (7.4)	2 (9.5)	3 (5.6)	
4+4	1 (3.7)	2 (9.5)	6 (11.1)	
4+5	0 (0)	0 (0)	1 (1.9)	
None	16 (59.3)	12 (57.1)	29 (53.7)	
	40-45 years	46-50 years	Over 50 years	p
Age	6.45 (3.9-15)	6.9 (4-19)	7.25 (3.9-20)	0.214
Initial PSA ng/ml	6 (3.8-16)	8 (3.8-15)	7.9 (3.8-19)	0.119
Control PSA ng/ml	3 (2-13)	3.25 (1-13)	3 (1-13)	0.970
PSA after antibiotics	3 (2-5)	3 (2-5)	4 (1-5)	0.637

PSA: Prostate specific antigen, mpMR: Multiparametric magnetic resonance, TRUS-BX: Transrectal ultrasonographic biopsy

Table 5. Gleason score distribution of patients who underwent TRUS Bx

	TRUS Bx		p
	No (n=50)	Yes (n=52)	
Gleason score			
3+3		24 (46.2)	<.001
3+4		4 (7.7)	
4+3		7 (13.5)	
4+4		9 (17.3)	
4+5		1 (1.9)	
None	50 (100)	7 (13.5)	

TRUS-BX: Transrectal ultrasonographic biopsy

The sensitivity value obtained from the ROC curve calculated based on the initial PSA value of the patients was 68.09 years and the specificity value was 48.15 years. At the same time, the cut-off PSA value calculated by examining the area under the ROC curve was determined to be <7.5 ng/dl (**Figure 1**).

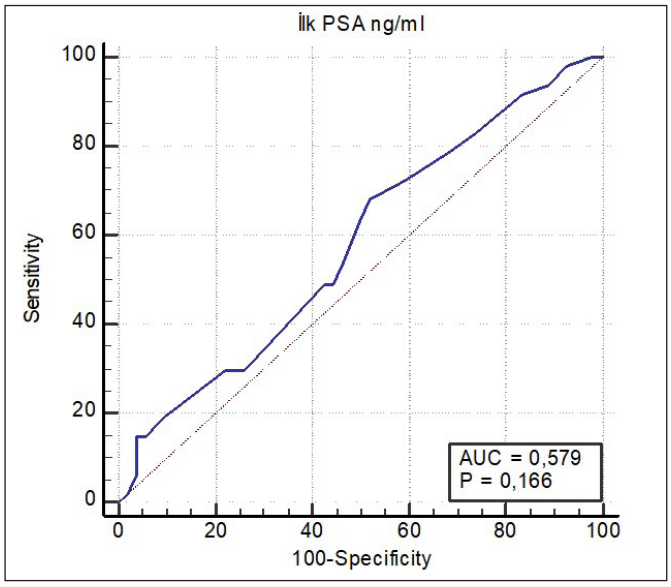

Figure 1. Sensitivity, specificity and cut-off values according to the ROC curve based on the initial serum PSA value

	Initial PSA	95% CI
AUC	0.579	0.476-0.676
Cut-off	<7.5	
Sensitivity	68.09	52.9-80.9
Specificity	48.15	34.3-62.2
+LR	1.31	1.0-1.8
-LR	0.66	0.4-1.1
PPV	53.3	45.3-61.2
NPV	63.4	51.2-74.1
p	0.166	

*p<0.05, **p<0.001, ROC curve

DISCUSSION

Clinically localized PCa is usually asymptomatic. Therefore, PSA and PRM are accepted as diagnostic tests to detect PCa while PCa is confined to the prostate (14). Although the first widespread screening results in the USA were associated with a decrease in mortality (6), in 2012 the US preventive services task force and 2013 AUA (American Urology) guidelines published a recommendation against PSA-based screening, resulting in a reduction in the use of PSA for early detection (15-17). However, Fenton et al. (18) in a systematic review conducted in 2018 and İliç et al. (7) as a result of their systematic review and meta-analysis, concluded that PSA population screening has a long-term benefit in reducing cancer-specific mortality. According to a Cochrane analysis published in 2013 by Ilic et al. (19), the diagnosis of PCa increased with screening and was associated with more localized disease. However, five available randomized controlled trials involving 341,000 men reported no overall survival benefit specific to PCa. Another issue among the questions of whether or not to perform screening is whether only PSA screening is sufficient? In their randomized clinical study investigating the effect of PSA-based screening on prostate cancer mortality in 2018, Martin et al. (20) found that a single PSA screening detected lower-risk PCa, but had no benefit for PCa mortality after 10 years of follow-up. Therefore, for screening and early detection of PCa, men should be offered PSA screening after being given detailed information about the potential risks and benefits and presenting a personalized and risk-adapted strategy to patients with a life expectancy of more than 10 years (EAU 2021).

Early screening for PCa is important for those with family history and inherited germline mutations. Significant cancers were detected at a younger age in male BRCA1 and 2 mutations as a result of PSA screening compared to carriers without mutations (21). Increasing evidence supports the use of genetic counseling and germline testing for early diagnosis and management of PCa. early screening and detection of germline mutations is essential for men with metastatic PCa; men with high-risk PCa and a family member <60 years of age diagnosed with PCa; men with multiple family members diagnosed with PCa at age <60 years, or a family member dying from PCa cancer; with a family history of high-risk germline mutations or a family history of more than one cancer on the same side (22).

PSA is prostate specific but not cancer specific; therefore, it may also increase due to benign prostatic enlargement (BPH), prostate inflammation (prostatitis) and other non-malignant causes. PSA, as an independent variable, predicts PCa better than PRM and TRUS, but serum PSA value is considered as <4 ng/dl despite the lack of a standard PSA value range.3 The European Association of Urology (EAU) prostate guidelines also contains a threshold value. Although not specified, the PSA<2.5-3 ng/dl range is recommended for young men. Broeck et al. reported that those with PSA >1 ng/dl at the age of 40 and PSA >2 ng/dl at the age of 60 are at risk of death due to PCa, and that these patients should be followed up every 2 years. Those who are not in this risk group according to their initial PSA value should be followed up but they suggested that it could be delayed to 8 years (23).

Apart from PSA, DRE is also important for the diagnosis of PCa. PCa develops from the prostate peripheral zone and the tumor volume must be at least >0.2 ml for cancer detection by DRE. At the same time, tumors can be detected in 18% of cases with DRE alone, regardless of PSA level (24). Imaging methods also play an important role in PCa detection. Smeenge et al. (25) reported that standard transrectal USG is not a reliable method for detecting PCa in their study. EAU guidelines suggest multiparametric magnetic resonance imaging (mpMR) for patients undergoing biopsy for the first time or for whom a repeat biopsy is recommended due to elevated

PSA to be performed before biopsy. If suspicious areas are detected in imaging (PI-RADS 3 and above lesion description), targeted and systematic biopsy should be performed by the transrectal route. TRUS Bx recommends taking at least 10-12 core biopsies from each lobe and region (EAU 2021 guideline). The most commonly used histological grading system pathologically after TRUS bx is the Gleason score. The Gleason score ranges from 2 (1+1) to 10 (5+5). It is calculated by adding the most common primary pattern and the second most common secondary pattern forming the tumor in the evaluated tissue and finding a value between 2-10 (International Society of Urological Pathology (ISUP) 2014). Treatment of localized PCa is radical prostatectomy. It is recommended for patients with organ-confined disease and a life expectancy of more than 10 years (23). Radiotherapy is another method that provides biochemical control and survival, similar to radical prostatectomy in the same patient group, and the standard recommended dose is 74-80 Gy (26). Hormone suppression therapy combined with radiotherapy, as well as luteinizing hormone-releasing hormone (LHRH) analogue therapy, are applied for 3 months, between 6 months and 3 years in medium and high risk groups, and its superiority was proven in this risk group compared to radiotherapy treatment along (27-29).

If the results of our study are evaluated in light of the above information, family physicians most frequently refer patients with PSA values of 7.5 ng/dl and below to our urology clinic. At the same time, the most sensitive age group in the patient group referred for PSA elevation was 68 years, while the most specific age group was 48 years. Although only 9 (8.8%) of the referred patients had a family history, these patients were screened for PSA under the age of 45 years in line with the literature. Although the lowest patient age was 40 years and the oldest was 75 years, the median age of the patients was 52 years. In light of this information, PSA screening was performed at around the age of 50 years in accordance with the literature, and the screening reached the target age group. As standard, according to the studies described above and EAU 2021 guideline recommendations, every patient with high PSA level, regardless of the PSA value, had prostate lesion screening with mpMR imaging and PIRADS risk classification before the biopsy. It was observed that the PIRADS risk classification in mpMR is relatively higher in patients over 50 years of age (4 and above), leading to more biopsies and more prostate cancer detection. Another issue that deserves attention is that only 52 (50.9%) of the 102 patients referred to us with PSA elevation were biopsied. Fifty patients who were not biopsied were called for 3-month PSA follow-up because the PSA value fell below 4 after antibiotic treatment, they were PIRADS 3 and below in mpMR images, and the control PSA value checked in our clinic was lower than the PSA value from family medicine center. One of the remarkable issues in our study are the results of the patients who underwent biopsy. Cancer was not detected in only seven (13%) of the patients who underwent biopsy. The most common pathological Gleason score in 45 (87%) patients with cancer was 3+3 (46.2%); in other words, most of the patients were caught at an early stage and this demonstrates the importance of screening. The first definitive treatment choice of patients with PCa as a result of biopsy was radical prostatectomy, with statistical significance, and cancer patients over 50 years of age choose surgery relatively more often. Among the patients with PCa as a result of biopsy, only one patient had metastatic disease (bone metastasis; M1b metastatic group), was referred to oncology and received chemotherapy (CT).

CONCLUSION

The issue of screening in prostate cancer is still controversial. An individualized, risk-adapted strategy for screening should be established. A shared decision-making process with the patient should be adopted, along with detailed information about the reasons for and consequences of PSA screening. At the end of the shared decision-making process between the family physician and the patient, if PSA screening is decided; instead of looking at PSA alone, digital rectal examination together with PSA should definitely be included in the screening. At the same time, PSA elevation does not mean that the patient has prostate cancer; it should be explained that PSA may increase due to many conditions. In addition, patients with PSA elevation were not directly biopsied by urology, control PSA was examined after treatment in patients with urinary tract infection, mpMR was taken before biopsy and biopsy was performed for those with 3 or more lesions according to PIRADS staging, other patients were followed up with 3-month PSA checks, if necessary. It should be noted that new mpMR imaging was performed.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was initiated with the approval of the Adana City Training and Research Hospital Clinical Researches Ethics Committee (Date: 2021, Decision No: 1595).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have participated in the design, execution, and analysis of the paper, and that they approved the final version.

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