ORIGINAL ARTICLE

Serum total prostate-specific antigen (tPSA): correlation with diagnosis and grading of prostate cancer in core needle biopsy

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ABSTRACT

Aim To investigate the impact of pre-treatment serum total prostate-specific antigen (PSA) level on prevalence of prostate carcinoma detection in prostate core needle biopsy, and its correlation with established prognostic factors.

Methods Prostate needle biopsy samples of 115 patients with available pre-treatment serum total PSA (tPSA) level were analysed. For all cases where morphology alone was insufficient, immunohistochemistry was performed using p63, CKHMW and AMACR antibody panel in order to confirm or exclude the existence of prostate carcinoma.

Results Statistically significant positive correlation between serum total PSA values and prevalence of finding prostate carcinoma in needle biopsy specimens was found (p=0.011), as well as in the case when the patients were classified into groups according to tPSA levels (p=0.028). Serum total PSA values and levels (level groups) showed significant positive correlation with Gleason score (p=0.029 and p=0.036, respectively) and Grade Group of prostate carcinomas (p=0.044 and p=0.046, respectively). Sensitivity of the screening test by using 4 ng/mL as cut off value for tPSA was 94.12% (CI: 80.32-99.28%), specificity 8.64% (CI: 3.55-17.00%), positive predictive value 30.19% (CI: 21.65-39.87%) and negative predictive value 77.78% (CI: 39.99-97.19%).

Conclusion The increase of serum tPSA value increases the likelihood of finding prostate cancer on needle biopsy specimens. Due to such findings and its positive correlation with a grade of prostate cancer, our study indicates that tPSA can still be considered as a useful tool both in detecting and predicting aggressiveness of prostate cancer.

Keywords: grade group, Gleason score, screening

INTRODUCTION

Prostate cancer remains a significant public health problem, since it is the second most common male malignancy and the fifth major cause of death worldwide. It is responsible for 3.8% of all deaths caused by cancer in male population (1).

Although it is prostate-specific rather than disease-specific, serum prostate-specific antigen (PSA), a glycoprotein normally expressed by prostate tissue, has been a marker of choice for early detection and follow up of patients with prostate carcinoma since its discovery in late 1980s (2). Since increased PSA serum levels can be found in other conditions, such as many benign changes, urinary tract infections, or after the instrumentation, prostate needle biopsy represents a gold standard for the diagnosis of prostate carcinoma (3).

Despite the findings of different studies indicating that PSA screening can help in early prostate cancer detection, there has been a lot of inconsistency about its clinical appliance as a screening marker, especially in the last decade (4). Some of the reasons include a high rate of false positive and negative results on needle biopsy and repeated unnecessary biopsy and delayed diagnosis (4). Screening with serum PSA aims to detect prostate cancer at an early stage in order to enable adequate treatment and to impact overall and disease-specific mortality (5). Recent randomized clinical trials demonstrated that PSA screening has small benefit in higher detection of low-risk prostate cancer, but do not support single PSA testing for population-based screening (6); meta-analysis based studies showed small benefit in the reduction of prostate cancer specific mortality but not the overall mortality, with current recommendations for clinicians and patients to outweigh benefits against harms of PSA screening (5).

Although PSA is not a perfect marker and PSA testing has limited specificity for prostate cancer detection, its appropriate clinical application remains a topic of debate (5).

This study is conducted to investigate a correlation between pre-treatment serum tPSA level and incidence of finding prostatic carcinoma in prostate core needle biopsy, as well to correlate serum PSA levels with Gleason score and Grade Group in cases of cancer presence.

PATIENTS AND METHODS

Patients and study design

In this retrospective study, 115 prostate needle biopsy specimens were analysed at the Department of Pathology, School of Medicine, University of Sarajevo in the five-year period (2015-2019). The patients with available pre-treatment serum total PSA (tPSA) level were included in the study. All patients underwent digital rectal examination and transrectal utrasonography (TRUS). Biopsies with inadequate material, other types of procedures, such as transurethral resection of prostate (TURP) and partial or total prostatectomy specimens, were excluded from the study (despite known pre-treatment tPSA level). Patients were divided into four subgroups according to total serum PSA level (Table 1).

Methods

Tissue specimens were fixed in 10% buffered formalin, paraffin-embedded, processed and stained with hematoxylin and eosin. According to current protocols, the Gleason score (7) and Grade Group (8) were determined for all patients.

For all prostate biopsy specimens where morphology alone was insufficient, immunohistochemistry was performed using p63, CKHMW and AMACR antibody panel in order to confirm or exclude the existence of prostate carcinoma. Tissue samples fixed in 10% formalin and embedded in paraffin were cut into 4-μm thick sections, mounted on coated slides and collected for immunohistochemical staining, according to the manufacturer's protocol with CKHMW (clone 34βE12, Dako; FLEX, Ready-to-Use, Glostrup, Denmark), p63 (clone DAK-p63, Dako, FLEX, Ready-to-Use, Glostrup, Denmark) and AMACR (clone 13H4, Dako, FLEX, Ready-to-Use Glostrup, Denmark).

Positive p63 staining was defined as dark brown nuclear staining while positive CKHMW staining was defined as dark brown cytoplasmic staining in basal cells of prostatic glands. To confirm foci of prostatic carcinoma, AMACR positivity was defined as dark brown cytoplasmic staining in the absence of p63 and CKHMW positivity in atypical glands.

All clinicopathological data are summarized in Table 1.

Statistical analysis

Patient and clinicopathological characteristics were evaluated using descriptive statistics. Spearman correlation test was used to investigate a possible correlation between two variables. In cases where normality of distribution lacked, non-parametric Spearman test was used and variables were presented by median and interquartile range. Positive (PPV) and negative predictive value (NPV), sensitivity and specificity were calculated using 4 ng/mL as the cut-off value for total serum PSA. $p \leq 0.05$ was considered statistically significant.

RESULTS

Out of total 115 patients, in 81 (70.44%) benign prostatic changes were found on core needle biopsy, while 34 (29.56%) patients were diagnosed with prostate carcinoma. High grade prostatic intraepithelial lesion (HGPIN) was present in majority of cases, both in patients with carcinoma, 23 (20.0%), and in patients with benign prostatic changes, 58 (50.43%).

Table 1. Clinicopathological characteristics of patients who underwent prostate needle biopsy

Variables	No (%) of patients		
	With prostate carcinoma	Without prostate carcinoma	Total
Prostate carcinoma	34 (29.57)	81 (70.43)	115 (100.0)
Age (years)			
50-59	8 (6.95)	8 (6.96)	16 (13.91)
60-69	16 (13.91)	50 (43.48)	66 (57.39)
70-79	12 (10.43)	18 (15.66)	30 (26.09)
80-89	2 (1.74)	1 (0.87)	3 (2.61)
Mean age (years)	68.35±7.99	65.51±5.97	NA
tPSA level (ng/mL)			
<4.0	2 (1.74)	7 (6.09)	9 (7.83)
4.0-9.99	12 (10.43)	40 (34.79)	52 (45.22)
10.0-19.99	7 (6.09)	22 (19.13)	29 (25.22)
≥20.0	13 (11.30)	12 (10.43)	25 (21.73)
HGPIN			
Present	23 (20.0)	58 (50.43)	81 (70.43)
Absent	11 (9.57)	23 (20.0)	34 (29.57)
Gleason score			NA
3+3=6	13 (38.24)	NA	
3+4=7	6 (17.56)	NA	
4+3=7	6 (17.56)	NA	
4+4=8	4 (11.76)	NA	
5+5=10	5 (14.70)	NA	
Grade Group			NA
1	13 (38.24)	NA	
2	6 (17.65)	NA	
3	6 (17.65)	NA	
4	4 (11.76)	NA	
5	5 (14.70)	NA	

HGPIN, high grade prostatic intraepithelial neoplasia; NA, not applied

Mean age of the patients at the time of the diagnosis was 66.35±6.72 years (range 54 to 86). Patients with prostate adenocarcinoma, 34 (29.57%) were older with mean age of 68.35±7.99 years

(range 55 to 86) compared to 81 (70.43%) patients with benign prostatic hyperplasia with or without HGPIN lesions, 65.51±5.97 years (range 54 to 81) (p=0.096) (Table 1).

Mean value of tPSA in patients with prostatic carcinoma was 29.37 ng/mL (range 3.2-275.0), while in patients without carcinoma it was 12.82±13.51 (range 2.15-98.23) (p=0.011).

A difference in serum tPSA level in cancer patients compared to patients with benign prostate changes was found, i.e. the majority of patients with prostate adenocarcinoma, 20 (58.8%), had a tPSA level >10.0 ng/mL, unlike patients without carcinoma whose tPSA level was predominantly between 4.0-9.99 ng/mL, 40 (49.4%). Statistically significant positive correlation between serum tPSA levels and the prevalence of prostate adenocarcinoma was observed (p=0.028) (Figure 1).

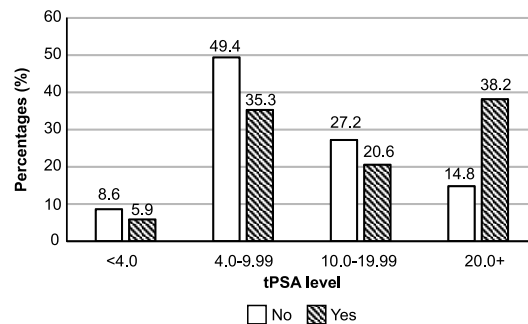Sensitivity, specificity, positive and negative predictive value were calculated using tPSA cut-off

Figure 1. Difference in total prostate specific antigen (tPSA) level in patients with prostate carcinoma and patients with benign changes

point of 4 ng/mL, showing sensitivity of 94.12% (CI= 80.32-99.28%), specificity 8.64% (CI=3.55-17.00%), positive predictive value 30.19% (CI = 21.65-39.87%) and negative predictive value 77.78% (CI = 39.99-97.19%).

Gleason score was analysed in the group of patients with prostatic adenocarcinoma, and showed positive correlation with serum values and levels (level subgroups of tPSA). In the group of patients with Gleason score 6, mean value of tPSA was 11.36 (range 3.67-37.93 ng/mL), while in patients with Gleason score 9 it was 149.61 (range 24.22-275.00) (p=0.029) (Figure 2).

Gleason score 3+3=6 was the most represented score with most cases having tPSA below 10.0 ng/mL, while higher Gleason score 3+4=7, 4+3=7, 4+5=9 and 5+4=9 were dominantly represented in the group of patients with tPSA level ≥20.0 ng/mL (p=0.036) (Table 2).

Table 2. The incidence of different Gleason scores among different total prostate specific antigen (tPSA) level

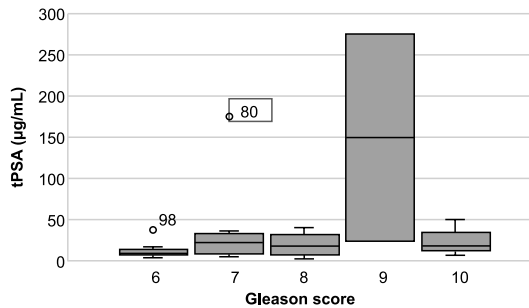| tPSA level (ng/mL)	No (%) of tumours with different Gleason score							
	3+3=6	3+4=7	4+3=7	4+4=8	4+5=9	5+4=9	5+5=10	Total
<4.0	1 (7.7)	0	0	1 (25.0)	0	0	0	2 (5.9)
4.0-9.99	7 (53.8)	1 (16.7)	2 (33.3)	1 (25.0)	0	0	1 (33.3)	12 (35.3)
10.0-19.99	4 (30.8)	1 (16.7)	1 (16.7)	0	0	0	1 (33.3)	7 (20.6)
20.0+	1 (7.7)	4 (66.7)	3 (50.0)	2 (50.0)	1 (100.0)	1 (100.0)	1 (33.3)	13 (38.2)
Total	13 (100.0)	6 (100.0)	6 (100.0)	4 (100.0)	1 (100.0)	1 (100.0)	3 (100.0)	34 (100.0)

Figure 2. Values of serum total prostate specific antigen (tPSA) according to Gleason score in patients with prostate carcinoma

An increase of tPSA level with the increase of prostate carcinoma Grade Group (GG) was found: the highest percentage of GG 1 (61.5%) carcinomas had tPSA level lower than 10 ng/mL, while 60% of GG 5 carcinomas had tPSA level >20.0 ng/mL (p=0.044 and p=0.046 respectively) (Figure 3).
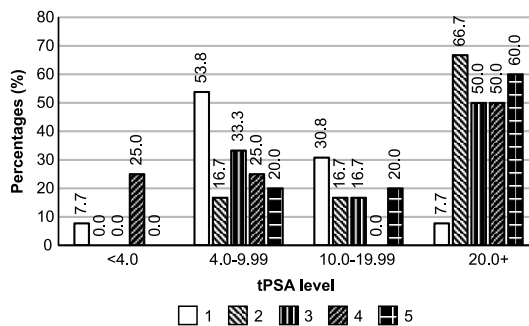

Figure 3. Serum total prostate specific antigen (tPSA) levels in different Grade Groups of prostate carcinoma

There was no statistically significant correlation between patients' age and Gleason score, or patients' age and Grade Group of prostatic adenocarcinoma (p>0.05).

DISCUSSION

It is well known that prostate cancer primarily affects elderly males with the incidence rate of almost 60% in men older than 65 years. The prevalence and mortality of prostate cancer correlate positively with age, with the average age of 66 years at the time of the diagnosis (1, 9). In our study, mean age of patients with prostate adenocarcinoma was 68.35±7.99 (range 55 to 86) in comparison to patients without proven cancer on needle biopsy, whose mean age at the time of the diagnosis was 65.51±5.97 (range 54 to 81) (without statistically significant correlation between patients' age and incidence of prostate carcinoma). Slight differences may be caused by ethnicity, false negative or positive findings on core needle biopsy, and a small sample as well.

Over the past years, serum PSA level has been a powerful tool for prostate cancer screening and early detection, especially in most Western countries (10). Although an increased usage of PSA as a screening marker has been followed by decreasing prostate cancer mortality risk, it has also led to over-diagnosis of many indolent tumours that would not have caused clinical disease (10,11). Despite many controversies in its clinical appliance, PSA is one of the biomarkers with the greatest impact on clinical practice and management (10).

Results of many other studies in recent years have accumulated evidence of PSA as a predictive marker, with low PSA level (<1.0 ng/mL) having extremely low prevalence of clinically significant prostate cancer, as well as a very low risk for advanced disease (12-14). In a study by Ghafoori et al. serum PSA level of 4 ng mL was found to be commonly used as an indication for prostate biopsy (15); in our study biopsies were performed even at lower PSA values, presumably due to patients' clinical symptoms. Also, in the study by Ghafoori et al. it was found that PSA level between 4- 10 ng/mL had low sensitivity, unlike values above 10 ng/mL and 15 ng/mL which had much higher sensitivity in detecting prostate cancer (15). Gerstenbluth et al. showed that serum PSA level above 50 ng/mL had 98.5% accuracy in predicting the presence of prostate cancer in tissue biopsy (16). Our results are quite similar to these findings with highest cancer prevalence in the group with PSA level ≥10.0 ng/mL (58.8%) as well as in the group with PSA level ≥ 20.0 ng/mL (38.6%).

In our study, out of 34 prostate cancer cases, only 2 patients had tPSA level lower than 4 ng/mL, but most of the patients without cancer also had the same. These results indicate that serum total PSA is sensitive, but not specific as a screening mar-

ker, with the test accuracy of 33.9% when using 4 ng/mL as cut-off value for total serum PSA. In 2018, the US Preventive Task Force reported that men aged 55-69 years had a potential benefit of PSA screening due to reduced death rates (17), but other studies gave fewer encouraging results for males over 70, for all races (18).

Gleason score, despite limitations and many changes in the clinical and histological diagnosis of prostate cancer, remains one of the most important predictors of biological behaviour of prostate carcinoma (7). Gleason scoring of prostate carcinoma allows objective assessment of the degree of tumour differentiation reflecting its aggressiveness and impacting a decision about treatment modalities (19). In our study, an additional fact which favours PSA as a predictive marker is the statistically positive correlation of tPSA level with Gleason score and Grade Group of prostate carcinoma, indicating that with the increase of serum total PSA level, GS and GG of prostate carcinoma also increase. Although the mean values were lower in Gleason score 10 (25.57 ng/mL) compared to Gleason score 9, a statistically significant positive correlation was noted. In our study, the most prevalent Gleason score was 6 (3+3=6) (38.24%) resulting in 53.8% prevalence of tPSA <10.0 ng/mL, unlike the patients with high Gleason level 4+5=9 and 5+4=9 which in 100% of cases had PSA serum level of ≥20 ng/mL. Investigating a correlation between PSA density and features of aggressiveness of prostate carcinoma, Kundu et al. found that PSA density correlated positively with Gleason score and adverse pathologic features (20). Loeb et al. investigated PSA velocity in radical prostatectomy specimens and found preoperative PSA velocity as a significant independent predictor of Gleason score and non-organ confined disease (21). Our results relating to correlation of initial serum total PSA and Gleason score are in contrast to the results of Nnabugwu et al. (19), who investigated correlation of initial serum total PSA and Gleason score on 43 core needle biopsy specimens. Milonas et al. (22) and Jayapradeep et al. (23) found no statistically significant correlation between PSA levels and Gleason score of prostate carcinomas obtained on transurethral resection specimens or radical prostatectomy specimens.

The Grade Group system, introduced in 2013 and accepted later in 2014 (24) comprises five Grade Groups (GG 1-5) that resulted in more accurate prognosis in comparison with the Gleason system risk stratification groups. According to this grading system, prognostic Grade Group 1 includes all prostate cancers with Gleason score 6 or less, which are indolent, lowest grade tumours with the best prognosis. Prognostic Grade Group 4 and 5 have lower 5-year biochemical recurrence free progression following radical prostatectomy and thus significantly worse prognosis (25,26). Our study showed a statistically significant positive correlation between serum tPSA level and GG of prostate carcinoma, although not completely linear, due to frequent high tPSA level (>20 ng/mL) in GG 2 prostate carcinomas. Considering limitations such as small sample size and insufficiently examined "grey zone" of tumours with the medium level of serum tPSA, further studies with larger sample size are imperative, together with comparison of the efficacy of some other markers.

Current recommendations indicate necessity of individualized approach to tPSA screening thus leaving plenty of space for new studies in this field. Our study indicates that tPSA can still be a useful screening marker for prostate carcinoma in combination with digital rectal examination and transrectal sonography (TRUS). Due to its positive correlation with well-established prognostic factors, serum tPSA should be seen as a continuum for recognizing the increasing risk of prostate malignancy and cancer aggressiveness.

In conclusion, our findings confirm the importance of serum tPSA in the detection of prostate carcinoma in needle biopsy, as well as its prognostic significance along with Gleason score and Grade Group. By reviewing available literature, we have not found studies in Bosnia and Herzegovina which are related to tPSA levels and prostate core needle biopsy specimens.

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TRANSPARENCY DECLARATION

Competing of interest: None to declare.

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