Usefulness of Total PSA Value in Prostate Diseases Diagnosis

Alden Prcic1, Edin Begic2, and Mustafa Hiros3

1Bahrain Specialist Hospital, Bahrain
2Association of Biochemists and Molecular Biologists in Bosnia and Herzegovina, BiH
3Clinic of Urology, University Clinical Center Sarajevo, BiH

Corresponding author: Alden Prcic

1. INTRODUCTION

Analysis of total value of prostate specific antigen (PSAT), with the unavoidable digital rectal examination (DRE) is the basis of prostate cancer detection. Positive DRE (subjective examination, depends on physicians skills) and increased PSA value (objective, numerical findings) indicate that there is a greater chance of cancer diagnosis. Prostate specific antigen (PSA) is a 33 kDa protein consisting of a single-chain glycoprotein of 237 amino acid residues, 4 carbohydrate side chains and multiple disulfide bonds (2) first identified in seminal plasma in 1971 by Hara et al. (3) and subsequently isolated from prostatic tissue in 1979 by Wang et al. (2). It belongs to the group of serine proteases (4) with extensive structural similarity to the glandular kallikrein (5), with which it shares considerable structural and functional homology and a gene location on the long arm of chromosome 19 (19q13.2-13.4) (6). It is produced by prostate secretory epithelium and vesiculae seminales (7) and is one of the most abundant proteins in seminal plasma where it is found in concentrations of 0.2–5.0 mg/mL (8). PSA is predominantly found in serum in 3 different molecular forms: free PSA (molecular mass 30 kDa), bound to alpha-2-macroglobulin (molecular mass 780kDa) and bound to alpha-anti-chymotrypsin (molecular mass 90kDa) (9). In the serum of healthy men in physiological conditions there is a very low concentration of PSA of prostate origin. PSA in serum is present only in case of disrupted microarchitecture of prostate gland tissue, which becomes the cause of PSA crossing into the surrounding extracellular space, where is being swept away by lymph in systemic circulation and is always an indication of trauma or prostate disease. In serum, normal range is from 0.1 to 4 ng/mL. PSA test allows doctors to detect prostate cancer, while they are still
small, low grade and localized (10). PSA is a prostate-spe-
cific, but not specific to prostate cancer, and is also increased
in other diseases of the prostate (prostatitis, benign prostatic
hyperplasia), and in diagnostic procedures, as well as some
of the physiological processes. PSA is increased to about 0.3
ng/mL per gram in benign prostatic hyperplasia (BPH) while
this level per gram in cancer rises 10 times, or 3 ng/mL. The
increased value of PSA is found in 20% to 50% of men with
benign prostatic hyperplasia (11). Approximately 10% of the
male population has a PSA value higher than 10 ng/mL, but
don't have cancer. When talked about non-specificity there
is a fact that PSA is found in many tissues, especially those
that are hormone active. PSA is located in male and female
periurethral and perianal glands, and is elevated in cystitis,
healthy endometrium and in many carcinomas (urethra,
bladder, penis, parotid, kidney, adrenal, colon, ovarian, lung,
hepatic, and breast). Elevation of PSA levels has been proven
in acute prostatitis, subclinical or chronic prostatitis and uri-
inary retention. There are no significant changes in the value
of PSA after DRE, but powerful massage of the prostate can
lead to short-term increase. A biopsy of the prostate increases
PSA, and it takes from 2 to 4 weeks to return to normal PSA
value. Prostate volume also affects the value of PSA (12). For
larger prostate (>40 cm³) PSAT is superior to Free to Total
PSA Ratio (PSAR) in the detection of prostate cancer, while
in smaller prostate PSAR is more important (13). The most
important role of PSA is monitoring of prostate cancer treat-
ment. The concentration of PSA is essential information that
helps evaluate the effectiveness of the therapy as well as to
determine the probability of finding residual disease (local or
distant). It also draws attention to the biochemical relapse and
occurrence of metastases before it is possible to identify
them with other conventional diagnostic procedures. Ap-
proximately 70% of patients with elevated PSA values do not
have prostate cancer (11). Between 25-40% of patients have
cancer at values below 10 ng/mL. This means that 40-75% of
them will have to go through unnecessary and uncomfort-
able examination. Also 15% of patients with PSA values from
2.5 to 4 ng/mL have prostate cancer. PSA values are increased
in proportion to the increase of age, and increases from 0.7
to 1.5 mL per year. On this basis normal, baseline PSA values,
vary according to the age of the patient (in patients <40 years
0-2 ng/mL, 50-59 years 0-3.5 ng/mL, >80 years 0-7.2 ng/
/mL). Oesterling et al. found that in 60-year-old man PSA in-
creases to about 0.04 ng/mL in one year (14). When PSA is
>10.0 ng/mL, the probability of cancer is high, and pro-
tate biopsy is usually recommended. In favor of non-specific-
ity of PSA are results according to which 20% to 30% men
with prostate cancer have PSA less than 4 ng/mL. The total
PSA range from 4.0 to 10.0 ng/mL is described as a diagnostic
“gray zone” (doctors before other diagnostic tests have to con-
sider digital rectal examination), in which are used many de-
veloped indexes (age-specific PSA, PSA density, acceleration
of PSA, PSA density of the transition zone, PSAR), which
help to determine relative risk of prostate cancer. PSA has the
highest positive predictive value for cancer and is objective
indicator of the risk of prostate cancer. Analysis showed that
men with prostate cancer have higher PSA levels than men
without cancer, years before conventional diagnosis with
DRE. The chances of the biopsy proven cancer are 1 in 50

2. MATERIAL AND METHODS

Research included 220 (n = 220) patients aged from 36 to
82. Data were collected from the “Register of PH biopsy”
Clinic of Urology, University Clinical Center Sarajevo, and
included all patients who underwent this method in last two
years. Total PSA values were recorded and four groups were
formed based on the diagnosis (prostate cancer, benign pro-
tatic hyperplasia, precancerous conditions and inflammatory and atrophic changes
of the prostate). Results are shown through number of cases,
percentage, arithmetic mean, standard deviation, median and
interquartile range, area under the curve (AUC), sensitivity
and specificity, and confidence interval (CI). Analysis of
the distribution by the Shapiro-Wilk test showed that none of
the observed variables did not meet the criteria of normal dis-
tribution and non-parametric tests (Mann-Whitney, Krus-
kal-Wallis and Spearman’s rank correlation coefficient) were
used in the analysis. Analysis of the ROC (receiver operating
curve) was used to determine the sensitivity and specificity.
All results of the analysis with p <0.05 or at the level of con-
fidence of 95% were considered statistically significant. Sta-

tistical analysis of the obtained data was done by software
package SPSS Windows (version 21.0, SPSS Inc., Chicago,
Illinois, USA) and Microsoft Excel (version 11th Microsoft
Corporation, Redmond, WA, USA). The research was con-
ducted in accordance to basic principles of the Declaration of
Helsinki (last revision in 2008) on the rights of patients in-
volved in biomedical research. During the realization of this
research identity and all personal data of patients are perma-
nently protected in accordance to regulations of protection
of identification data. Identification number was assigned to
every patient in order to protect personal information and
that number was used in statistical analysis.

3. RESULTS

Histogram with normal distribution curve shows that the
majority of patients were 50 to 80 years old (64.6 ± 8.1 years)
(Figure 1).

Analysis of correlation between the diagnosis and the
PSAT value shows statistically significant negative correla-
tion (r =-0.186; p = 0.006) in the sense that the value of the
Usefulness of Total PSA Value in Prostate Diseases Diagnosis

PSAT is highest in cancer patients, and the lowest in patients with benign prostatic hyperplasia (Figure 2).

The correlation between PSAT value and age shows a positive, statistically significant value ($r = 0.152; p = 0.025$) in the sense that the value of the PSAT increases with age (Figure 3).

PSAT shows the highest sensitivity at a specificity of 95% for prostate cancer - 12.05% (4.82-19.28), then specificity for benign prostatic hyperplasia - 8.00% (2-13.33), atrophic and inflammatory changes of the prostate - 6.45% (0-22.58), and the lowest for precancerous conditions - 5.56% (0-11.1). Statistically significant AUC was recorded only for prostate cancer (Table 1).

Specificity at 95% sensitivity was also the highest for prostate cancer – 12.41% (0.73-21.97), slightly lower for atrophic and inflammatory changes of the prostate - 11.64% (4.56-24.46), and then benign prostatic hyperplasia - 8.57% (0-15.71). The lowest sensitivity is for precancerous conditions - 2.72% (0-11.41) (Table 1).

Analysis of the ROC curve estimates the best possible sensitivity and specificity at a specific cut-off value (Table 2).

For prostate cancer optimal sensitivity and specificity for PSAT value occurs at cut off value of > 6.08 ng/mL.

When the value of PSAT > 20 ng/mL, cancer was diagnosed in 57.1% of patients, but when values were from 10 to 20 ng/mL, cancer was diagnosed in 46.6% of patients. When the value of PSAT was in the range from 4 to 10 ng/mL, cancer was diagnosed in 40.9% of patients. Sensitivity and specificity of the PSAT is changing in relation to the range of values PSAT, as well as positive predictive value (PPV) and negative predictive value (NPV) (Table 3). Values lower than 2 ng/mL, and higher than 10 ng/mL are most specific values of PSAT, and PPV increases with increasing value of PSAT (Table 3).

### Table 1. Analysis of sensitivity and specificity of PSAT in relation to individual diagnosis

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precancerous conditions</td>
<td>5.56 (0-11.1)</td>
<td>2.72 (0-11.41)</td>
<td>0.196</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>12.05 (4,82-19.28)</td>
<td>12.41 (0.73-21.97)</td>
<td>0.624 (0,0015)</td>
</tr>
<tr>
<td>Atrophic and inflammatory changes of the prostate</td>
<td>6.45 (0-22.58)</td>
<td>11.64 (4.56-24.46)</td>
<td>0.637 (p=0,0097)</td>
</tr>
<tr>
<td>Benign prostatic hyperplasia</td>
<td>8.00 (2-13.33)</td>
<td>8.57 (0-15.71)</td>
<td>0.552</td>
</tr>
</tbody>
</table>

### Table 2. Evaluation of the best possible sensitivity and specificity at a specific cut-off value

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Range (ng/mL)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer</td>
<td>&lt;2</td>
<td>25%</td>
<td>61.3%</td>
<td>4.8%</td>
<td>91.2%</td>
</tr>
<tr>
<td>Precancerous conditions</td>
<td>2–4</td>
<td>29.1%</td>
<td>59.4%</td>
<td>19.3%</td>
<td>71.5%</td>
</tr>
<tr>
<td>Atrophic and inflammatory changes of the prostate</td>
<td>4–10</td>
<td>62.7%</td>
<td>45.3%</td>
<td>40.9%</td>
<td>66.7%</td>
</tr>
<tr>
<td>Benign prostatic hyperplasia</td>
<td>10–20</td>
<td>8.4%</td>
<td>94.2%</td>
<td>46.7%</td>
<td>62.9%</td>
</tr>
</tbody>
</table>

### Table 3. The sensitivity and specificity of the PSAT at different ranges

<table>
<thead>
<tr>
<th>Range (ng/mL)</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 2</td>
<td>25%</td>
<td>61.3%</td>
<td>4.8%</td>
<td>91.2%</td>
</tr>
<tr>
<td>2–4</td>
<td>29.1%</td>
<td>59.4%</td>
<td>19.3%</td>
<td>71.5%</td>
</tr>
<tr>
<td>4–10</td>
<td>62.7%</td>
<td>45.3%</td>
<td>40.9%</td>
<td>66.7%</td>
</tr>
<tr>
<td>10–20</td>
<td>8.4%</td>
<td>94.2%</td>
<td>46.7%</td>
<td>62.9%</td>
</tr>
<tr>
<td>&gt; 20</td>
<td>4.8%</td>
<td>97.8%</td>
<td>57.1%</td>
<td>62.9%</td>
</tr>
</tbody>
</table>

4. DISCUSSION

In addition to digital rectal examination, PSA testing is essential in the diagnosis of prostate cancer. In a European study on screening of prostate cancer, it was found that if the dig-
Usefulness of Total PSA Value in Prostate Diseases Diagnosis

This research showed that the value of PSAT is the highest in patients with prostate cancer, compared to other prostate diseases. However, the value of PSAT correlates with a greater volume of cancer as well as with clinical and pathological stages of disease (30). With a negative DRE, when the PSA is less than 4 ng/mL, the probability of localized disease is 81-84%; when the PSA is in the range of 4 to 10 ng/mL, the probability of localized disease is 53-67%, and when the PSA is in the range of 10-20 ng/mL, this probability is 31-50%.

With PSA below 20 ng/mL, the likelihood of distant metastases is very small. Despite the limitations of the PSA, this cancer marker used for predicting the stage of the disease is combined with other parameters, so a separate spreadsheet system called nomograms was created. The most famous, and the one with the most widespread clinical use, Partin nomogram, was made in 1993 (31). To this date, more than 80 different types of nomograms were made to help determine the stage of the disease, survival without biochemical relapse, predicting lymph node involvement or seminal vesicle cancer, bone metastases (most nomograms take into account the value of PSA). As this study has shown, the risk of cancer increases with the age of patients. The incidence of cancer increases with age; for men aged 40-44 years, the incidence was 9.2 / 100,000, and in men between 70-74 years, it was 984.8 / 100,000 (28). Results with all restrictions have confirmed that the highest incidence is between the age of 50 and 70, and that the value of PSAT increases with age. Our research showed that the lowest values of PSAT were found in BPH. Preden-Kerekovic et.al. in their study also proved that the PSA was significantly higher in prostate cancer compared to benign prostatic hyperplasia (29). Chakraborty et.al. have proven the same point (32). This research showed that when the level of PSAT is lower than 2.0 ng/mL, the chances for the existence of cancer are small, and the search of free PSA will give the doctor more information (32). Values over 10.0 ng/mL, generally indicate the necessity of biopsy, and values between 4.0 and 10.0 ng/mL are a diagnostic gray zone, and require an interpretation of PSAR (33). In this research, PSAT sensitivity was 62.7% and specificity 45.3% for range of 4-10 ng/mL. Spencer determined for this value sensitivity of over 80 % and specificity of 50 % (33). Our research has found that the detection of prostate cancer optimal cut-off value is PSAT > 6.8 ng/mL, with the sensitivity of the test 60.2% and specificity of 45.7%. In atrophic and inflammatory changes of the prostate, the optimal cut-off value is < 5 ng/mL (sensitivity 71%, specificity 59.8%). Several European countries conducted a screening for prostate cancer, including Netherlands (Rotterdam) and Finland. In Rotterdam, data was recorded for the 7943 men, aged 55 to 74. Amongst 534 men who had PSA levels between 3.0 ng/mL and 3.9 ng/mL, 446 (83.5%) had a biopsy, and 96 (18%) of them had prostate cancer (a total of 4.7% of population that underwent the screening was diagnosed with prostate cancer) (34).

In a screening trial involving 6630 men, the positive predictive value of the PSA test increased from approximately 10% in men with a PSA <4 ng/mL, to greater than 80% in men with a PSA >20 ng/mL (35). In Finland, 15.685 of men were screened and at least 14% of them had PSA levels of at least 3.0 ng/mL. All men with a PSA higher than 4.0 ng/mL...
Usefulness of Total PSA Value in Prostate Diseases Diagnosis

were recommended to undergo diagnostic monitoring which consisted of digital rectal examination, ultrasound and biopsy; 92% have complied with the recommendation and 2.6% of 15,685 screened men were diagnosed with prostate cancer (36). Out of 801 men with PSA levels between 3.0 ng/mL and 3.9 ng/mL (all patients underwent biopsy), 22 (3%) had cancer. Out of 1116 men with PSA levels between 4.0 ng/mL and 9.9 ng/mL, 247 (22%) had cancer, and out of 226 men with PSA levels of at least 10 ng/mL, 139 (62%) had cancer (36). Our results confirmed that levels of PSAT< 2 ng/mL in prostate cancer show a 25% sensitivity, 61.3% specificity, PPV 4.8% and NPV 91.2%. Levels of PSAT between 10 and 20 ng/mL have 8.4% sensitivity and 94.2% specificity, while levels of PSAT greater than 20 ng/mL have 4.8% sensitivity and 97.8% specificity. While the specificity is 95%, PSAT has the greatest sensitivity in detecting prostate cancer (12.05%) followed by detecting BPH (8.00%). Tanguay et al. showed a 18% specificity for the given cut off level of 3 ng/mL in their research, so did Muller et al. too. Muller et al. had similar results with a 6.7% specificity while having a 95% sensitivity (cut off- 4-6 ng/mL) (38). Although the cut off level of 4.0 ng/mL is mostly used for quick prostate biopsies, screening studies showed that a decrease of the PSA cut off level will increase the number of diagnosed cancers (39). Furthermore, lower PSA cut off levels are related with a high percentage of negative biopsies (false positive biopsies) (40). Aganovic et al proved that prostate cancer occurs in 34.4% of patients when PSAT levels are 4-10 ng/mL, in 23% when PSAT is lower than 4 ng/mL and in 37.5% of patients when PSAT is higher than 10 ng/mL (41). Our results showed the occurrence of prostate cancer in 40% of patients when PSAT levels are 4-10 ng/mL. Regarding other prostate diseases, our research showed that for precancerous conditions, when PSAT had the optimal cut off level <6.18, it showed a 66.7% sensitivity and 45.7% specificity. In atrophic and inflammatory changes, when PSAT had the optimal cut off level <5.02, it had 71% sensitivity and 59.8% specificity. In benign prostatic hyperplasia, when PSAT had the optimal cut off level <8.5, it had 85.7% sensitivity and 28% specificity. A combination of digital rectal examination and PSA level analysis (PSAT and PSAR) represents a screening method that greatly helps in early detection of prostate cancer and in that way allows a prompt action of the clinician. Similarly, when the PSA and DRE levels are normal, the probability of missing the cancer is 10% (42).

Although the results of specificity and sensitivity for prostate cancer detection were slightly below the value of the results obtained by other researchers, this research showed levels of sensitivity and specificity for other most common prostatic diseases. This can be a valuable tool in clinicians daily work. PSA level is still a tool, but it is not a method whereby a final diagnosis can be given, and requires the complementarity of other non-invasive and invasive diagnostic methods. However, it should be emphasized that the proper diagnosis of prostate diseases can be difficult due to the lack of specificity and sensitivity of diagnostic tests.

5. CONCLUSION

PSA (PSAT) at values of <2 ng/mL and > 10 ng/mL are at high levels of specificity, and a value > 10 ng/mL is also of high sensitivity in the detection of prostate cancer, and in this moment these values represent the optimal mode for the subsequent treatment. Levels of PSAT between 4-10 ng/mL still remain unknown in the daily work of clinicians and require the complementarity of all the mentioned non-invasive and invasive diagnostic tests, with more frequent reevaluations. PSAT has a relative significance in the detection of prostate cancer, and should not be used as a guideline without prior clinical examination (digital rectal examination). Prostate biopsy remains the gold standard for final diagnosis of prostate disease. Since the value of PSAT is affected by many etiological factors, especially age, PSAT values are not fully reliable and exclusive analysis is not enough specific nor sensitive for the distinction between prostate diseases.

REFERENCES


• Conflict of interest: None declared.