Original Article

PROSTATE INTERNATIONAL

Prostate Int 2014;2(3):133-139 • http://dx.doi.org/10.12954/PI.14054

Correlation and diagnostic performance of the prostate-specific antigen level with the diagnosis, aggressiveness, and bone metastasis of prostate cancer in clinical practice

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Purpose: The common tool for diagnosing prostate cancer is serum prostate-specific antigen (PSA) testing and digital rectal examination, but the disadvantage of the high sensitivity and low specificity of PSA testing in the diagnosis of prostate cancer is a problem in clinical practice. We studied the correlation and diagnostic performance of the PSA level with cancer diagnosis, aggressiveness of prostate cancer (Gleason score > 7), and bone metastasis.

Methods: A total 1,116 patients who underwent transrectal ultrasound and prostate biopsy were retrospectively studied. The patients were divided into subgroups by baseline PSA level as follows: ≤4, 4.1–10, 10.1–20, 20.1–50, 50.1–100, and >100 ng/mL. The area under the receiver operating characteristic curve (AuROC), sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio of each PSA level were evaluated for correlation and diagnostic performance with positive biopsy, Gleason score for aggressiveness, and bone metastasis.

Results: A positive biopsy result was found in 395 patients (35.39%). The PSA level corresponded well with the diagnosis of prostate cancer and a positive bone scan but moderately well with Gleason score as shown by AuROC for diagnosis of prostate cancer (0.82), positive bone scan (0.88), and Gleason score > 7 (0.78). The specificity of a PSA level of 4.1–10, 10.1–20, 21.1–50, 50.1–100, and >100 ng/mL in the diagnosis prostate cancer was 9.3, 55.5, 87.5, 98.2, and 99.7, respectively.

Conclusions: The data showed a strong correlation of PSA level with tumor diagnosis, tumor aggressiveness, and bone metastasis. The prevalence of prostate cancer in this cohort was 35.39%. The chance of diagnosis of prostate cancer was greater than that for benign prostatic hyperplasia when the PSA level was higher than 20 ng/mL.

Keywords: Prostate-specific antigen, Diagnosis, Gleason score

INTRODUCTION

The prevalence of prostate cancer is increasing in Asia [1-4]. Currently, the common tools for diagnosis of prostate cancer are the digital rectal examination (DRE) and a serum prostate-specific antigen (PSA) test. The combination of both DRE and PSA testing leads to a greater detection of prostate cancer. If abnormal results are shown on both tests, a prostate biopsy is recommended for a definitive tissue diagnosis of prostate cancer.

The high sensitivity and low specificity of PSA testing in the diagnosis of prostate cancer is a problem in clinical practice [5-8]. Use of PSA testing alone has reduced specificity owing to the influence of prostate volume and other factors such

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Submitted: 17 May 2014 / Accepted after revision: 30 July 2014

as infection and manipulation. Even with this disadvantage, however, PSA measurement is still used in clinical practice given that no new biomarkers are currently accepted for the diagnosis of prostate cancer. The general cutoff for the PSA level is 4.0 ng/mL. With the use of this cutoff, the cancer detection rate ranges from 35% to 42.3% for 10- to 12-core biopsy [9,10]. A higher PSA level may relate to a greater likelihood of positive tissue diagnosis, a higher Gleason score, and a greater likelihood of bone metastasis.

We studied the correlation and diagnostic performance of the PSA level for cancer diagnosis, aggressiveness of prostate cancer (Gleason score > 7), and bone metastasis in real clinical practice.

MATERIALS AND METHODS

Data for 1,116 patients who underwent an initial transrectal ultrasound and prostate biopsy at the Faculty of Medicine, Chiang Mai University, were retrospectively studied. All 10- to 12-core biopsy procedures were performed as outpatient procedures with local anesthesia. The patients' demographic data such as age, PSA level, details of the pathologic report such as a positive diagnosis of cancer, Gleason score, and the result of the bone scan were recorded. The patients were divided into subgroups by baseline PSA level as follows: less than or equal 4, 4.1–10, 10.1–20, 20.1–50, 50.1–100, and more than 100 ng/mL. The area under the receiver operating characteristic curve (AuROC), sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio (LHR+), and negative likelihood ratio (LHR–) of each PSA level were evaluated for the correlation and diagnostic performance with positive biopsy result, Gleason score for aggressiveness, and bone metastasis. This protocol was reviewed and approved by the Ethics Committee (Institutional Review Board) of the Faculty of Medicine, Chiang Mai University.

The statistical analysis of diagnostic values included the AuROC, sensitivity, specificity, positive predictive value, negative predictive value, LHR+, and LHR– of each PSA level.

RESULTS

Data from a total of 1,116 patients were analyzed. The patients' average age was 68.02 ± 8.23 years (range, 42–93 years). The average PSA level for biopsy was 102.45 ng/mL (range, 1–5,000 ng/mL). A positive biopsy result was found in 395 patients (35.39%). Plots between PSA level and percentage of correlation for diagnosis of prostate cancer, Gleason score, and bone metastasis showed that the higher the PSA level, the higher the positive results for all variables studied (Fig. 1). The PSA level corresponded very well with the diagnosis of prostate cancer and a positive bone scan but only moderately well with Gleason score. This result was consistent with the area under the ROC curve for all variables. As shown in Table 1 and Figs. 2-4, the PSA level provided high overall accuracy for the diagnosis of prostate cancer (0.82) and a positive bone scan (0.88) and moderate accuracy for Gleason score > 7 (0.78). The chance of diagnosis of prostate cancer was more than that of benign prostatic hyperplasia when the PSA level was higher than 20 ng/mL.

Table 1. Overall accuracy of serum PSA in the prediction of tissue diagnosis, aggressiveness, and bone metastasis by AuROC

Serum PSA	AuROC (95% CI)
Positive cancer	0.821 (0.792–0.849)
Aggressiveness	0.780 (0.737–0.823)
Bone	0.883 (0.808–0.886)

PSA, prostate-specific antigen; AuROC, area under the receiver operating characteristic curve; CI, confidence interval.

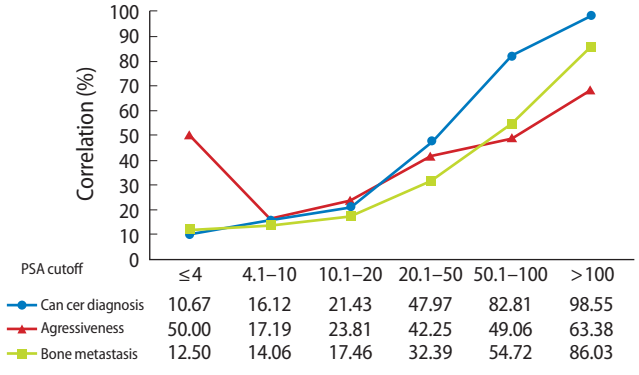

Fig. 1. Correlation of the prostate-specific antigen level with cancer diagnosis, agressiveness, and bone metastasis.

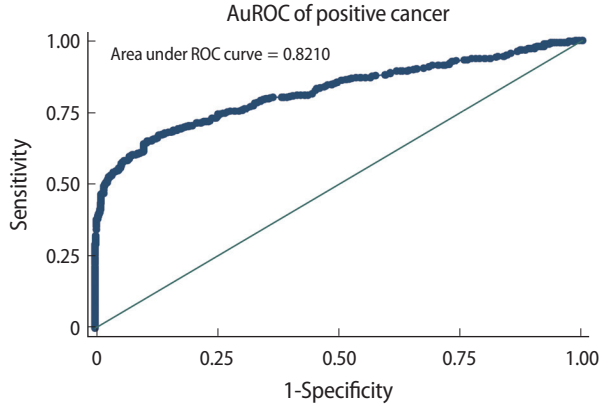

Fig. 2. Area under the receiver operating characteristic curve (AuROC) of serum prostate-specific antigen in the prediction of tissue diagnosis.

http://dx.doi.org/10.12954/PI.14054

The sensitivity and specificity in the diagnosis of prostate cancer for a PSA level of 4.1–10 ng/mL were 98.0% and 9.3%, respectively, and those for a PSA level of 10.1–20 ng/mL were 81.5% and 55.5%, respectively. Lower sensitivity was found at higher PSA levels, whereas the specificity was elevated when the PSA level was higher. The specificity of PSA levels of 4.1–10, 10.1–20, 21.1–50, 50–100, and >100 ng/mL in the diagnosis of prostate cancer was 9.3, 55.5, 87.5, 98.2, and 99.7, respectively. The positive predictive value of PSA in prostate cancer diagnosis at a PSA level of 4.1–10 and 10.1–20 ng/mL was 37.2 and 50.1, respectively. For a cancer diagnosis, the LHR+ was more than 5.0 (theoretical suggested LHR+) for a PSA level higher than 20 ng/mL (Table 2).

For tumor aggressiveness (tumor with Gleason score>7); at a PSA cutoff of 4 ng/mL, the specificity of detection of prostate cancer with a Gleason score higher than 7 was 1.99%. A higher positive predictive value was found at higher PSA levels. The LHR+ was less than 5 at all PSA levels (Table 3). For bone metastasis, the results showed that the higher the cutoff, the higher the sensitivity, positive predictive value, and LHR+ (Table 4).

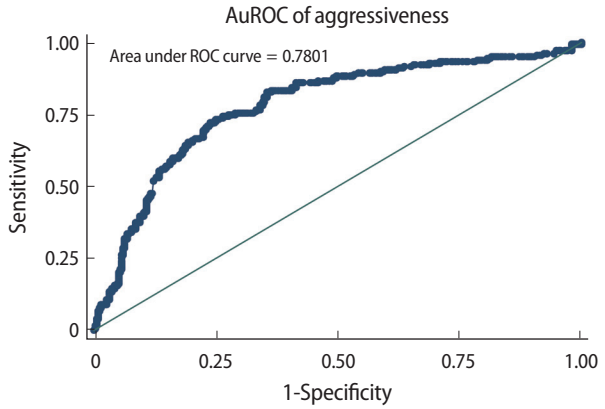

Fig. 3. Area under the receiver operating characteristic curve (AuROC) of serum prostate-specific antigen in the prediction of aggressiveness (Gleason score>7).

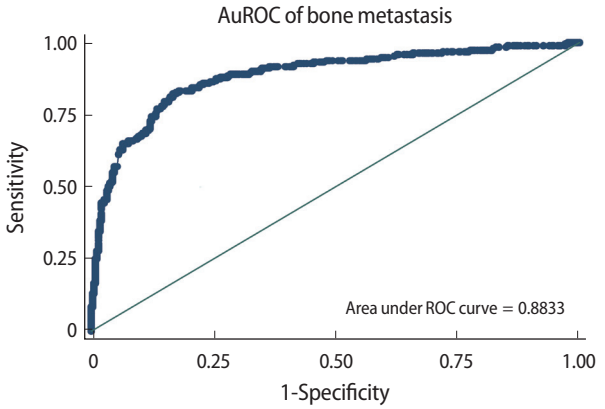

Fig. 4. Area under the receiver operating characteristic curve (AuROC) of serum prostate-specific antigen in the prediction of bone metastasis.

Table 2. Diagnostic values of each PSA cutoff for tumor diagnosis

PSA (ng/mL) cutoff point	Sensitivity	Specificity	PPV	NPV	LHR+	LHR–	AuROC
4	98.0 (97.2–98.8)	9.3 (7.6–11.0)	37.2 (34.3–40.0)	89.3 (87.5–91.1)	1.08 (1.05–1.11)	0.22 (0.10–0.45)	0.536 (0.524–0.549)
10	81.5 (79.2–83.8)	55.5 (52.6–58.4)	50.1 (47.1–53.1)	84.6 (82.4–86.7)	1.83 (1.67–2.01)	0.33 (0.26–0.41)	0.685 (0.658–0.711)
20	65.8 (63.0–68.6)	87.5 (85.6–89.5)	74.3 (71.7–76.8)	82.4 (80.1–84.6)	5.27 (4.29–6.48)	0.39 (0.34–0.45)	0.767 (0.740–0.793)
50	47.8 (44.9–50.8)	98.2 (97.4–99.0)	93.6 (92.1–95.0)	77.5 (75.0–79.9)	26.54 (15.3–45.9)	0.53 (0.48–0.58)	0.730 (0.705–0.755)
100	34.4 (31.6–37.2)	99.7 (99.4–100.0)	98.6 (97.8–99.2)	73.5 (70.9–76.1)	124.12 (30.89–498.66)	0.66 (0.61–0.71)	0.671 (0.647–0.694)

95% Confidence interval in parentheses.
PSA, prostate-specific antigen; PPV, positive predictive value; NPV, negative predictive value; LHR+, positive likelihood ratio; LHR–, negative likelihood ratio; AuROC, area under the receiver operating characteristic curve.

Table 3. Diagnostic values of each PSA cutoff for aggressiveness (Gleason score>7)

PSA (ng/mL) cutoff point	Sensitivity	Specificity	PPV	NPV	LHR+	LHR–	AuROC
4	97.8 (96.5–99.0)	1.99 (0.8–3.2)	33.6 (29.6–37.7)	63.6 (59.5–67.7)	1.00 (0.97–1.02)	1.12 (0.33–3.79)	0.500 (0.486–0.511)
10	91.6 (89.3–94.0)	36.4 (32.3–40.5)	42.3 (38.1–46.5)	89.5 (86.9–92.1)	1.44 (1.32–1.58)	0.23 (0.14–0.38)	0.730 (0.608–0.672)
20	83.2 (80.1–86.4)	62.8 (58.7–66.9)	53.2 (49.0–57.5)	88.0 (85.3–90.8)	2.24 (1.92–2.60)	0.27 (0.19–0.37)	0.700 (0.693–0.767)
50	66.5 (62.5–70.5)	79.3 (75.8–82.7)	62.0 (57.8–66.1)	82.3 (79.0–85.6)	3.20 (2.55–4.03)	0.42 (0.34–0.52)	0.540 (0.688–0.769)
100	52.0 (47.7–56.2)	87.8 (85.0–90.6)	68.4 (64.4–72.3)	78.2 (74.7–81.7)	4.25 (3.11–5.82)	0.55 (0.47–0.64)	0.699 (0.658–0.739)

95% Confidence interval in parentheses.
PSA, prostate-specific antigen; PPV, positive predictive value; NPV, negative predictive value; LHR+, positive likelihood ratio; LHR–, negative likelihood ratio; AuROC, area under the receiver operating characteristic curve.

Table 4. Diagnostic values of each PSA cutoff for bone metastasis

PSA (ng/mL) cutoff point	Sensitivity	Specificity	PPV	NPV	LHR+	LHR–	AuROC
4	99.5 (98.9–100.0)	3.4 (1.6–5.2)	48.8 (43.9–53.8)	87.5 (84.2–90.8)	1.03 (1.00–1.06)	0.15 (0.02–1.24)	0.514 (0.500–0.528)
10	94.7 (92.5–96.9)	30.7 (26.2–35.3)	55.9 (51.0–60.8)	86.3 (82.9–89.7)	1.37 (1.24–1.51)	0.17 (0.09–0.32)	0.627 (0.592–0.663)
20	89.0 (85.9–92.4)	55.6 (50.7–60.5)	65.0 (60.3–69.7)	84.4 (80.9–88.0)	2.00 (1.70–2.35)	0.20 (0.13–0.30)	0.722 (0.682–0.764)
50	76.8 (72.7–81.0)	79.0 (75.0–83.0)	77.2 (73.1–81.3)	78.6 (74.6–82.7)	3.66 (2.78–4.83)	0.29 (0.22–0.38)	0.779 (0.738–0.820)
100	61.6 (56.8–66.4)	90.7 (87.9–93.6)	86.0 (82.6–89.4)	71.8 (67.4–76.2)	6.6: 4 (4.27–10.34)	0.42 (0.35–0.51)	0.762 (0.722–0.802)

95% Confidence interval in parentheses.
PSA, prostate-specific antigen; PPV, positive predictive value; NPV, negative predictive value; LHR+, positive likelihood ratio; LHR-, negative likelihood ratio; AuROC, area under the receiver operating characteristic curve.

DISCUSSION

Nowadays, the accepted tools for the diagnosis of prostate cancer are the DRE and serum PSA. PSA testing has been used in clinical practice since 1986 and has led to changes in screening and the early diagnosis of prostate cancer, which is followed by earlier treatment [5-8]. The widespread use of PSA screening had led to an increase in overall survival. More early-stage prostate cancer is diagnosed. The number of prostate cancer patients with metastatic stages and comorbidities has decreased more than 25% owing to greater detection of confined tumors early. The usefulness of PSA testing has been shown for early diagnosis, assessing the response of treatment, and determining tumor progression [11-13].

The strengths and weaknesses of PSA testing have also been reported. A limitation of PSA testing is the risk of overdiagnosis and resultant negative biopsies owing to poor specificity. Several conditions can affect the PSA level; PSA is prostate-specific but is not prostate-cancer-specific. Elevations of the PSA level can be caused by other conditions such as large benign prostatic hyperplasia, prostatitis, prostate manipulations, and recent ejaculation within 24 hours [14]. In clinical practice, the general PSA cutoff is 4.0 ng/mL. A lower cutoff leads to increased sensitivity but reduced specificity, which increases the detection of clinically insignificant prostate cancer. For patients with PSA between 4.0 and 10.0 ng/mL, the mean positive predictive valve of the diagnosis of prostate cancer is 21% (range, 18%–25%) [9]. In a pooled meta-analysis study, the positive predictive value of PSA > 4.0 ng/mL was only 25% [9].

In patients with PSA < 4 ng/mL and a normal DRE or an abnormal DRE result, the incidence of prostate cancer ranges from 4% to 9% and from 10% to 20%, respectively. Many prostate cancers are missed with this cutoff. With a PSA level > 4 ng/mL, in patients with a normal DRE or an abnormal DRE result, the incidence of prostate cancer is from 12% to 32% and from 42% to 72%, respectively [15-20]. Among a total of 10,523 patients, Schroder et al. [21-25] diagnosed more prostate cancer (430 cancer cases) in patients with a normal DRE result and PSA between 3.0 and 4.0 ng/mL [26]. Morgan et al. [26] studied age-specific reference ranges for PSA in 411 black men with a PSA cutoff of 4 ng/mL. They found that 40% of cancers would be missed in black men with the use of traditional cutoff values. In men aged > 50 years, the possibility of prostate cancer in patients with serum PSA of 2.5–4 ng/mL, > 4 ng/mL, and > 10 ng/mL was 27.0%, 20% to 30%, and 42% to 64%, respectively.

In a report using the PSA level to identity non–organ-confined disease, the percentage of tumors with extraprostatic extension increased when patients had a high PSA level. The incidence of extraprostatic extension was 50% and 80% at a PSA level of 4 to 10 ng/mL and > 20 ng/mL, respectively [27].

Age-adjusted PSA, free PSA, and PSA isoforms are used to increase the specificity of the detection of clinically significant cancer. Oesterling et al. [14] recommended the concept of age-related reference ranges. They showed that such ranges improve cancer-specific detection in old men and increase cancer detection in younger men. The detection of prostate cancer increased 18% in younger men and decreased 22% in older men. The 8% increase in organ-confined prostate cancer diminished in men aged < 59 years. In men aged > 60 years, 21% fewer biopsies were performed with the result of missing 4% of organ-confined tumors.

Free PSA is usually lower in prostate cancer than in benign prostatic hyperplasia. A ratio of free PSA to total PSA (%f PSA) greater than 25% lowers the chance of prostate cancer compared with a %f PSA < 10% [28]. PSA isoforms are also useful in clinical practice among men who have a PSA level of 4 to 10 ng/mL. With a cutoff of ≤ 25%, the detection of cancer is 95%, and the rate of sparing of biopsies is 20%. This test is most useful in men with persistently elevated PSA levels who a have negative biopsy result. The [-2]proPSA isoform in prostate cancer serum is 25% to 95% of the free PSA function, when associated 6% and 19% in biopsy-negative men. At a sensitivity

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of 95% in men with PSA between 4 and 10 ng/mL, the specificity of proPSA, total PSA, and free PSA alone is 37%, 15%, and 27%, respectively [29,30].

Our study showed the prevalence of prostate cancer to be 35.39% and the positive predictive value in the diagnosis of prostate cancer when the PSA level was higher than 4 ng/mL to be 37.2%, which is a little higher than in a pooled meta-analysis study (25%). The incidence of prostate cancer in patients with serum PSA < 4 ng/mL, > 4–10 ng/mL, > 10–20 ng/mL, > 20–50 ng/mL, > 50–100 ng/mL, and > 100 ng/mL was 10.67%, 16.12%, 21.43%, 47.97%, 82.81%, and 98.55%, respectively. The chance of detection of prostate cancer was about 50% when biopsy was performed at a PSA level of more than 20 ng/mL. There was a strong correlation of PSA level with tumor diagnosis, tumor aggressiveness (Gleason score > 7), and positive bone metastasis, as demonstrated by the AuROC in Table 1 and Figs. 1-4. The average PSA level for biopsy was extraordinarily high (102.45 ± 411.27 ng/mL) in this study, which can be explained by the very high PSA level (5,000 ng/mL) in one patient with bone metastasis. When we excluded this patient, the average PSA level was the same as in previous reports. We followed the National Comprehensive Cancer Network guideline for the definition of high-grade prostate cancer, which is cancer with a Gleason score > 7. We did not include patients with a Gleason score of 4+3 as high-grade cancer in this study even though such cancers may be aggressive.

Diagnostic performances of the different cutoffs of the PSA level (4, 10, 20, 50, and 100 ng/mL) were determined for all variables. For diagnosis of prostate cancer, the higher the PSA cutoff, the lower the sensitivity and negative predictive value. Meanwhile, higher sensitivity and a higher LHR+ were found with a higher PSA level. In this study (Table 2), the cutoff of 20 ng/mL may be the most appropriate for prostate cancer diagnosis owing to acceptable sensitivity, specificity, and LHR+ (more than 5.0, theoretically suggested LHR+) and the highest AuROC (0.767). In real practice, the PSA cutoff for use as the screening tool should be 4 ng/mL. Use of this level may provide a definite cure by radical therapy.

Although an elevated correlation was found for Gleason score and PSA level, it did not perform well with the cutoffs assigned in clinical practice. The trend in diagnostic indexes toward the Gleason score were similar to prostate cancer diagnosis. Even at the highest PSA cutoff (100 ng/mL), specificity, positive predictive value, and LHR+ were only 80.1%, 68.4%, and 2.61, respectively (Table 3). At the cutoff point for bone metastasis, 50 ng/mL, the AuROC was highest (0.779) and LHR+ was moderate (3.66 times), meaning that in patients who had a PSA level higher than 50 ng/mL, the chance of a bone scan being positive will be 3.66 times that in all patients tested in this dataset. One patient with a PSA level less than 4 ng/mL, Gleason score of 8, and positive DRE result had bone metastasis (1 in 8 patients, or 12.5%). This finding can be explained according to the study of Wymenga, which showed that 15.7% of prostate cancer cases had bone metastasis when the PSA level was less than 10 ng/mL [31]. Because bone metastasis is very important for staging and treatment of prostate cancer, we also recommend that a bone scan be performed in patients with a PSA level of more than 10 ng/mL or a Gleason score of more than 7 or in patients with a clinical stage higher than T2 (intermediate/high risk) as the standard guideline.

The limitation of this study was that only serum PSA was used for the diagnosis of prostate cancer, aggressiveness of cancer, and bone metastasis. The combination of PSA testing with DRE of the prostate and ultrasound imaging should enhance the sensitivity, specificity, and AuROC for the diagnosis of prostate cancer.

In conclusion, with the use of serum total PSA in clinical practice, the prevalence of prostate cancer in this cohort was 35.39%. A strong correlation was found between the PSA level and tumor diagnosis, tumor aggressiveness, and bone metastasis. In real-life practice with serum total PSA testing, a greater chance of a positive cancer result, high-grade cancer, and bone metastasis was found in patients with a higher PSA level.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

ACKNOWLEDGMENTS

We would like to thank Faculty of Medicine, Chiang Mai University for funding this study.

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