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The impact of diurnal variation of PSA on timing of measurement in prostate biopsy

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Abstract

Background: Prostate-specific antigen (PSA) synthesis is related to testosterone, which has a diurnal rhythm. PSA might have a diurnal variation and the timing of measurement could change the clinical practice for prostate biopsy.

Methods: Male patients complaining of lower urinary tract symptoms (group 1) and diagnosed with prostate cancer (group 2) were recruited into the study. Morning fasting blood samples were withdrawn between 9.00 and 11.00 AM for the determination of biochemical parameters, PSA (PSA1), total testosterone (T1), and estradiol (E1) levels. In the afternoon, between 15.00 and 15.30 PM, blood samples were again obtained from the same participants at the same day and the serum concentration of PSA (PSA2), total testosterone (T2), and estradiol (E2) were measured.

Results: A total of 160 and 30 patients were enrolled in groups 1 and 2, respectively. One hundred forty (87.5%) and 26 (86.6%) patients had a decrease in the PSA levels when measured in the afternoon. The Wilcoxon signed-rank test determined a statistically significant difference between the PSA levels measured in the morning and in the afternoon in each group. An analysis of covariance test revealed no statistically significant difference in PSA concentration between the groups after adjustment for baseline concentration ($F(1.187) = 0.203$, $P = .653$). There was a weak positive correlation between PSA1/PSA2 and T1/T2, r_s (160) = 0.163, $P = .034$. An extra unit increase in PSA1 concentration leads to a 0.805 (95% confidence interval [CI], 0.781-0.830) and 0.828 (95% CI, 0.807-0.849) ng/mL increase in PSA2 concentration in groups 1 and 2, respectively, that is, patients with and without prostate cancer had a similar decrease in the PSA levels. When measured in the afternoon, 66.6% and 50% patients with a morning PSA level over 3 or 4 ng/mL had a PSA drop below these levels, respectively.

Conclusions: PSA has a diurnal variation and the timing of measurement may alter the decision of the clinician for transrectal ultrasound prostate biopsy.

KEYWORDS
diurnal variation, prostate, PSA, testosterone

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1 | INTRODUCTION

Prostate-specific antigen (PSA) is a low molecular weight kallikrein-like serine protease, expressed almost exclusively by normal, hyperplastic, and malignant prostatic epithelial cells.[1] PSA is the most widely used biochemical tumor marker in medicine and the cornerstone in the diagnosis and management of prostate cancer. Serum PSA levels are directly proportional to hyperplastic gland, tumor volume, and advancing age[1] and high levels are accepted as an indication for prostate biopsy.

Prior to PSA era, prostatic acid phosphatase (PAP) was used as the prostate cancer marker.[2] PAP was found to have a wide diurnal variation and was limited to be a predictive tumor marker.[3-7] A few number of studies investigated the diurnal variation of PSA with serial measurements, but most of these studies conducted former biochemical analytical methods with a very small study population having low PSA levels.[5-10]

PSA synthesis in prostatic epithelial cells is partly dependent on the sex steroidal hormones. It is well known that men with Klinefelter syndrome have atrophic or small testes, decreased testosterone levels, and atrophic prostate with very low PSA levels.[11] In patients with prostate cancer, PSA levels drop to undetectable levels after castration. In addition, in patients with benign prostatic hyperplasia (BPH), PSA levels decrease after treatment with 5-α reductase inhibitors. All of this evidence point out the intense relationship of PSA with sex steroids. It is well known that testosterone has a diurnal rhythm, with increasing levels from 5.00 AM to 8.00 AM and starting to decrease in the afternoon after 2.00 PM.[12] The relationship between PSA and testosterone made us think that PSA might have a diurnal variation similar to testosterone.

Many urology clinics practice from 08.00 AM and upto 04.00 PM worldwide and the patients have a blood test for the measurement of PSA between these hours. PSA levels of 3 or 4 ng/mL have been used as the standard cut-off value for prostate biopsy.[13,14] It is crucial to investigate the diurnal variation of PSA levels in order to make the right decision in patients with or without prostate pathology.

In this study, we aimed to investigate the diurnal variation of PSA and its impact on the clinical decision of prostate biopsy to clarify the relation between diurnal changes in the serum levels of testosterone and PSA.

2 | MATERIALS AND METHODS

This was a prospective study designed to assess the diurnal variation of serum PSA and testosterone levels in patients with lower urinary tract symptoms (LUTS) of ≥50 years, comparable in age to patients diagnosed with prostate cancer. The study was compliant with ethical principles laid down in the Declaration of Helsinki, following approval of the protocol by a properly constituted Instutional Independent Ethics Committee. Written informed consent was obtained from each study participant.

Male patients complaining of LUTS (group 1) or diagnosed with prostate cancer (group 2) were recruited from our urologic outpatient clinic between September 2016 and November 2017. For group 1, patients were not enrolled if they had a history of malignancy, previous prostatic operation or prostate biopsy, pyuria, urinary tract infection, or urinary tract instrumental intervention during the last 3 months. In addition, patients with ureteral or bladder stones, urethral stricture, chronic pelvic pain syndrome, digital rectal examination (DRE) in the last 72 hours, and diseases or medication known to alter hypothalamic-pituitary-gonadal axis were not included. No absolute threshold value for PSA level was attributed to carry out transrectal ultasound (TRUS)–guided prostate biopsy. Patients with a positive finding on DRE, a rising PSA level, comorbidities, and older age were taken in consideration for biopsy. Only patients diagnosed with prostate cancer were included in group 2.

2.1 | Study population

All patients included in the study were subjected to a diagnostic work-up including medical history, physical examination, International Prostate Symptom Score (IPSS), uroflowmetry, postvoiding bladder volume measurement, urinalysis, biochemistry, and ultrasonography of the urinary tract.

Morning fasting blood samples were withdrawn from all participants between 9.00 and 11.00 AM for the quantitative determination of biochemical parameters, hemogram, PSA (PSA1), and circulating sex steroidal hormones including total testosterone (T1), and estradiol (E1). In the afternoon, between 15.00 and 15.30 PM, blood samples were again obtained from the same participants on the same day. Samples withdrawn in the afternoon were centrifuged, separated into aliquots, and the serum was stored at −80°C until assay. Serum concentration of total testosterone (T2), estradiol (E2), and PSA (PSA2) were measured.

2.2 | Assays

Blood samples were collected via venipuncture to the SST tubes (BD Vacutainer SST II Advance, Becton, Dickinson and Company, Franklin Lakes, NJ). After clot formation, each blood sample was centrifuged for 10 minutes at 1000*g*. Serum samples were separated immediately and were stored at −80°C until PSA, testosterone, and estradiol measurement. Serum PSA levels were measured by chemiluminescent microparticle immunoassay (CMIA) method using Abbott Architect i2000 autoanalyzer with Architect Total PSA commercial reagent (Abbott Diagnostics, Ireland) according to the manufacturer's instructions. The analytical sensitivity of the assay was stated as 0.008 ng/mL by the manufacturer. Serum PSA values of 0 to 4 ng/mL are considered normal by this method.

2.3 | Statistical analysis

χ^2 was used for the comparison of categorical variables for the differences between the groups (groups 1 and 2) and the Mann

TABLE 1 Baseline descriptives and biochemical characteristics

		Group 1 (n = 160), 84.3%	Group 2 (n = 30), 15.6%	*P*-value
Age	Mean (SD) Median (range)	66.6 (6.6) 66 (49-83)	70 (7.2) 70 (58-84)	.06
Hypertension (n, %)	Yes No	114 (71.2) 46 (28.8)	19 (63.3) 11 (36.7)	.43
DM (n, %)	Yes No	44 (27.5) 116 (72.5)	9 (30.0) 21 (70.0)	.09
Height, cm	Mean (SD)	166.3 (5.8)	164.8 (3.3)	.85
Weight, kg	Mean (SD)	88.8 (14.1)	85.6 (13.1)	.80
BMI	Mean (SD)	32.2 (12.7)	30.5 (15.2)	.87
Waist circumference, cm	Mean (SD)	114.5 (25.1)	120.6 (24.0)	.29
IPSS total	Mean (SD)	14.9 (10.2)	16.0 (9.0)	.72
Insulin, mIU/L	Mean (SD)	10.0 (8.5)	8.6 (4.9)	.53
Glucose, mg/dL	Mean (SD)	125.4 (59.9)	121.6 (50.2)	.69
HOMA-IR	Mean (SD)	3.01 (2.6)	2.56 (1.7)	
CRP, mg/dL	Mean (SD) Median (range)	0.82 (1.21) 0.42 (0.1-8.0)	0.94 (1.02) 0.68 (0.16-4.3)	.17
WBC, 10^9/L	Mean (SD)	7.3 (1.9)	6.9 (1.5)	.43
Lymphocyte, 10^9/L	Mean (SD)	2.2 (0.8)	2.1 (0.6)	.65
Neutrophil, 10^9/L	Mean (SD)	4.5 (4.5)	3.9 (1.2)	.54
NLR	Mean (SD)	2.25 (2)	2 (0.9)	.11
Hemoglobin, g/dL	Mean (SD)	14.8 (1.4)	14.1 (1.7)	.30
RDW	Mean (SD)	13.4 (5.6)	17.1 (10)	**.006**
Platelet, 10^9/L	Mean (SD)	253.8 (77.9)	255.6 (88.5)	.80
MPV	Mean (SD)	9.9 (1.2)	10.2 (0.8)	.43
Creatinine, mg/dL	Mean (SD)	1.0 (0.3)	1.1 (0.3)	.13
Total cholesterol, mg/dL	Mean (SD)	207.8 (41.8)	187 (58.5)	**.05**
LDL, mg/dL	Mean (SD)	136.2 (35.3)	133.7 (51.1)	.36
Trygliceride, mg/dL	Mean (SD)	143.8 (71.8)	141.8 (68.6)	.87
HDL, mg/dL	Mean (SD)	41.9 (10.4)	46.9 (18.5)	.16
PSA1, ng/dL	Mean (SD) Median (range)	3.5 (4.8) 2.0 (0.1-44.3)	56.9 (145.8) 12.8 (3.7-674)	<0.0005
PSA2, ng/mL	Mean (SD) Median (range)	2.9 (3.9) 1.7 (0.07-31.7)	47.6 (121) 11 (2.9-559)	<0.0005
Testosterone 1 (T1), ng/dL	Mean (SD) Median (range)	554.4 (220.1) 518 (85-1223)	465 (165.9) 436 (193-776)	.10
Estradiol 1 (E1), ng/dL	Mean (SD) Median (range)	29.9 (11.1) 27 (10-86)	26.7 (12.8) 26 (12-68)	.14
Testosterone T2, ng/dL	Mean (SD) Median (range)	455.7 (193.8) 429.4 (56.1-1215.2)	378.7 (150.6) 348.2 (189.8-678.1)	.09
Estradiol 2 (E2), ng/dL	Mean (SD) Median (range)	26.8 (8.8) 25 (10-64)	27.9 (9.2) 25 (17-48)	.23

Abbreviations: BMI, body mass index; CRP, C-reactive protein; DM, diabetes mellitus; HDL, high density lipoprotein; HOMA-IR, homeostatic model assessment for insulin resistance; IPSS, International Prostate Symptom Score; LDL, low density lipoprotein; MPV, mean platelet volume; NLR, neutrophyl lymphocyte ratio; PSA, prostate-specific antigen; RDW, red cell distribution width; WBC, white blood cell.

Whitney *U*-test for continous variables including descriptives, biochemical parameters, and sex steroidal hormones. The average score of each domain in the questionnaire was reported as mean and standard deviation. The primary objective was to estimate the difference between the patients in groups 1 and 2 in change from baseline in mean serum levels of T, E, and PSA. This was assessed using an analysis of covariance (ANCOVA) model, which included the corresponding baseline values as covariate. All ANCOVA analyses employed two-sided tests at 5% significance level. To understand the daily rhythm of PSA, estimated median differences between the PSA

TABLE 2 Wilcoxon signed-rank test determined a statistically significant difference between the prostate-specific antigen levels measured in the morning and in the afternoon in each group

Groups	Positive ranks	Negative ranks	Ties	*Z*	*P*-value
1	140	17	3	−8.123	<.0005
2	26	4	0	−3.181	<.001

values obtained in the morning and in the afternoon in both groups were determined with 95% confidence intervals (CIs), and *P*-values were calculated using the Wilcoxon signed-rank test. The ratio of PSA1 to PSA2 was correlated with the ratio of T1/T2 and E1/E2 with Spearman rank-order correlation to investigate if the change in the values of PSA is related to change in the values of testosterone or estradiol. A Spearman's rank-order correlation and a linear regression analysis was run to analyze the relationship between PSA1 and PSA2 concentration and to understand the effect of average PSA levels measured in the morning (PSA1) on PSA concentration measured in the afternoon (PSA2) in both groups. $P < .05$ was considered statistically significant. The SPSS system (version 23; IBM, Armonk, NY) was used for the calculations.

3 | RESULTS

A total of 190 patients were randomly enrolled into the study between September 2016 and November 2017. While 160 patients had LUTS (group 1), the remaining 30 patients were diagnosed with prostate cancer (group 2). The median (range) age of patients in groups 1 and 2 were 66 (49-83) and 70 (58-84) years; PSA1 2.0 (0.1-44.3) and 12.8 (3.7-674) ng/dL, respectively (Table 1). Of the 160 patients with LUTS enrolled in the group 1, 34 (21.2%) were on tamsulosin or silodosin treatment at the first visit at our outpatient clinic. Thirty (18.7%) patients had mild LUTS and were not advised to take any medication for the relief of the symptoms. Seventy three patients had TRUS-guided prostate biopsy and 30 patients (group 2) were diagnosed with prostate cancer. Baseline descriptives and biochemical characteristics are summarized in Table 1; red cell distribution width (RDW) and total cholesterol were the only biochemical parameters with a statistically significant difference between the groups. There were no statistically significant differences between the groups in terms of T1 and E1.

TABLE 4 Correlation between PSA1/PSA2 and T1/T2 and E1/E2 levels

	Group 1				Group 2			
	T1/T2		E1/E2		T1/T2		E1/E2	
PSA1/PSA2	r_s	*P*	r_s	*P*	r_s	*P*	r_s	*P*
	.163	**.034**	−0.125	.105	−0.062	.788	.257	.260

Note: E1: estradiol in the morning; E2: estradiol in the afternoon; PSA1: prostate-specific antigen in the morning; PSA2: prostate-specific antigen in the afternoon; T1: testosterone in the morning; T2: testosterone in the afternoon.

A change in the values of PSA measured in the afternoon was observed when compared to values measured in the morning. The Wilcoxon signed-rank test was used to understand if there is a statistical difference between these values obtained in the morning and in the afternoon in each group. Data are medians unless otherwise stated. While 140 (87.5%) and 26 (86.6%) patients had a decrease in PSA levels when measured between 15.00 and 15.30 PM, 17 and four patients had a slight increase in both groups, respectively, whereas no difference in the PSA levels was observed in three patients in group 1. The difference in the scores were symmetrically distributed, as assessed by a histogram. A Wilcoxon signed-rank test determined a statistically significant difference between the PSA levels measured in the morning and in the afternoon in each group (Table 2). Among 17 patients with an increase in PSA value measured in the afternoon, 10 had an increase below 0.1 ng/dL and four and three patients had an increase between 0.15 and 0.36 ng/dL and 0.9-1.09 ng/dL, respectively.

An ANCOVA test was used to understand if there is a difference in PSA values between the groups and no statistical significant difference was found in PSA concentration after adjustment for baseline concentration ($F(1.187) = 0.203$, $P = .653$; Table 3).

A Spearman rank-order correlation was run to assess the relationship between PSA1/PSA2 ratio and both T1/T2 and E1/E2 in both groups. Preliminary analyses for the relationship of PSA1/PSA2 and T1/T2 showed the relationship to be monotonic, as assessed by visual inspection of a scatterplot. There was a weak

TABLE 3 Analysis of covariance test for the difference in PSA values between the groups

	Group	Unadjusted means		Change from baseline in each group, adjusted means		Mean difference (BPH-Prostata ca)	95% confidence interval for difference	*P*-value	η^2
		Mean	Std	Mean	SEM				
PSA2	1	3.1	3.9	8.01	.17	−0.246	(−1.324, 0.832)	.653	.001
	2	47.5	121	8.26	.51	.246			
T2, ng/dL	1	455.7	193.8	448.16	7.34	8.679	(−35.245, 52.6)	.697	.001
	2	378.7	150.6	439.48	20.9	−8.679			
E2	1	26.8	8.8	26.60	.472	−2.899	(−5.709, −0.88)	**.043**	**.022**
	2	27.9	9.2	29.50	1.34	2.899			

Note: E2: estradiol in the afternoon; PSA2: prostate-specific antigen in the afternoon; T2: testosterone in the afternoon.
Bold values indicate statistical significance.

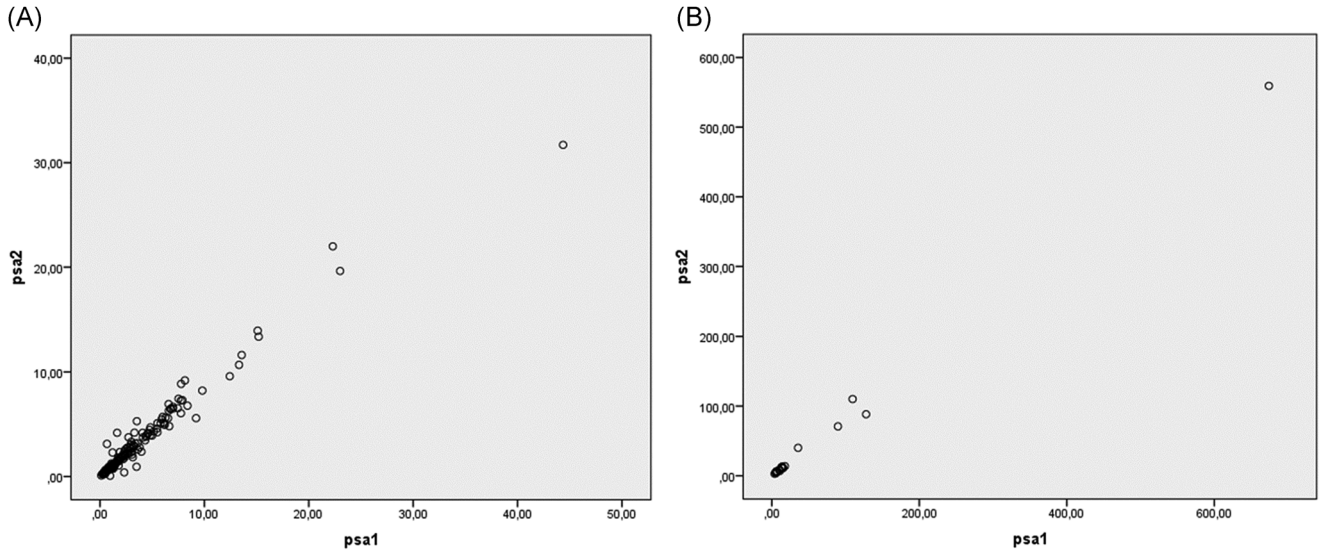

FIGURE 1 A, B, Scatterplot for the relation between prostate-specific antigen (PSA) 1 and PSA2 in groups 1 and 2

positive correlation between PSA1/PSA2 ratio and T1/T2 ratio, r_s (160) = 0.163, P = .034 (Table 4).

3.1 | Correlation and linear regression analysis of PSA1 and PSA2 in both groups

Relationship between PSA1 and PSA2 concentration in both groups was assessed with the Spearman rank-order correlation. Preliminary analysis showed the relationship to be monotonic, as assessed by visual inspection of a scatterplot in patients with BPH and prostate cancer (Figure 1A and 1B, respectively). There was a strong positive correlation between PSA levels measured in the morning and in the afternoon in both groups, rs(160) = 0.957, P < .0005 and rs(30) = 0.966, P < .0005, respectively.

A linear regression was run to understand the effect of average PSA levels measured in the morning (PSA1) on PSA concentration measured in the afternoon (PSA2) for both groups. To assess linearity, a scatterplot of PSA1 concentration against PSA2 concentration with superimposed regression line was plotted. Visual inspection of these two plots indicated a linear relationship between the variables. There was homoscedasticity and normality of the residuals. There was no outlier in group 1. In group 2, there were two outliers, which were kept and a linear regression was run.

In group 1, the following was the prediction equation: PSA1 concentration = 0.264 + (0.805 × PSA2). Average PSA1 concentration statistically significantly predicted PSA2 concentration, F (1.158) = 4112.72, P < .0005 and PSA1 levels accounted for 98% of the explained variability in PSA2 concentration with adjusted R^2 = 96.1%, a strong size effect according to Cohen (1998). An

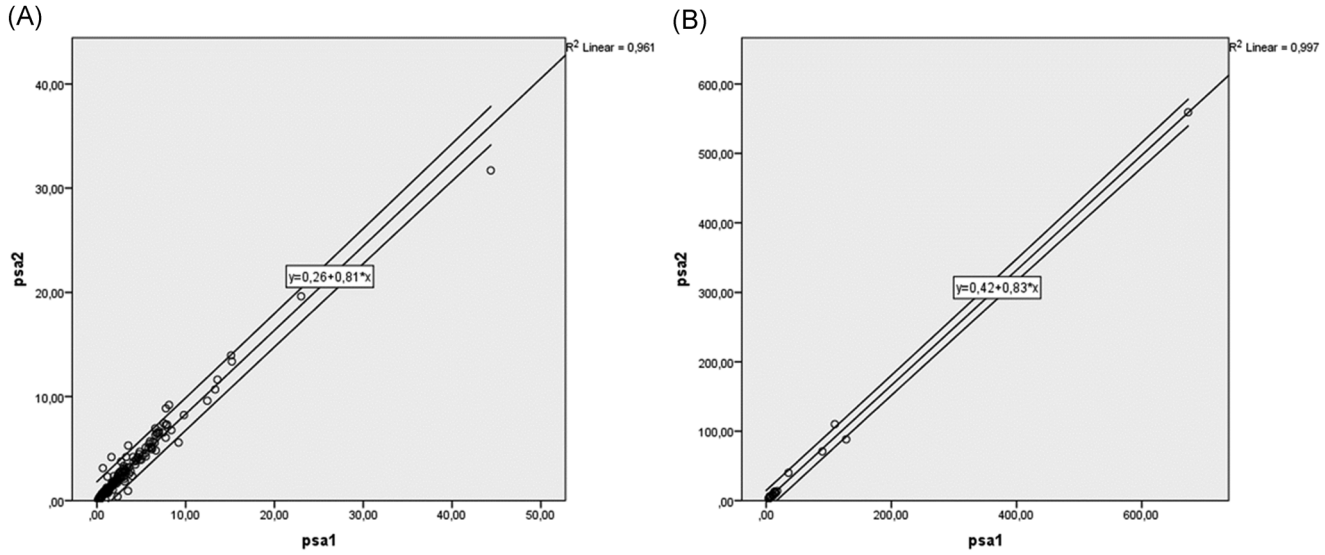

FIGURE 2 A, B, Simple linear regression with confidence and prediction intervals graphically using a scatterplot in groups 1 and 2

TABLE 5 Predictions to determine PSA2 concentration for PSA1 at 3, 4, and 10 ng/mL concentrations

	PSA1 concentration, ng/dL	Contrast estimate, ng/dL	95% confidence interval
Group 1	3.0	2.68	2.560-2.799
	4.0	3.485	3.365-3.604
	10.0	8.317	8.118-8.516
Group 2	3.0	2.90	−0.314-6.117
	4.0	3.730	0.522-6.938
	10.0	8.700	5.534-11.866

Note: Contrast estimate: predicted mean PSA2 concentration.

extra unit increase in PSA1 concentration leads to a 0.805 (95% CI, 0.781-0.830) ng/mL increase in PSA2 concentration. The results of the simple linear regression are shown graphically using a scatterplot (Figure 2A).

In group 2, the prediction equation was PSA1 concentration = 0.417 + (0.828 × PSA2). Average PSA1 concentration statistically significantly predicted PSA2 concentration, F(1.28) = 6739.56, $P < .0005$, and PSA1 levels accounted for 99.9% of the explained variability in PSA2 concentration with adjusted $R^2 = 99.7\%$, a strong size effect according to Cohen (1998). An extra unit increase in PSA1 concentration leads to a 0.828 (95% CI, 0.807-0.849) ng/dL increase in PSA2 concentration. The results are graphically shown using a scatterplot (Figure 2B).

Predictions were made to determine mean PSA2 concentration for patients who had measurement of PSA in the morning at 3, 4, and 10 ng/dL concentrations in both groups (Table 5).

Three or 4 ng/dL cut-off value for PSA has been widely accepted for TRUS-guided prostate biopsy throughout the world. In our study, we found 18 in 190 patients with a PSA value between 3 and 4 ng/dL. While 12 of 18 patients (66.6%) had a PSA below 3 ng/dL when measured in the afternoon, PSA had not dropped below 3 ng/dL in six of 18 (33.3%) patients. In case of 4 ng/dL as the cut-off value for TRUS biopsy, six of 12 (50%) patients with a PSA value between 4 and 5 ng/mL had a drop in PSA below 4 ng/dL, while the remaining six (50%) patients did not. Only one patient with a PSA of 5.6 ng/mL measured in the morning had the PSA decreased below 4 ng/dL. In addition, the PSA value of 2.96 increased to 3.04 when measured in the afternoon in one patient.

4 | DISCUSSION

In our study, we measured serum PSA both in patients with or without prostate cancer and found that there is a significant difference between the morning and afternoon samples in both groups. However, there was no significant difference between the groups, that is, patients with and without prostate cancer had a similar decrease in the PSA levels. A weak correlation between the ratio in testosterone (T1/T2) and PSA (PSA1/PSA2) levels indicates that diurnal variation in PSA levels might be hormonal but not directly related to testosterone levels.

PAP was used as a tumor marker in prostate cancer diagnosis before the invention of PSA. However, the widespread use of PAP resulted in the observation that serum levels of this enzyme may vary significantly over the course of the day.[5] In the 90s, daily variation in serum PSA levels had been reported in small series, mostly it was based on younger subjects with low PSA levels, with controversial results.[5-9]

These small studies were not designed to investigate the impact of daily variation in the diagnosis and follow-up of patients with prostate cancer. Shirbiny et al[7] noted random fluctuations only in three of 19 patients, however, the remaining 16 patients were younger with a mean age of 36 years and were free of symptomatic BPH or prostate cancer with low PSA values. However, Dejter et al[5] investigated the diurnal rhythm of PSA in 10 patients with prostate cancer and found that the secretion of PSA into serum is not cyclic. They reported a trend of lower PSA values when measured between 12 and 4 PM compared to samples obtained at 8 AM. They advised that clinicians should rely only on trends of PSA over long-time intervals rather than a single measurement. In another study, the investigators found that there was a diurnal variation in serum PSA levels in approximately half of the eight patients with prostate cancer, with a peak value in the morning and decreasing steadily throughout the day.[8] In favor of daily variation, Manini et al[6] found a large daily fluctuation of PSA ranging between −72% and +190% in 32 patients with advanced prostate cancer. A study investigating patients hospitalized for benign conditions other than prostate cancer reported that subjects in whom PSA was measured over 4 ng/mL in the morning were accompanied with a larger amplitude of daily fluctuation and there was a gradual decline throughout the day in 61.5% of the subjects.[10]

In our study, we found that 87.5% and 86.6% of patients with or without prostate cancer had decreased PSA levels in the afternoon, respectively. Interestingly, we observed a very similar decrease in PSA levels in patients with or without prostate cancer (0.805 and 0.828 ng/mL decrease per an extra unit). Dejter et al reported no significant difference in mean percent of variation between patients with prostate cancer, BPH, and healthy men for PSA. According to our results, we consider that diurnal variation in PSA levels might not be related to cancer metabolism. Both prostatic acinar and cancerous cells might have similar pathogenetic pathways for PSA production.

Although diurnal variation of PSA was noticed by the investigators, the impact of this variation on the indication and results of TRUS biopsy has not been questioned. In many parts of the world, PSA over 3 or 4 ng/mL without suspicious findings at DRE is widely accepted as a threshold for TRUS-guided prostate biopsy. Therefore, small variation in PSA levels could change the decision for biopsy and differ the correlation of PSA values with biopsy results, especially in patients with PSA values between 3 and 5 ng/mL with negative DRE. In our study, 18 patients with negative DRE and PSA values between 3 and 4 ng/mL and 66.6% had a PSA drop below the threshold value for biopsy 3 ng/mL. However, 50% of 12 patients with PSA value between 4 and 5 ng/mL

had PSA2 values under 4 ng/mL. These findings show that if sampling of PSA is practiced in the afternoon in our daily practice, the rates of TRUS biopsy will inevitably and significantly decrease in more than half of the patients with negative DRE and PSA value between 3 and 5 ng/mL. On the other hand, PSA is the only marker in the follow-up of patients treated with radical prostatectomy, radiotherapy, chemotherapy, or androgen deprivation therapy and very small variations as 0.1 ng/mL could have a great impact on the next treatment option. Further studies are needed.

It is well known that testosterone and PSA have a close relationship. 5-α-reductase inhibitors block the conversion of testosterone to dihydrotestosterone in the prostate and reduce PSA levels. In addition, androgen deprivation therapy decreases the PSA levels almost to undetectable levels in patients with prostate cancer. These well-known associations point a close relationship between testosterone and PSA expression. Two reports have investigated the relationship of testosterone rhythmicity with PSA. Akimoto et al[9] observed circadian rhythms for the serum levels of PSA but fewer patients showed similar pattern than that for serum testosterone with some time delay. The other study observed a significantly inverse correlation of overall 24-hour means for testosterone and PSA.[1] Both studies concluded that the relationship between testosterone levels and that of PSA is ambiguous and single time values may give an incomplete picture of the physiologic relationship between these two variables. In our study, testosterone rhythmicity had a weak correlation with PSA diurnal variation. We suggest that there is an indirect relation between testosterone and PSA expression and further molecular studies may eventually reveal the casual links.

The major limitation of our study is the small number of subjects with PSA value between 3 and 4 ng/mL, and 4 and 5 ng/mL, which prevented the significance of decrease in TRUS biopsy rates on the rate of clinical significant prostate cancer and survival of patients. According to our results, a new large trial including patients with PSA value between 3 and 4 ng/mL, and 4 and 5 ng/mL is needed. In addition, PSA was measured two times in our study, in the morning and close to late afternoon. Whether a third PSA measurement in the middle of the day at about 12 or 13 o'clock could also give a significant decrease in the levels is obscure. Clinical value of these findings should be further investigated.

5 | CONCLUSIONS

PSA has a diurnal variation and the timing of measurement may alter the decision of the clinician for TRUS prostate biopsy.

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