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ORIGINAL PAPER

Predictive value of PSA density in the diagnosis of prostate cancer in lebanese men

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Summary ***Objective: Being the second most common cancer in men, prostate cancer detection relies on laboratory tests, imaging, and surgical procedures, although biopsy remains the mainstay in diagnosis of prostate cancer. No clear cut-off of prostate specific antigen density (PSAD) for suspecting prostate cancer has been established in the Lebanese population. Our primary objective was to evaluate the diagnostic strength of the PSAD value versus total prostate specific antigen (tPSA) level in the Lebanese men in correlation with biopsy outcome to avoid unnecessary prostate biopsy.***
Methods: A retrospective study of 347 patients with history of prostate biopsy done for cancer suspicion included tPSA, prostate volume, and prostate density values and results of prostate biopsy. Data was collected from Bahman hospital and statistical analysis of the mean values of tPSA, prostate volume and PSAD in different age groups was done. Significance of the results was tested using.
Results: On average, patients with negative biopsies were younger and they had lower tPSA levels, lower PSAD values and larger prostate volume compared to patients with positive biopsies. A PSAD cutoff of 0.185 ng/ml^2 revealed the highest predictive strength for prostate cancer (6 times risk) compared with other parameters. These findings were mainly referred to patients with PSA > 10 ng/ml.
Conclusions: A multifactorial approach must be conducted including all parameters in order to decide upon the need for prostate biopsy. PSAD proved to be a good marker in favor or against a prostate biopsy with a cut-off of 0.185 ng/ml^2, especially in patients with tPSA level higher to 10 ng/ml. A multicenter study was recommended for better and more reliable results and more precise cut-offs.

KEY WORDS: PSAD; Prostate biopsy; PSA; Age; Prostate volume.

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INTRODUCTION

Normal ranges of *prostate specific antigen* (PSA) and prostate volume vary among ethnicities and communities at different geographic locations and of different socioeconomic statuses (3). Therefore, pathological PSA and prostate volume values might as well vary between ethnicities (3).
In the Lebanese men, prostate cancer incidence is expected to reach 69 cases per 100000 by 2020, the highest prevalence in the region (4). Prostate cancer is expected to become the most common cancer in males in 2020 (4).
A general goal of this study was to estimate the level at which PSA value and prostate volume value are indicative for a biopsy procedure in the Lebanese population.
The primary objective was to evaluate the diagnostic strength of *prostate specific antigen density* (PSAD) *versus* PSA level in the Lebanese men in correlation with biopsy outcomes to avoid unnecessary prostate biopsy.
The secondary objectives of the study were: 1) to identify age-related cutoffs which may be used in the clinical practice for the diagnosis of prostate cancer, 2) to identify a cutoff for the PSA level which may be used in the clinical practice for the diagnosis of the prostate cancer, 3) to identify a cutoff for the PSAD level which may be used in the clinical practice for the diagnosis of the prostate cancer.

METHODS

Study design and patient population

This study was a retrospective chart review, conducted in Bahman hospital, including patients who were screened for prostate cancer and underwent prostate biopsy.
All patients were admitted to Bahman hospital during the last 15 years, between January 2006 and December 2019. Patients were selected according to predefined inclusion and exclusion criteria (Table 1) and PSA testing was primarily used to screen for prostate cancer. Accordingly, patients were chosen, and data was collected and submitted for statistical calculation and further analysis.
The protocol was reviewed and granted written study approval from the research committee in the Lebanese University, and approval from the ethical committee of the hospital. The study was conducted in accordance with the US Code of Federal Regulation 45-CFR-46.107, 21-CFR-56.107, *Good Clinical Practice ICH* Section 3 and the principles laid down by the *18th World Medical Assembly* (*Helsinki, 1964*) and all applicable amendments. All participants had a designated code. Records will be stored, and none can access the sheets except the researchers.
The sample size was estimated on the assumption of an incidence of prostate cancer in the Lebanese males of

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1503 new cases in 2018 and a 5-year prevalence of 3405 according to GLOBOCAN (5). Hence, we estimated a minimum sample size of 10% of the estimated prevalence that is 300 patients who must fulfill the inclusion and exclusion criteria as shown in Table 1.

Table 1.
Inclusion and exclusion criteria utilized in the study.

Inclusion criteria	Exclusion criteria
PSA level ≥ 3 ng/ml	Past diagnosis of prostate cancer
Transabdominal prostate US result available	Incomplete patient record
Histologically confirmed diagnosis of csPca	

Table 2.
Prostate volume and density.

		Prostate volume (ml)	Density (ng/ml^2)
Mean		59.25	0.56
Median		53.00	0.18
Std. Deviation		30.84	1.15
Minimum		12.00	0.04
Maximum		214.00	9.75
Percentiles	25	39.00	0.12
	50	53.00	0.18
	75	72.00	0.44

Figure 1.
Distribution of PSA levels.

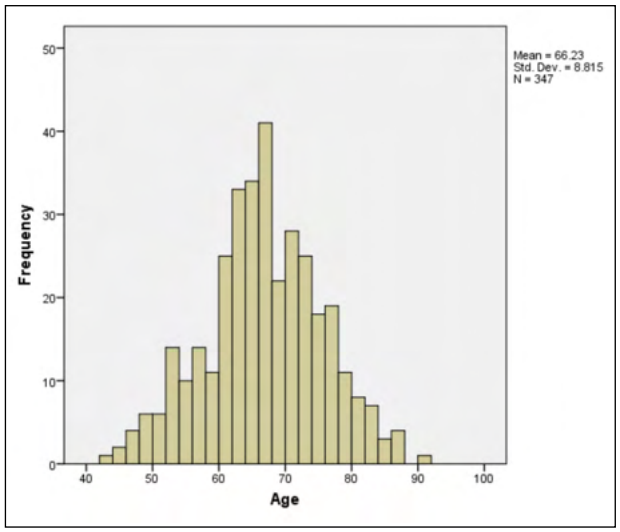


Table 3.
Correlation between variables and biopsy outcome.

	Biopsy outcome	N	Mean	Std. deviation	95% Confidence interval for mean Lower bound	Upper bound	Min-max	P value
Age	Benign	172	63.38	8.30	62.13	64.63	44-87	0.000
	Prostate cancer	175	69.03	8.42	67.77	70.28	43-90	
PSA ng/ml	Benign	172	11.47	11.89	9.68	13.26	2-100	0.000
	Prostate cancer	175	37.42	55.93	29.07	45.76	3.5-394	
Prostate volume (ml)	Benign	172	64.66	34.40	59.48	69.84	13-214	0.003
	Prostate cancer	175	53.92	25.92	50.06	57.79	12-175	
Density (ng/ml^2)	Benign	172	0.23	0.30	0.18	0.27	0.04-1.98	0.000
	Prostate cancer	175	0.89	1.52	0.66	1.11	0.05-9.75	

Data collection

The researchers contacted the "*Archive Department*" manager at Bahman and set a schedule to reach the medical records and collect the data.
An electronic validated database was used in the data collection process.
The data includes the following: demographic characteristics (age), laboratory results (PSA ng/ml), transabdominal prostate ultrasound results (prostate volume ml) and histology results (Gleason score).
Prostate specific antigen density was calculated by dividing the PSA value by the prostate volume.
A Gleason Score ≥ 7 was used to define a *clinically significant prostate cancer* (csPCa).

Statistical analysis

Data was analyzed using the SPSS version 22.
A descriptive analysis was done, and variables were presented as per their type. The categorical variables were presented as frequency and proportions. The continuous variables were presented as frequency, mean, median and standard deviation.
A binary logistic analysis was done to test the factors predicting the biopsy outcome.
The dependent variable was "*Biopsy outcome*". The correlation was tested between the dependent variable and the secondary variables using the Chi-square and Fisher exact test. In addition, non-parametric tests were used as Kruskas Wallis test and Mann-Whitney test.
A statistically significant correlation was set at 5% (p-value less than 0.05).

RESULTS

Demographic results

The mean age of the patients was 66.2 (± 8.8) with a minimum of 43 years and a maximum of 90 years. The median age was 66 years.

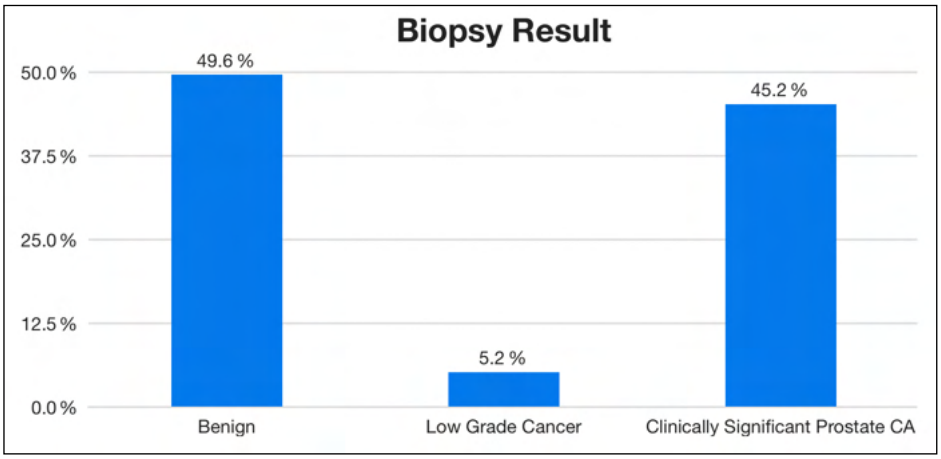
Prostate cancer and laboratory values

The mean prostate volume was 59.2 (± 30.8) ml with a minimum of 12 ml and a maximum of 214 ml. The median prostate volume was 53 ml.
The mean PSAD was 0.56 (± 1.15) ng/ml^2 with a minimum of 0.04 ng/ml^2 and a maximum of 9.75 ng/ml^2.
The median prostate density was 0.18 ng/ml^2 (Table 2).
The mean PSA level was 24.56 (± 42.57) ng/ml with a minimum of 2 ng/ml and a maximum of 394 ng/ml.
The median PSA level was 10 ng/ml (Figure 1).

Histology results

Histology demonstrated that 49.6% of patients had benign prostatic tissue (BPH, prostatitis), 5.2% had low-grade prostate cancer (Gleason score = 6), and 45.2% had clinically significant prostate cancer csPCa (Gleason Score ≥ 7) (Figure 2).

Figure 2.
Distribution of the patients according to biopsy outcome.



Factors affecting the biopsy outcome

A statistically significant correlation existed between age, PSA, prostate volume, and PSAD and the biopsy outcome (*Mann-Whitney test; p < 0.05*) (Table 3).

The results showed that age was higher in prostate cancer patients (mean = 69.03 years) in comparison to patients with benign prostatic tissue (mean = 63.4 years) (p < 0.0001); PSA was significantly higher in prostate cancer patients (mean = 37.4 ng/ml) in comparison to patients with benign prostatic tissue (mean = 11.5 ng/ml) (p < 0.0001); prostate volume was significantly higher in patients with benign prostatic tissue (mean = 66.7 ml) in comparison to prostate cancer patients (mean = 53.9 ml) (p = 0.003) and PSAD was significantly higher in prostate cancer patients (mean = 0.89 ng/ml^2) in comparison to patients with benign prostatic tissue (mean = 0.23 ng/ml^2) (p < 0.0001).

A binary logistic analysis was done to identify the factors predicting the biopsy outcome. The results showed that the biopsy outcome is affected by three variables: patients' age (p = 0.000), PSA (p = 0.000), and prostate volume (p = 0.000).

The logistic analysis showed that the biopsy outcome is at risk times "1" to deviate to be "csPCa" when patient's age is high, PSA level is high and prostate volume is low.

Table 4.
Correlation between age and biopsy outcome.

		Age		Total	P value
		40-64 years	65-90 years		
Biopsy outcome	Benign	97 56.4%	75 43.6%	172 100.0%	< 0.0001
	Prostate cancer	51 29.1%	124 70.9%	175 100.0%	
Total		148 42.7%	199 57.3%	347 100.0%	

Cutoff by age: factors affecting the biopsy outcome

Patients were distributed into two groups according to median of age (65). The first group was aged less than 65 (148 patients) and the second group was aged 65 years and more (199 patients).

A statistically significant correlation existed between the age groups and the biopsy outcome (Chi-square; p < 0.0001) (Table 4). The results showed that 70.9% of the patients aged 65 years and more, had prostate cancer and 56.4% of the patients aged less than 65 years had no prostate cancer.

In the group of patients aged less than 65 years, a statistically significant correlation existed between PSA, and PSAD and biopsy outcome (Mann-Whitney test; p < 0.05) (Table 5). The results showed that PSA was higher in prostate cancer patients (mean = 33.1 ng/ml), and PSAD was significantly higher in prostate cancer patients (mean = 0.81 ng/ml^2) comparing to patients with benign prostatic tissue.

In the group of patients aged more than 65 years, a statistically significant correlation existed between PSA, prostate volume, and PSAD and the biopsy outcome (Mann-Whitney test; p < 0.05) (Table 5).

The results showed that PSA was higher in prostate cancer patients (mean = 39.2 ng/ml), prostate volume was lower in prostate cancer patients (mean = 56.5 ng/ml), and PSAD was significantly higher in prostate cancer patients (mean = 0.92 ng/ml^2) comparing to patients with benign prostatic tissue.

A binary logistic analysis was done to identify the factors affecting the biopsy outcome in the patients aged less than 65 years.

Age	Variables	Biopsy outcome	N	Mean	Std. deviation	95% Confidence interval for mean		Min-max	P value
						Lower bound	Upper bound		
40-64 Years	PSA ng/ml	Benign	97	10.35	11.32	8.07	12.63	2-85	0.010
		prostate cancer	51	33.15	67.00	14.30	51.99	4-394	
	Prostate volume (ml)	Benign	97	57.10	29.98	51.05	63.14	13-200	0.038
		prostate cancer	51	47.73	14.82	43.56	51.89	22-78	
	Density (ng/ml^2)	Benign	97	0.23	0.30	0.17	0.29	0.04-1.98	0.002
		prostate cancer	51	0.81	1.67	0.34	1.28	0.05-7.30	
65-90 Years	PSA ng/ml	Benign	75	12.91	12.52	10.03	15.79	3.7-100	0.000
		prostate cancer	124	39.17	50.89	30.13	48.22	3.5-300	
	Prostate volume (ml)	Benign	75	74.45	37.36	65.85	83.04	21-214	0.000
		prostate cancer	124	56.47	28.95	51.33	61.62	12-175	
	Density (ng/ml^2)	Benign	75	0.23	0.30	0.16	0.30	0.04-1.89	0.000
		prostate cancer	124	0.92	1.46	0.66	1.18	0.06-9.75	

Table 5.
Correlation between the variables and biopsy outcome.

Table 6.
Correlation between the PSA and the biopsy outcome.

		Biopsy outcome		P value	OR	CI (95%)
		Benign	Prostate cancer			
PSA	PSA 3-9.9 ng/ml	106	62	< 0.0001	2.927	1.89-4.53
		63.1%	36.9%			
	PSA 10-19.9 ng/ml	66	113			
		36.9%	63.1%			

Table 7.
Correlation between the PSA density and the biopsy outcome.

		Biopsy outcome		P value	OR	CI (95%)
		Benign	Prostate cancer			
PSA	PSAD < 0.184	114	59	< 0.0001	3.831	2.45-5.98
		65.9%	34.1%			
	PSAD > 0.185	58	115			
		33.5%	66.5%			

Table 8.
Correlation between the PSA density and the biopsy outcome in terms of the age groups.

Age	PSAD	Gleason score		P value	Risk	CI (95%)
		Benign	Prostate cancer			
40-64 years	PSAD < 0.184	65	23	0.010	2.473	1.234-4.956
		73.9%	26.1%			
	PSAD > 0.185	32	28			
		53.3%	46.7%			
65-90 years	PSAD < 0.184	49	36	< 0.0001	4.554	2.465-8.416
		57.6%	42.4%			
	PSAD > 0.185	26	87			
		23.0%	77.0%			

** Chi-Square Test.*

The results showed that the Gleason score was affected by PSA (p = 0.012), and prostate volume (p = 0.048).
The logistic analysis showed that the biopsy outcome was at risk times "1" to deviate to be "csPCa" when PSA level was high and prostate volume was low.
A binary logistic analysis was done to identify the factors affecting the biopsy outcome in the patients aged more than 65 years.
The results showed that the biopsy outcome was affected by two variables: PSA (p = 0.000), and prostate volume (p = 0.003). The logistic analysis showed that the biopsy outcome was at risk times "1" to deviate to be "csPCa" when: PSA level was high and prostate volume was low.
Cutoff by PSA: factors affecting the biopsy outcome
Patients were distributed into two groups according to median of PSA (10). The first group had a PSA level less than 10 ng/ml (168 patients) and the second group had a PSA level 10 ng/ml and more (179 patients). A statistically significant correlation existed between the PSA groups and the biopsy outcome (Chi-square; p < 0.0001) (Table 6). The results showed that 63.1% of the patients, who had a PSA equal to 10 ng/ml and more, were diagnosed with prostate cancer and 63.1% of the patients who had a PSA less 10 ng/ml were not diagnosed with prostate cancer.
A patient with a PSA equal to 10 ng/ml and more had a risk of 2.9 to have a prostate cancer.
A binary logistic analysis was performed to predict the factors affecting the biopsy outcome in patients having a PSA level less than 10 ng/ml. The results showed that the biopsy outcome is affected by two variables: the age (p = 0.000), and the prostate volume (p = 0.049). The logistic analysis showed that the biopsy outcome is at risk times "1" to deviate to be "csPCa" when: the age is high and prostate volume is low.
A binary logistic analysis was performed to predict the factors affecting the biopsy outcome in the patients having a PSA level equal to 10 ng/ml and more. The results showed that the biopsy outcome was affected by two variables: age (p = 0.004), and PSAD (p = 0.000). The logistic analysis showed that the biopsy outcome is at risk times "1" to deviate to be "csPCa" when the age is high and at risk of "6" times" when PSAD is high.

Cutoff by PSA density: factors affecting the biopsy outcome

A statistically significant correlation existed between PSAD groups and the biopsy outcome (chi-square; p < 0.0001) (Table 7). The results show that 66.5% of the patients, who had a PSAD more than 0.185, were diagnosed with prostate cancer and 65.9% of the patients who had a PSAD less than 0.185 were not diagnosed with prostate cancer. A patient with a high PSAD had a risk of 3.8 to have a prostate cancer.
A statistically significant correlation existed between the PSA density groups and the biopsy outcome in each of the two age groups (Chi-square; p < 0.05) (Table 8). The results showed that 46.7% of the patients aged less than 65 years, who had a PSA equal to 10 ng/ml and more, were diagnosed with prostate cancer with an odds Ratio equal to 2.5. In addition, 77% of the patients aged 65 years and more, who had a PSA equal to 10 ng/ml and more, were diagnosed with prostate cancer with an odds Ratio equal to 4.5.
A statistically significant correlation existed between the median PSAD and the biopsy outcome when the PSA level was ≥ 10 ng/ml. The risk of being diagnosed with prostate cancer was 4.2% higher (95% CI 0.263-0.691) when the PSA was more than 10 ng/ml (p < 0.0001) (Table 9).

Discussion

In this study, the profiles of patients submitted to prostate biopsy were outlined. The variables considered were tPSA (total PSA), prostate volume, PSAD, age and prostate biop-

Table 9.
Individual risk of benign and prostate cancer with PSA level ≥ 3 ng/ml by PSA density.

PSA	PSAD	Biopsy outcome				P value	Risk	CI (95%)	
		Benign		Prostate cancer				Lower	Upper
PSA 3-9.9 ng/ml	< 0.184 ng/ml^2	87	82.1%	47	77.0%	0.432*	0.827	0.522	1.309
	> 0.185 ng/ml^2	19	17.9%	14	23.0%				
PSA > 10 ng/ml	< 0.184 ng/ml^2	27	40.9%	12	10.6%	0.000*	0.427	0.263	0.691
	> 0.185 ng/ml^2	39	59.1%	101	89.4%				

** Chi-Square Test.*

sy findings. The results showed that age, tPSA level, prostate volume, and PSAD were important factors to consider in the decision of whether to do a biopsy of prostate or not. This study showed that each of these factors has a certain median relative to which the *positive predictive value* (PPV) of prostate cancer at prostate biopsy differs.

Age

First, about age, the results showed that above two thirds of the biopsies proved evidence of high grade cancer (Gleason > 7) in patients older than 65 years, while less than half biopsies done in patients younger than 65 years diagnosed csPCa. Accordingly, advanced age added one times risk to the detection of csPca. Hence, patients older than 65 years who had urinary symptoms that advocated prostate pathology proved to be candidates for a prostate biopsy with a high PPV for prostate cancer. These findings were anticipated in the literature. More than 65% of prostate cancer patients are expected to be above 65 years of age (6).

Volume

We reported a one-time risk of prostate cancer detection in association with a low prostate volume in both age groups. Of note, the mean of prostate volume was higher in BPH patients compared to prostate cancer patients in either age groups. However, we observed an increase of mean volume with age in both BPH and prostate cancer patients. This sheds light of the possibility of concomitant occurrence of BPH and of its evolution before or along with prostate cancer.

Many studies in the literature confirmed that in patients with small volume prostates, PSA levels superior to 4 ng/ml and suspicious on *digital rectal examination* (DRE) were more likely to show pathological evidence of prostate cancer at biopsy (7, 8). A retrospective study by *Camur et al.* noted that prostate volume has no significant effect on upgrading in active surveillance of appropriate patients9. This result addressed the prostate volume as a single factor, conversely correlation of volume with PSA level proved that volume has a role in the of prostate cancer in the indication to prostate biopsy.

PSA

Evaluation of PSA levels showed that a value of 10 ng/ml (0.38 nmol/l) represented a median that departed values similarly to what was observed for age with a median value of 65 years.

In fact, 52% of the patients in this study had a PSA superior to 10 ng/ml. The prevalence of prostate cancer in this PSA group was remarkably differentiable with the PSA value. Nearly, two-thirds of patients whose PSA level was below 10 ng/ml have benign biopsy outcome compared to two-thirds of patients who have proved csPca on their prostate biopsy with a PSA level above 10 ng/ml.

These values were concordant with the findings reported by *Schmid et al.* (10), whereas according to *Park et al.* (11) and *Kobayashi et al.* (12), there is no significant different detection rate of cancer and pathological findings between the group with tPSA 2-4 ng/ml and 4-10 ng/ml. In the present study patients were divided in only two groups according to PSA (4-9.9 ng/ml and > 10 ng/ml). Nevertheless, a tPSA level higher to the 10 ng/ml median added a risk of 1 times to the detection of csPca, similarly to the age factor. Of note, the mean PSA level increased in either BPH or prostate cancer patients as they grow old similarly to the increase of prostate volume observed between the two age groups (19-28% relative increase in mean prostate volume versus 18-29% increase in mean PSA levels).

The joint increase of both age and PSA in relation to the outcome of prostate biopsy demonstrated that none of the two factors could be a major predictive value by itself. A PSA value higher to the cutoff (10 ng/ml) was predictive of a high risk of prostate cancer if the patient's age was higher of the age cutoff (65 years old). In fact, for a PSA value above 10 ng/ml, no more than 50% of prostate biopsies demonstrated a prostate cancer unless the age was superior to 65 years.

DRE, TRUS and tPSA level are commonly used methods of screening for prostate cancer. The detection of any abnormality in the prostate volume through DRE or TRUS, and the detection of a higher than age-related tPSA level are usually followed by an ultrasound or MRI-guided biopsy of the prostate to rule out prostate cancer.

On note, tPSA was initially utilized as a post-operative laboratory test for recurrence detection. Its implementation as a screening method has lowered morbidity associated with prostate biopsies and the number of unnecessary biopsies, and allowed earlier detection of csPca up to 81% as compared to DRE alone (13).

PSAD

Benson et al. in 1992, introduced the concept of PSAD, to correct PSA value by prostate volume to differentiate patient with high volume benign disease from those with prostate cancer (14). However, many authors questioned this concept, because the utilization of PSAD with a cut-off of 0.15 ng/ml^2 showed a sensitivity of only 60% (14). The diagnostic efficacy of PSA density has been thoroughly discussed in relation to its stratification for each PSA level interval showing that for tPSA levels higher than 10ng/ml, a high prostate density indicated a 6 times risk of csPca detection on a prostate biopsy.

This finding defined prostate density as an extremely important tool for the indication of a biopsy for this tPSA level interval. When the tPSA level is higher to 10 ng/ml, the risk of diagnosing a prostate cancer for a prostate density higher than 0.185 ng/ml^2 was 4.2% (95% CI 0.263-0.691) higher. On the contrary, when PSA level is below 10 ng/ml, a high prostate density value proved to be unreliable using the 0.185 ng/m^2 cut-off. Conversely, in the PSA interval with higher incidence of prostate cancer, the risk of prostate cancer at biopsy dropped when PSAD is below the 0.184 ng/ml^2 cut-off.

In addition, the joint evaluation of age and prostate density showed that higher values of both was predictive of a higher risk of prostate cancer detection on a prostate biopsy (77% of the patients whose PSAD and age were superior to the considered cutoffs had prostate cancer compared to only 26% when both parameters were inferior to the considered cutoffs).

The results from this study confirmed previous reports on the value of PSAD in the biopsy indication. *Jue et al.* demonstrated that PSAD is better in predicting prostate

Table 10.
Redistribution of patients with PSA > 10 ng/ml after lowering PSAD cut-off to 0.09 ng/ml².

	Biopsy outcome	
PSAD	**Prostate cancer**	**Benign**
> 0.09 ng/ml²	109	43
< 0.09 ng/ml²	4	23

cancer versus the use of PSA level or prostate volume alone (15). Similarly, *Stephan et al.* showed the PSA density to perform better than the tPSA level for patients whose PSA level ranged between 2 and 20 ng/ml (16). *Van Iersel et al.*, similarly to many other authors, concluded that the PSAD cutoff to distinguish between prostate cancer and BPH could be 0.15 ng/ml² where a higher value is significant of a higher malignancy probability (17). Although similar results were obtained in this retrospective study with a PSAD cut-off of 0.185 ng/ml² and 0.13 ng/ml², these values are population specific and their variance relied on a multitude of factors (18).
The reliability of the prostate volume measurement dramatically affects the significance of cut-offs used for biopsy decisions. Two methods were implemented in the calculation of the prostate volume: the ellipsoid method or planimetric method. *Stone et al.* found that the three plane method (ellipsoid method) had a variability of 30% compared to the 3D-planimetric method which showed only 5% variation.
Furthermore, *Holmang et al*. stated that the 3-plane method underestimated the volume by 20% compared to the 3D-planimetric method (19). Hence, the higher is the accuracy of the method of volume assessment, the better PSAD would assess the need for a prostate biopsy and the less unnecessary biopsies would be made. In a multi-centric study of 773 patients, *Catalona et al.* (20) considered lowering the PSAD cut-off to 0.078 ng/ml², because at that cut-off, 95% of tumors would be detected.
In the present study, for a tPSA level between 3 and 9.9 ng/ml, when the PSAD cut-off value of 0.184 ng/ml² was utilized, only 42.4% of csPca patients would have been diagnosed with prostate biopsy with a 57% specificity.
A p-value of 0.432 for this tPSA level rendered the results less reliable. For a tPSA > 10 ng/ml, using a PSAD cut-off of 0.184 ng/ml², the utilization of prostate biopsy was 89.4% sensitive and 40.9% specific, with a p-value of < 0.0001.
Lowering the cut-off to 0.09 ng/ml², sensitivity increased to 96% while specificity decreased to 35%. This result could be justified by the fact that 89.4% of csPca patients have a PSAD superior to 0.185 ng/ml² compared to only 59.1% of benign patients being superior to the aforementioned value. Lowering the PSAD cut-off led to a new distribution of patients as shown in Table 10 and consequently to a change of sensitivity. It can be intuitive of the fact that most prostate cancer patients have relatively high PSAD and that lowering the PSAD cut-off recruited more patients into this category and favored an increase of the sensitivity and decrease in the specificity.
Therefore, this study proved PSAD was a good predictor of the biopsy outcome for tPSA ranging between 4 to 20 ng/ml. PSAD cut-off of 0.18 ng/ml/cc could minimize the number of unnecessary biopsies. Consideration of a lower cutoff may promote better sensitivity with a slight decrease in the false negative results, which remains acceptable for a screening test. However, the acknowledgment of a PSAD cut-off mandates further studies for an optimal value that balances the sensitivity and false negative results of the prostate biopsy.

Study limitations
Every study has limitations and this study is no exception. The limitations can be sorted under two titles.

Population
The number of the patients and the fact that they were from the same hospital limited the credibility of our results. A multicenter study with a larger population size will impart to those results more credibility, render them more reliable, help achieve more precise cut-offs, averages of minimal standard deviation, and allow generalization of the findings as representative of the whole population.

Retrieval of data
The missing data prevented the estimation of the *positive predictive value* (PPV), *negative predictive value* (NPV), sensitivity and specificity of the prostate biopsy procedure. This limited the comparison of the results versus other studies.

References

1. Rogers OC, Anthony L, Rosen DM, et al. PSA-selective activation of cytotoxic human serine proteases within the tumor microenvironment as a therapeutic strategy to target prostate cancer. Oncotarget. 2018; 9:22436-22450.

2. Prcic A, Begic E, Hiros M. Usefulness of total PSA value in prostate diseases diagnosis. Acta Inform Med. 2016; 24:156-61.

3. Mittal RD. Reference range of serum prostate-specific antigen levels in Indian men. Indian J Med Res. 2014; 140:480-1. PMID: 25488440; PMCID: PMC4277132.

4. Shamseddine A, et al. Cancer trends in Lebanon: a review of incidence rates for the period of 2003-2008 and projections until 2018. Popul Health Metr. 2014; 12:4.

5. https://gco.iarc.fr/today/data/factsheets/populations/422-lebanon-fact-sheets.pdf

6. Instituto Brasileiro de Geografia e Estatística; Ministério do Planejamento, Orçamento e Gestão. Estimativas populacionais 1980-2010: Brasil, regiões geográficas e unidades da federação. Rio de Janeiro (Brasil): IBGE; 2010. [citado em 15 de junho de 2010]. Disponível em: http://www.ibge.gov.br

7. Nickel JC. Inflammation and benign prostatic hyperplasia. Urol Clin North Am. 2008; 35:109-15

8. Çamur E, Coskun A, Kavukoglu O, et al. Prostate volume effect on Gleason score upgrading in active surveillance appropriate patients. Arch Ital Urol Androl. 2019; 91:93.

9. Babaian RJ, Fritsche HA, Evans RB. Prostate-specific antigen and prostate gland volume: correlation and clinical application. J Clin Lab Anal. 1990; 4:135-7.

10. Bell N, et al. Canadian Task Force on Preventive Health Care.

Recommendations on screening for prostate cancer with the prostate-specific antigen test. CMAJ. 2014; 186:1225-34.

11. Park HK, Hong SK, Byun SS, Lee SE. Comparison of the rate of detecting prostate cancer and the pathologic characteristics of the patients with a serum PSA level in the range of 3.0 to 4.0 ng/mL and the patients with a serum PSA level in the range 4.1 to 10.0 ng/mL. Korean J Urol. 2006; 47:358-61.

12. Kobayashi T, Nishizawa K, Ogura K, et al. Detection of prostate cancer in men with prostate-specific antigen levels of 2.0 to 4.0 ng/mL equivalent to that in men with 4.1 to 10.0 ng/mL in a Japanese population. Urology. 2004; 63:727-31.

13. Gomes R, Rebello LEFS, Araújo FC, et al. A prevenção do câncer de próstata: uma revisão da literatura. Ciencia & Saude Coletiva. 2008; 13:235-46.

14. Benson MC, et al. Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. J Urol. 1992; 147:815-6.

15. Jue JS, et al. Re-examining prostate-specific antigen (PSA) density: defining the optimal PSA range and patients for using PSA density to predict prostate cancer using extended template biopsy. Urology. 2017; 105:123-128.

16. Stephan C, et al. The ratio of prostate-specific antigen (PSA) to prostate volume (PSA density) as a parameter to improve the detection of prostate carcinoma in PSA values in the range of < 4 ng/mL. Cancer. 2005; 104:993-1003.

17. Van Iersel MP, Witjes WP, de la Rosette JJ, Oosterhof GO. Prostate-specific antigen density: correlation with histological diagnosis of prostate cancer, benign prostatic hyperplasia and prostatitis. Br J Urol. 1995; 76:47-53.

18. Ediz C, Akan S, Temel MC, Yilmaz O. The importance of PSA-Density in active surveillance for prostate cancer. Arch Ital Urol Androl. 2020; 92:136.

19. Holmäng S, Lindstedt G, Mårin P, Hedelin H. Serum concentration of prostate-specific antigen in relation to prostate volume in 50 healthy middle-aged men. Scand J Urol Nephrol. 1993; 27:15-20.

20. Catalona WJ, et al. Comparison of percent free PSA, PSA density, and age-specific PSA cutoffs for prostate cancer detection and staging. Urology. 2000; 56:255-60.

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