

Appraisal of the Diagnostic Performance of proPSA and LDH in Comparison with PSA for Detection of Prostate Cancer with Special Reference to Smoking Status

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Abstract

Background: Prostate cancer (PCa) is one of the most common malignant diseases among middle-aged and elderly men, therefore, PCa screening is critical for early detection and control of the disease, as well as a better life for the patient. **Objective:** Designed to compare the diagnostic performance of proenzyme PSA (proPSA) and lactate dehydrogenase (LDH) to prostate-specific antigen (PSA) for detecting prostate cancer. **Methods:** Serum samples from 101 men, with an age range of 50-87 years, were tested. PSA, proPSA, and LDH were the serum biomarkers measured. Twenty-four patients were diagnosed with PCa according to prostate biopsy, 42 patients with benign prostate diseases, and 35 healthy men, which was defined as a control group. **Results:** The control group displayed a median PSA serum level of 1.79 ng/mL, which increased to 8.05 ng/mL in patients with benign prostate diseases and 21.58 ng/mL in men with PCa. The corresponding median serum levels of proPSA in these subjects were 0.154, 0.228, and 2.65 ng/mL, respectively. Whereas the median levels of serum LDH were 282.3, 282.3, and 506.8 U/L, respectively. The current study also revealed that some men have PCa, yet their PSA levels are normal for their age, while other individuals have elevated PSA levels but do not have PCa. Cigarette smoking was positively associated with elevated serum levels of these biomarkers in the patient population. **Conclusions:** This study concluded that proPSA and LDH have shown potential for improving PCa detection, particularly in men with elevated PSA levels.

Keywords: Prostate cancer, prostate-specific antigen, proPSA, lactate dehydrogenase

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Introduction

PCa is the second most prevalent cancer in men and the fifth most common cause of cancer-related deaths globally [1]. This kind of cancer is commonly discovered through routine screening rather than symptoms because it usually develops slowly and may not show any signs in its early stages [2]. Many cases of PCa are identified due to high serum levels of prostate-specific antigen (PSA > 4 ng/mL), a key protein found in semen that is an androgen-regulated serine protease generated by both prostatic epithelial cells and PCa [3]. However,

because men without cancer have been reported to have elevated PSA levels, an ultrasound-guided prostate biopsy sample is currently the gold standard tool for confirming the existence of malignancy [4]. Moreover, several biomarkers were investigated to overcome the PSA's limitations; one of these markers is proPSA [5], a precursor form of prostate-specific antigen that could improve prostate cancer detection and reduce the number of negative prostate biopsies when compared with PSA [6- 8]. There are various forms of proPSA, but the most

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widely studied form is -2 proPSA (p2PSA). This isoform of proPSA has been demonstrated to correlate more closely with malignant prostate tissue than PSA and is therefore useful in distinguishing prostate cancer from other benign prostate conditions [9, 10].

On the other hand, an essential enzyme in the anaerobic metabolic process is LDH. The enzyme's job is to catalyze the reversible conversion of lactate to pyruvate while reducing NAD^+ to NADH and vice versa [11]. Elevated LDH levels in cancer patients correlated with adverse clinical outcomes and resistance to therapy [12- 14]. Furthermore, smoking is a well-known risk factor for many types of cancer; however, evidence linking smoking to PCa is still conflicting [15, 16]. In this study, the diagnostic value of proPSA and LDH in comparison to conventional PSA employed for the detection of people suspected of having PCa was assessed. As well, the correlation between cigarette smoking and PSA, proPSA, and LDH was evaluated.

Materials and Methods

Patients

This study is an observational, analytical, case-control study that included 66 men in the 50–87 age range who attended Erbil Teaching Hospital, Nanakali Hospital, and some private clinics in Erbil City/Iraq, between January 2025 and September 2025, for urological issues. They have been scheduled by the referring urologist for a transrectal ultrasound-guided biopsy of the prostate due to an increased PSA level ($\text{PSA} > 4 \text{ ng/mL}$) and an abnormal digital rectal examination (DRE) of the prostate. In addition, 35 apparently healthy men were included in the study as a control group.

Ethical consideration and patient consent agreement

The study methodology has been approved by the Ethics Committee of the Hawler Medical University as per the reference no. (HMU-Ph-Ec 17092025-413), and all participants signed informed permission. Information about cigarette smoking status was collected by a questionnaire from patients who were categorized into two groups: smokers (ever smokers) and non-smokers (never smokers). Patients who reported smoking cessation within the past few years were excluded.

Sampling and Diagnostic Serum Biomarkers

Venipuncture was used to obtain blood samples, which were then centrifuged at 4,000 rpm for 5 minutes. Sera were collected and stored at -20°C for subsequent steps. The following biomarkers were measured: PSA (ng/mL) by I-CHROMA (Boditech Med Inc., USA) and pro-PSA (ng/mL) using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Biotechnology KOMABIOTECH, USA), while the LDH analyses (U/L) were performed by the Cobas 6000 analyzer (Roche Diagnostics, USA) with the LDH kit (BioSystems, Spain) depending on measuring the NADH rate at 340 nm. All tests were done in accordance with the manufacturer's instructions. The results of these tests were compared

with histopathological examination results following a transrectal ultrasound-guided prostate biopsy, which differentiates PCa (malignant) from other prostatic conditions (benign).

Statistical analysis

The data were processed with the statistical program GraphPad Prism Version 8 and expressed with the range and median, where * $p < 0.05$; ** $p < 0.01$; or **** $p < 0.0001$ was considered statistically significant. The comparison among groups was done using the Kruskal-Wallis test followed by Dunn's multiple comparison test, while the Mann-Whitney U test was used to compare two independent groups. Correlations between variables were assessed using Spearman's correlation. Linear regression analysis was used to estimate the relationship between each of the studied biomarkers and smoking status among patients diagnosed with and without malignancy.

Results

General details regarding the study population

The main clinical profiles of the study population, including the biomarker results, are summarized in Table 1. In total, 101 men were enrolled in this study; there were 66 in the patient group and 35 in the control group. No significant differences ($p < 0.05$) were found between the patient groups and controls according to age. The patients underwent transrectal prostate biopsy and were classified into two groups: 24 patients were diagnosed with prostate cancer (malignant), and 42 patients without malignancy (benign). Regarding the smoking status of the patients, 28 were smokers (ever smokers), while 38 were non-smokers (never smokers). They were further categorized as having PCa or not (Figure 1).

Diagnostic performance of PSA, proPSA, and LDH in all groups

Overall, serum PSA, proPSA, and LDH median levels were remarkably higher ($p < 0.05$) in patients with PCa compared to those without this malignancy (21.58, 2.650 ng/mL, and 506.8 U/L, respectively, vs 8.05, 0.228 ng/mL, and 282.3 U/L) (Table 1, Figures 2, 3, and 4). Moreover, similar findings have been observed

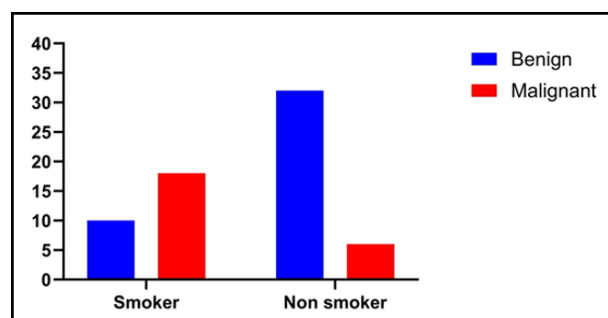


Figure 1. Distribution of Patient Group Based on Smoking Status. Smokers comprised 28 patients, 18 diagnosed with PCa (malignant) and 10 without malignancy (benign). Non-smokers accounted for 38 patients, 6 with PCa (malignant) and 32 without malignancy (benign).

Table 1. Main Clinical Profiles of the Study population

Parameter	Patients (n=66)		Control (n=35) Median (range)	p-value
	Malignant (n= 24) Median (range)	Benign (n=42) Median (range)		
Age	66.00 (55.00-80.00) ^a	61.50 (50.00-87.00) ^a	60.50 (50.00-77.00) ^a	0.247
PSA (ng/mL)	21.58 (4.260-96.00) ^a	8.05 (3.920-220) ^b	1.790 (0.120-3.790) ^c	< 0.0001
proPSA (ng/mL)	2.650 (1.290-16.88) ^a	0.228 (0.096-0.852) ^b	0.154 (0.100-0.338) ^c	< 0.0001
LDH (U/L)	506.8 (389.8-720.5) ^a	282.3 (193.6-420.3) ^b	303.5 (207-414) ^b	< 0.0001

Different letters indicate that the median difference is statistically significant at the 0.05 level.

in groups of patients (malignant and benign) compared to those of controls; however, according to this analysis, the difference in the serum median LDH levels between the benign patient group and the control group was not statistically significant (282.3 U/L vs. 303.5 U/L, respectively) (Table 1, Figures 2, 3, and 4). On the other hand, upon closer examination of the results, high levels of PSA in patients without malignancy (benign) were recorded (Table 1 and Figure 2). In contrast, the results in (Table 1 and Figure 3) demonstrate that proPSA performed better than PSA. In particular, proPSA was significantly more accurate in detecting benign cases compared to PSA.

Correlations among various biomarkers in patients with and without malignancy

(Figures 5, 6, and 7) display scatter diagrams with varied Spearman's correlations between the studied parameters in patients with and without malignancy. The findings indicate no statistically significant correlation ($p \geq 0.05$) between PSA and proPSA in patients diagnosed with PCa (Figure. 5A) and those without malignancy (Figure. 5B). Similarly, PSA and LDH (Figures. 6A and B) show no significant correlation ($p = 0.7098$, $r = 0.08013$ and $p = 0.5381$, $r = -0.1149$), respectively. Additionally, there were non-significant correlations ($p \geq 0.05$) between proPSA and LDH ($p = 0.0788$, $r = 0.3657$ and $p = 0.3475$, $r = 0.1486$) in malignant and benign cases, as illustrated in (Figures 7A and 7B), respectively.

The effect of cigarette smoking on serum PSA, proPSA,

and LDH levels in patient groups

Smokers had significantly higher median serum PSA, proPSA, and LDH levels ($p < 0.05$) compared to non-smokers (Table 2 and Figure 8). Additionally, a linear regression analysis was conducted to evaluate the relationship between serum PSA, proPSA, and LDH levels and smoking status among patient groups. Smoking status was coded as a binary variable (0 = smoker, 1 = non-smoker), and the serum level of each studied biomarker served as the dependent variable. The regression yielded slope coefficients for PSA, proPSA, and LDH levels of -21.90, -3.111, and -127.5, respectively, with smoking status (Figure 9). This indicates that non-smokers have PSA, proPSA, and LDH levels lower than smokers, holding PCa and other potential confounders constant. In other words, smoking was positively associated with elevated PSA, proPSA, and LDH levels in this patient population.

Discussion

Although PSA screening has helped earlier detection of PCa, false-positive results are common and occur when the PSA level is high but there is no malignancy. Therefore, the current study aimed to evaluate the effectiveness of the proPSA and LDH in comparison with PSA for detecting PCa in a population consisting of patients diagnosed by prostate biopsy with PCa (malignant), patients without malignancy (benign), as well as healthy people. The result revealed that proPSA and LDH could distinctly distinguish PCa patients from other groups. In particular, the median

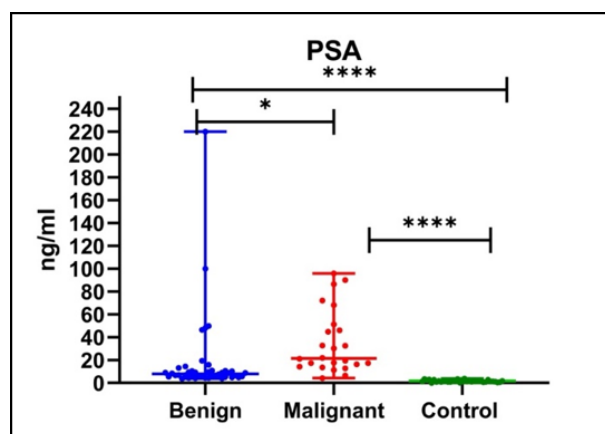


Figure 2. A comparison of Serum PSA Median Levels in the Various Study Groups Using Kruskal-Wallis Test. Controls= 35 healthy men; patients diagnosed with PCa (malignant) = 24; patients without malignancy (benign) = 42. $p < 0.05$ significant *, and $p < 0.0001$ significant ****

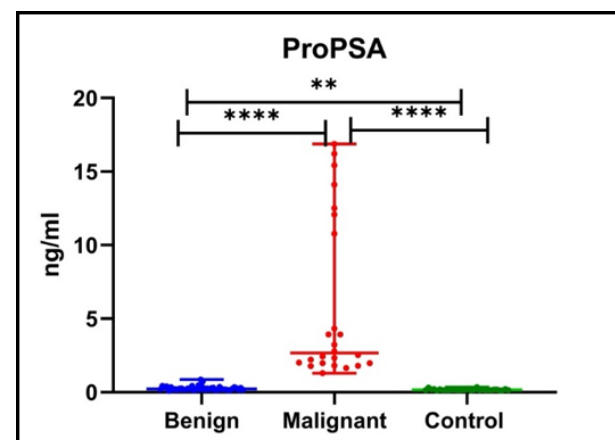


Figure 3. A Comparison of Serum ProPSA Median Levels in the Various Study Groups Using Kruskal-Wallis Test. Controls= 35 healthy men; patients diagnosed with PCa (malignant) = 24; patients without malignancy (benign) = 42. $p < 0.01$ significant **, and $p < 0.0001$ significant ****

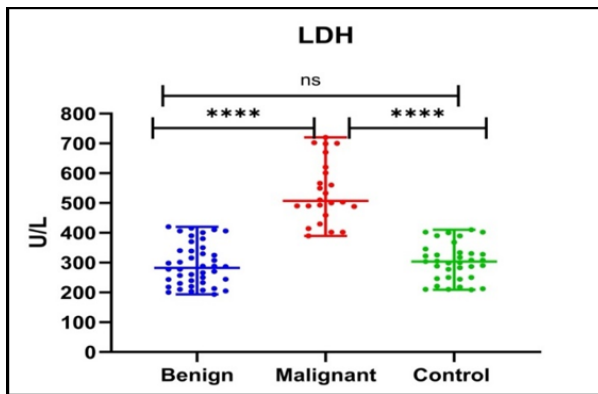


Figure 4. A Comparison of Serum LDH Median Levels in the Various Study Groups Using Kruskal-Wallis Test. Controls= 35 healthy men; patients diagnosed with PCa (malignant) = 24; patients without malignancy (benign) = 42. $p \geq 0.05$ not significant (ns), and $p < 0.0001$ significant ****

serum levels of proPSA and LDH were markedly higher in the PCa patients compared to both the control group and patients with benign prostate diseases. In line with the findings of the present study, several studies showed that proPSA represents a more cancer-specific marker that better differentiates PCa from other benign diseases [17- 20]. Similarly, elevated LDH has been identified as a predictive biomarker in PCa, contributing significantly to tumor cell proliferation and related to an increased risk of mortality in patients with metastatic PCa [14, 21]. Moreover, Santotoribio and Jimenez-Romero suggested that elevated LDH serum levels in PCa patients could be attributed to tumor cells having high glycolysis activity, which increases glucose intake and lactate release, thus requiring increased LDH enzymatic activity regardless of oxygen availability [21].

On the other hand, serum PSA level, commonly used as a screening tool for prostate cancer detection, was significantly higher in both patient groups (benign and malignant) compared with the healthy control, but it was an unreliable sign to specifically differentiate benign from malignant prostate disease, as some men have elevated PSA levels but don't have PCa. Several studies reported that PSA is specific to the prostate but not PCa; therefore, the high serum PSA levels could also be due to several factors that do not indicate cancer, such as age, ejaculation within the last 48 hours, vigorous exercise, prostatitis, or a urinary tract infection (UTI) [22- 24]. Furthermore, no statistical correlations were

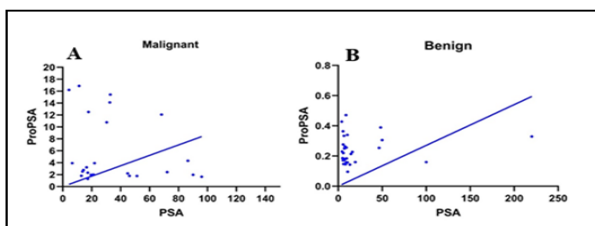


Figure 5. Scattergrams with Spearman's Correlation between Serum PSA and ProPSA Levels (A): in Patients Diagnosed with PCa (Malignant) (n = 24); (B): in Patients without Malignancy (Benign) (n = 42)

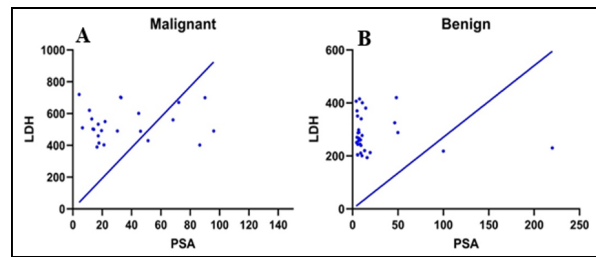


Figure 6. Scattergrams with Spearman's Correlation between Serum PSA and LDH Levels (A): in Patients Diagnosed with PCa (Malignant) (n = 24); (B): in Patients without Malignancy (Benign) (n = 42)

found between serum levels of various biomarkers ($p > 0.05$); therefore, they can be considered as independent biomarkers. On the other hand, linear regression models were employed to evaluate whether smoking status was a significant predictor of biomarker levels. The results showed negative slope coefficients for smoking status, indicating that non-smokers have PSA, proPSA, and LDH levels lower than smokers. This clearly shows that smoking is associated with higher PSA, proPSA, and LDH levels, regardless of whether the patient has benign or malignant prostate disease. Some earlier studies observed higher PSA and related biomarkers such as proPSA levels among smokers, potentially due to tobacco-induced prostate inflammation, hormonal changes, or increased cell turnover [25]. Other investigations, notably large population surveys, found lower PSA levels in current and former smokers compared to never smokers [15, 26, 27] and suggested that smokers' poor adherence to PCa screening could explain this negative relationship [28, 29].

In Conclusion, this study concluded that proPSA and LDH have shown potential for improving PCa detection, particularly in men with elevated PSA levels, in whom

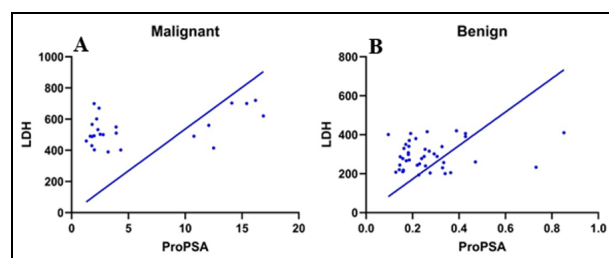


Figure 7. Scattergrams with Spearman's Correlation between Serum ProPSA and LDH Levels (A): in Patients Diagnosed with PCa (malignant) (n = 24); (B): in Patients without Malignancy (benign) (n = 42)

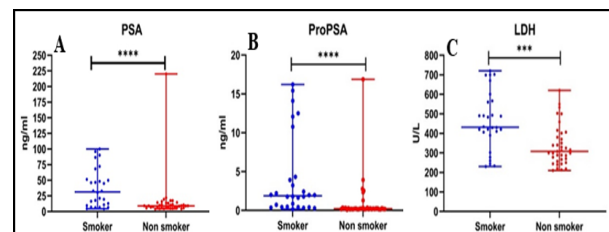


Figure 8. A Comparison between Smoking Status and Serum Median Level of Each Biomarker (A): PSA; (B): ProPSA; (C): LDH in Patient Groups Using ANOVA Test. Smokers (n = 28); Non- smokers (n = 38). $p < 0.001$ Significant **, and $p < 0.0001$ Significant ****

Table 2. The Effect of Cigarette Smoking on Serum PSA, ProPSA and LDH Levels in Patient Groups

Parameter	Patients (n=66)		p-value
	Smokers (n= 28) Median (range)	Non-smokers (n=38) Median (range)	
PSA (ng/mL)	31.45 (4.26-100.00)	8.90 (4.10-220)	< 0.0001
proPSA (ng/mL)	1.895 (0.185-16.20)	0.228 (0.096-16.88)	< 0.0001
LDH (U/L)	432.0 (230.2-720.5)	307.8 (210.6-620.3)	0.0004

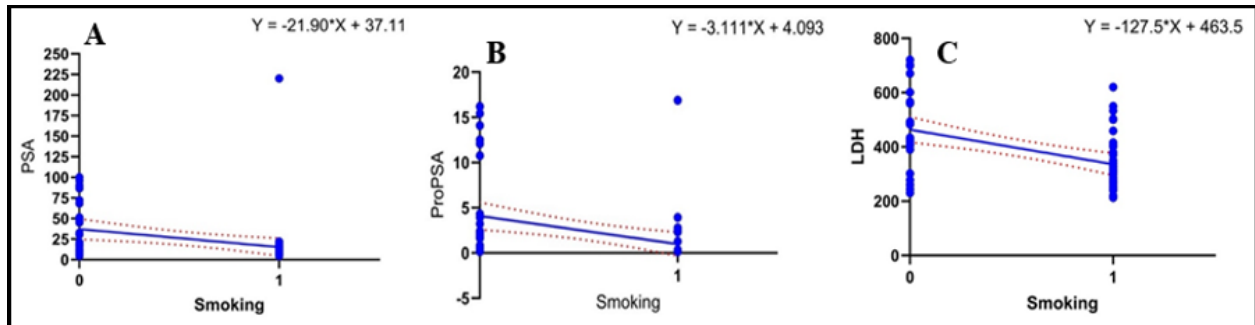


Figure 9. Regression Analysis of Smoking Status in Patient Groups and Revealed Biomarker. (A): The Relationship with Serum PSA Level; (B): The Relationship with Serum proPSA Level; (C): The Relationship with Serum LDH Level. Smoking status was coded as a binary variable (0 = smoker, 1 = non-smoker), and the serum level of each studied biomarker served as the dependent variable

they provide a potentially useful tool for identifying PCa in the clinical context by increasing specificity and decreasing needless biopsies. Furthermore, it is highly recommended that screening programs be performed yearly for males above the age of 50 years by digital rectal examination with transrectal ultrasound and measuring serum PSA and proPSA. In cases suspected of having PCa, transrectal guided biopsy should be done. The current study also suggested that smoking could contribute to higher levels of biomarkers, which are often linked to PCa. Therefore, addressing smoking history could be crucial when evaluating PSA, proPSA, and LDH levels in both benign and malignant prostate conditions.

Limitations of the study

This study was limited by the relatively small sample size, challenges in patient follow-up, and uneven distribution of cancer stages among participants, which may have impacted the estimated diagnostic accuracy of the biomarkers. Despite these limitations, the study offers significant evidence supporting the role of proPSA and LDH in the diagnosis of prostate cancer and emphasizes the necessity of more extensive studies.

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Nil.

Disclosure statement

The authors report no conflict of interest.

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