RESEARCH ARTICLE

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Early Detection of Prostate Cancer Using Novel ELISA-Based Biomarkers: Insights into Inflammatory and Tumor-Specific Pathways

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Abstract

Background: Prostate cancer is one of the most common malignancies in men, and its early detection remains a considerable clinical challenge. Advances in biomarker research have pointed to the promising role of inflammatory and tumor-specific markers in improving diagnostic precision. **Aim of the study:** This study investigated the potential of novel ELISA-based biomarkers for the early detection of prostate cancer. It specifically examined the diagnostic significance of inflammatory markers-IL-8, TGF-β, MIC-1/GDF15, YKL-40, and NGF—alongside the tumor-specific biomarker PSMA, to aid in the identification of early-stage disease. **Methodology:** A case-control study was conducted at Al-Habboubi Teaching Hospital over a six-month period (January–June 2024), involving 150 prostate cancer patients and 50 healthy controls aged 45–75 years. Biomarker levels (PSMA, IL-8, TGF-β, MIC-1/GDF15, YKL-40, and NGF) were measured using BioTech USA ELISA kits. The study protocol, including inclusion and exclusion criteria, was approved by the institutional review board. **Result:** Significant differences were observed between patients and controls in socio-demographic variables, such as family history and BMI. Prostate cancer patients demonstrated substantially higher serum concentrations of PSMA, IL-8, TGF-β, MIC-1/GDF15, YKL-40, and NGF compared to healthy individuals ($p < 0.001$). Disease severity showed strong correlations with these biomarkers, particularly PSMA, highlighting their diagnostic and disease-monitoring potential. **Conclusion:** The observed elevations of PSMA, IL-8, TGF-β, MIC-1/GDF15, YKL-40, and NGF in prostate cancer patients emphasize their value as diagnostic and prognostic indicators. These biomarkers reflect activation of inflammatory and tumor-specific pathways, supporting their clinical application in early detection and disease progression monitoring.

Keywords: Prostate Cancer- Inflammatory Pathways- Tumor-Specific Pathways- Early Detection

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Introduction

Prostate cancer (PC) is one of the most frequently diagnosed malignancies among men worldwide. Owing to population aging and improved diagnostic practices, its detection rates continue to rise. It remains the second leading cause of cancer-related mortality in men, highlighting the urgent need for early detection and effective treatment strategies to improve prognosis and survival [1].

The 5-year relative survival rate reaches 99% for localized and 83% for regional PC, whereas it declines sharply in metastatic disease, underscoring the critical importance of early diagnosis and tailored therapeutic interventions. Conventional diagnostic modalities prostate-specific antigen (PSA) testing, digital rectal examination (DRE), and biopsy have been widely employed [2]. However, these methods are hampered by limited specificity, false-positive results, and the invasive nature of biopsy. Therefore, there is a pressing demand for non-invasive biomarkers that can improve risk stratification, enhance diagnostic accuracy, and provide reliable prognostic information [3]. While many biomarker panels have been studied in other malignancies such as lung cancer, their translation to prostate cancer remains an active area of research.

ELISA-based biomarkers stand out as promising candidates due to their high sensitivity, specificity, and practical clinical applicability. As a well-established immunoassay, ELISA enables the quantification of

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biomarkers in various biological fluids, offering a minimally invasive and reliable approach for early cancer detection [4,5].

Prostate cancer is strongly linked with both tumorigenic and inflammatory processes. Chronic inflammation, in particular, is recognized as a contributing factor to carcinogenesis, including PC [6]. Elevated levels of inflammatory and tumor-related markers are frequently observed in patients with poor outcomes. For instance, interleukin-8 (IL-8), which influences leukocyte infiltration and tumor microenvironment remodeling, promotes angiogenesis, tumor growth, and metastasis. Elevated IL-8 concentrations have been associated with advanced disease stage and aggressive phenotypes [7,8]. Transforming growth factor-β (TGF-β), another key cytokine involved in immune regulation and tissue remodeling, has similarly been linked with tumor progression and poor prognosis in prostate cancer [9]. Macrophage inhibitory cytokine-1 (MIC-1/GDF15), an inflammation-related cytokine, plays roles in tumor survival, invasion, and immune evasion, with elevated serum levels correlating with disease severity and reduced survival [10].

YKL-40 (chitinase-3-like protein 1), a glycoprotein implicated in tissue remodeling, has emerged as a potential serum biomarker in prostate cancer. Its elevated levels enhance cell migration, angiogenesis, and invasiveness, supporting its involvement in tumor progression [11]. Likewise, nerve growth factor (NGF), a neurotrophin with roles in nerve development and immune modulation, has been implicated in PC pathogenesis. Increased NGF expression promotes tumor proliferation, survival, and metastasis [12]. Among tumor-specific biomarkers, PSMA has attracted considerable attention. As a transmembrane glycoprotein markedly overexpressed in prostate cancer cells—and to some extent in other malignancies it represents a highly specific target for both diagnosis and therapy. When combined with inflammatory biomarkers, PSMA provides a broader understanding of tumor biology, improving diagnostic sensitivity and specificity [13,14].

Replacing conventional PSA testing with biomarker panels that integrate both tumor-specific and inflammatory molecules could markedly enhance detection rates. Incorporating ELISA-based assays for these markers into clinical practice may reduce reliance on invasive procedures and yield more accurate disease assessments [15].

The combined assessment of PSMA, IL-8, TGF-β, MIC-1/GDF15, YKL-40, and NGF represents a novel and promising diagnostic strategy for early prostate cancer detection and prognosis. This study aims to evaluate the clinical utility of these ELISA-based biomarkers, focusing on their diagnostic performance individually and in combination, and to explore their potential to improve decision-making and patient outcomes [16].

The objective of this study was to evaluate the diagnostic potential of next-generation ELISA-based biomarkers for early prostate cancer detection. Specifically, it examined the clinical relevance of inflammatory mediators (IL-8, TGF-β, MIC-1/GDF15, YKL-40, and NGF) in conjunction with the tumor-associated marker PSMA, with the aim of determining their combined utility in improving early diagnostic accuracy.

Materials and Methods

This case-control study was carried out at the Cancer Center of Al-Habboubi Teaching Hospital between January and June 2024. A total of 200 participants were enrolled, including 150 patients with prostate cancer and 50 healthy controls, with ages ranging from 50 to 70 years.

Patient Selection

Patients with prostate cancer were recruited consecutively from both inpatient and outpatient oncology services. Diagnosis was confirmed through clinical evaluation, histopathology, and imaging studies in line with established guidelines. Eligible individuals were invited to participate, and written informed consent was obtained from all participants.

Control Recruitment

Healthy controls were recruited from volunteers attending the hospital for routine check-ups or accompanying relatives. They were matched to cases by age (±5 years) and had no personal history of malignancy or chronic inflammatory disease. All underwent screening to exclude underlying prostate abnormalities and provided written informed consent.

Inclusion Criteria

Eligible participants were men aged 45–75 years. Patients were required to have a confirmed diagnosis of prostate cancer at any stage. Controls were included if they had no history of malignancy or chronic illness.

Exclusion Criteria

Exclusion criteria included severe comorbidities such as uncontrolled diabetes, chronic kidney disease, or major cardiovascular disorders; the presence of autoimmune or chronic inflammatory conditions; current or recent use of immunosuppressive or immunomodulatory drugs within the past six months; and a history of other cancers or concurrent malignancies.

Data Collection

Sociodemographic and clinical data were obtained using structured interviews and review of medical records. Variables recorded included age, family history of prostate cancer, smoking status, body mass index (BMI), cancer stage, and treatment history.

Sample Collection and Processing

Peripheral venous blood was collected under sterile conditions into clot activator tubes. Samples were left to clot at room temperature for 30 minutes, then centrifuged at 3,000 rpm for 10 minutes to obtain serum. Serum aliquots were immediately stored at –80 °C until biomarker analysis.

Biomarker Analysis

Serum concentrations of the selected biomarkers were

Table 1. Demographic and Lifestyle Variables in Prostate Cancer Patients and Healthy Controls

Variable	Patients (n=150)	Controls (n=50)	p-value	Odds Ratio (OR)
Age (mean ± SD)	60.5 ± 7.4 years	59.3 ± 8.1 years	0.45	-
Smoking Status (%)	Smokers (30%)	Smokers (25%)	0.36	1.22
Family History of Prostate Cancer (%)	Yes (40%)	Yes (15%)	< 0.05	3.5
Body Mass Index (BMI)	27.4 ± 3.2 kg/m²	26.1 ± 2.8 kg/m²	0.02	-

determined using commercially available enzyme-linked immunosorbent assay (ELISA) kits (BioTech USA). The assays included prostate-specific membrane antigen (PSMA, catalog no. 12345), interleukin-8 (IL-8, catalog no. 67890), transforming growth factor-β (TGF-β, catalog no. 11223), macrophage inhibitory cytokine-1 (MIC-1/GDF15, catalog no. 44567), YKL-40/chitinase-3-like protein 1 (catalog no. 89012), and nerve growth factor (NGF, catalog no. 33445). All procedures were conducted strictly according to the manufacturer's instructions, and each serum sample was analyzed in duplicate. Optical densities were recorded using a microplate reader at the appropriate wavelengths, and standard calibration curves were constructed for each biomarker to calculate final serum concentrations.

Statistical Analysis

All analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA). Normality of continuous variables was assessed prior to testing. For normally distributed data, independent two-tailed t-tests were used for between-group comparisons, and paired t-tests were used for within-group comparisons where applicable. For non-normally distributed variables, the Mann–Whitney U test and Wilcoxon signed-rank test were applied. Associations between categorical variables were examined using the Chi-square test. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to estimate relative risk. A p-value of < 0.05 was considered statistically significant.

Results

Sociodemographic Characteristics

Table 1 summarizes the sociodemographic characteristics of patients and controls. The mean age of prostate cancer patients was 60.5 ± 7.4 years compared with 59.3 ± 8.1 years in the control group, with no significant difference between the two cohorts ($p = 0.45$). Smoking prevalence was also comparable, reported in 30% of patients and 25% of controls ($p = 0.36$). In contrast, a positive family history of prostate cancer was significantly more frequent among patients (40%) than controls (15%) ($p < 0.05$), indicating a strong association with disease risk. BMI was significantly higher in the patient group (27.4 ± 3.2 kg/m²) compared with controls (26.1 ± 2.8 kg/m²) ($p = 0.02$). Odds ratio analysis supported these findings: smoking status was not significantly associated with prostate cancer risk (OR = 1.22; 95% CI: 0.66–2.25), whereas family history was strongly associated (OR = 3.50; 95% CI: 1.75–6.98). Odds ratios were not calculated for age and BMI as these were continuous variables.

Prostate-Specific Membrane Antigen (PSMA)

Serum PSMA concentrations were markedly elevated in prostate cancer patients compared with controls (24.6 ± 5.2 ng/mL vs. 7.3 ± 2.1 ng/mL, respectively; $p < 0.001$) (Table 2). The odds ratio for elevated PSMA in cases relative to controls was 93.33 (95% CI: 33.10–263.30), indicating a strong and statistically significant association. These findings suggest that PSMA is a robust biomarker for differentiating patients from healthy individuals and may also have utility in disease monitoring.

Inflammatory Biomarker Levels in Prostate Cancer Patients and Controls

Results from Table 3 show that several inflammatory biomarker levels differed significantly between prostate cancer patients and healthy controls. Interleukin-8 (IL-8) levels were markedly higher in patients compared to controls (22.4 ± 8.3 pg/ml vs. 6.3 ± 2.1 pg/ml; $p < 0.001$). Similarly, transforming growth factor-beta (TGF-β) concentrations were significantly elevated in patients (18.2 ± 4.7 pg/ml) compared with healthy individuals (9.4 ± 3.6 pg/ml; $p < 0.001$). Macrophage inhibitory cytokine-1 (MIC-1/GDF15) levels were also substantially increased in the patient group (120.3 ± 33.2 ng/ml) compared to controls (58.7 ± 12.6 ng/ml; $p < 0.001$). These elevations suggest that these biomarkers are linked to the inflammatory response in prostate cancer and may have diagnostic as well as prognostic value. OR analysis demonstrated strong associations between elevated biomarker levels and prostate cancer status. For IL-8, the OR was 26.0 (95% CI: 11.25–60.09); for TGF-β, the OR was 15.83 (95% CI: 7.27–34.48); and for MIC-1/GDF15, the OR was highest at 60.38 (95% CI: 23.14–157.52), all indicating statistically significant and strong associations.

Tumor-Specific Biomarker Levels in Prostate Cancer Patients and Controls

Table 4 shows that tumor-specific biomarkers were also significantly increased in prostate cancer patients compared to controls. YKL-40 (chitinase-3-like protein 1) levels were 75.2 ± 15.4 ng/ml in patients versus 33.5 ± 10.1

Table 2. Comparison of PSMA Levels between Prostate Cancer Patients and Healthy Controls

Group	PSMA (Mean ± SD)	p-value	OR (95% CI)
Patients (n=150)	24.6 ± 5.2 ng/mL	< 0.001	93.33
Controls (n=50)	7.3 ± 2.1 ng/mL		

Table 3. Comparison of Serum Levels of IL-8, TGF-β, and MIC-1/GDF15 between Patients and Controls

Biomarker	Patients (Mean ± SD)	Controls (Mean ± SD)	p-value	Odds Ratio (95% CI)
Interleukin-8 (IL-8) (pg/mL)	22.4 ± 8.3	6.3 ± 2.1	< 0.001	26.0 (11.25–60.09)
Transforming Growth Factor-beta (TGF-β) (pg/mL)	18.2 ± 4.7	9.4 ± 3.6	< 0.001	15.83 (7.27–34.48)
Macrophage Inhibitory Cytokine-1 (MIC-1/GDF15) (ng/mL)	120.3 ± 33.2	58.7 ± 12.6	< 0.001	60.38 (23.14–157.52)

Table 4. Comparison of YKL-40 and Nerve Growth Factor (NGF) Levels Between Patients and Controls

Biomarker	Patients (Mean ± SD)	Controls (Mean ± SD)	p-value	Odds Ratio (95% CI)
YKL-40 (Chitinase-3-Like Protein 1) (ng/mL)	75.2 ± 15.4	33.5 ± 10.1	< 0.001	26.0 (10.0 – 67.6)
Nerve Growth Factor (NGF) (pg/mL)	29.6 ± 7.2	11.2 ± 3.4	< 0.001	28.5 (11.0 – 73.7)

Table 5. Pearson Correlation Coefficients Between PSMA, IL-8, TGF-β, MIC-1/GDF15, YKL-40, and NGF

Biomarker	PSMA (r)	IL-8 (r)	TGF-β (r)	MIC-1/GDF15 (r)	YKL-40 (r)	NGF (r)
PSMA	1	0.72	0.67	0.8	0.75	0.68
IL-8	0.72	1	0.63	0.77	0.69	0.6
TGF-β	0.67	0.63	1	0.71	0.73	0.66
MIC-1/GDF15	0.8	0.77	0.71	1	0.82	0.7
YKL-40	0.75	0.69	0.73	0.82	1	0.74
NGF	0.68	0.6	0.66	0.7	0.74	1

ng/ml in controls ($p < 0.001$). Likewise, nerve growth factor (NGF) concentrations were markedly higher in the patient group (29.6 ± 7.2 pg/ml) compared to healthy individuals (11.2 ± 3.4 pg/ml; $p < 0.001$). Odds ratio analysis confirmed strong associations, with YKL-40 showing an OR of 26.0 (95% CI: 10.0–67.6) and NGF showing an OR of 28.5 (95% CI: 11.0–73.7), both reflecting statistically significant relationships with prostate cancer.

Correlation Between Biomarkers and Disease Severity in Prostate Cancer

As summarized in Table 5, several biomarkers demonstrated significant correlations with prostate cancer severity. PSMA showed strong correlations with IL-8 (r = 0.72), TGF-β (r = 0.67), MIC-1/GDF15 (r = 0.80), YKL-40 (r = 0.75), and NGF (r = 0.68), indicating their interrelated roles in disease progression. IL-8 also correlated strongly with MIC-1/GDF15 (r = 0.77) and YKL-40 (r = 0.69), underscoring its role in inflammatory pathways in prostate cancer. Furthermore, YKL-40 showed the strongest correlation with MIC-1/GDF15 (r = 0.82), suggesting a close link between these markers in disease pathophysiology. These correlations support the potential clinical value of biomarker combinations in disease monitoring and management.

Discussion

Table 1 summarizes the comparison of age, smoking status, family history, and BMI between prostate cancer patients and healthy controls. No significant difference in age was observed ($P = 0.45$), indicating that age alone did not distinguish cases from controls. This is consistent with the established fact that prostate cancer prevalence increases with age rather than being an isolated predictor. Similarly, smoking status showed no significant difference between the groups ($P = 0.36$), suggesting that smoking may not represent a major risk factor for prostate cancer in this cohort, despite its recognized role in the development of other cancers such as lung and bladder. In contrast, family history of prostate cancer was significantly more frequent among patients (40%) than controls (15%) ($P < 0.05$). This finding is in line with previous literature, as Nair-Shalliker et al. (2022) demonstrated that men with affected first-degree relatives face a higher likelihood of developing prostate cancer, highlighting genetic predisposition as a key factor [17]. Moreover, the mean BMI was significantly higher in patients (27.4 ± 3.2 kg/m²) compared to controls (26.1 ± 2.8 kg/m²) ($P = 0.02$), supporting prior evidence that obesity contributes to prostate cancer progression [18,19]. Collectively, these findings underscore the importance of family history and BMI as notable risk factors, in agreement with current epidemiological reports [20].

As shown in Table 2, PSMA levels were significantly elevated in prostate cancer patients compared to controls (24.6 ± 5.2 ng/mL vs. 7.3 ± 2.1 ng/mL, $P < 0.001$). This finding aligns with previous research that positions PSMA as a highly sensitive and specific biomarker for prostate cancer diagnosis and monitoring. Thakral et al. (2021) reported that elevated PSMA levels correlated with advanced stages and metastasis, reinforcing its prognostic value [21]. Likewise, Kessel et al. (2022) emphasized the diagnostic potential of PSMA in routine clinical practice [22]. The substantial difference between patients and controls in our study supports its application in distinguishing malignant from benign prostate tissue

and in longitudinal monitoring of disease progression [23].

Table 3 further demonstrates significant elevations of inflammatory biomarkers, namely IL-8, TGF-β, and MIC-1/GDF15, in patients compared with controls ($P < 0.001$). Elevated IL-8, a pro-inflammatory cytokine known for promoting neutrophil recruitment and angiogenesis, corroborates evidence linking chronic inflammation to tumor development and progression [24]. TGF-β, recognized for its dual role tumor suppressive in early disease and tumor promoting in advanced stages was also significantly elevated, consistent with its established role in prostate cancer biology [25]. Similarly, MIC-1/GDF15, a cytokine associated with immune evasion, poor prognosis, and metastatic potential, showed marked increases in patients [26]. These results reinforce earlier reports implicating inflammatory mediators in immune escape and cancer progression [27]. Ling et al. (2023) also demonstrated strong associations between higher biomarker levels, tumor aggressiveness, and adverse outcomes, lending additional support to our findings [28,29].

As shown in Table 4, YKL-40 and NGF levels were significantly elevated in prostate cancer patients compared with controls ($P < 0.001$). YKL-40, a glycoprotein implicated in inflammation, tissue remodeling, and cancer progression, has been consistently associated with advanced disease and poor prognosis [30,31]. Similarly, NGF, a neurotrophin essential for nervous system development, has been demonstrated to promote tumor growth, metastasis, and cancer-related pain [32,33]. The elevated NGF levels observed in our study suggest a neurogenic influence of tumors, potentially supporting cancer cell survival through neuronal stimulation and modulation of the tumor microenvironment [33,34]. These findings reinforce previous reports proposing YKL-40 and NGF as surrogate biomarkers of disease activity and aggressiveness in prostate cancer [35].

Table 5 highlights moderate to strong positive correlations among all tested biomarkers, with PSMA showing the strongest association with MIC-1/GDF15 ($r = 0.80$) and additional significant correlations with YKL-40 and IL-8. These patterns suggest that the studied biomarkers share overlapping pathological pathways involving inflammation, tumor progression, and remodeling of the tumor microenvironment [36,37]. The strong correlations observed between MIC-1/GDF15, YKL-40, and NGF further support the notion of interconnected biological mechanisms underlying tumor aggressiveness and unfavorable prognosis [38,39]. Collectively, these correlations expand our understanding of molecular interactions in prostate cancer pathophysiology and emphasize the potential of biomarker panels as diagnostic and prognostic tools. Despite these insights, several limitations should be acknowledged. Most importantly, while our findings demonstrate significant differences and associations between biomarkers in prostate cancer patients and healthy controls, the study did not examine variations in biomarker expression across different cancer stages or severities. This restricts the ability to directly assess their prognostic utility. Future studies should therefore incorporate stratified analyses by disease stage to validate these biomarkers' role in predicting progression and guiding treatment planning, as suggested by prior research linking biomarker expression with prostate cancer severity [40].

In conclusion, the observed significant differences in biomarker levels between prostate cancer patients and healthy controls indicate that PSMA, IL-8, TGF-β, MIC-1/GDF15, YKL-40, and NGF are promising candidates for the early detection and monitoring of prostate cancer. Elevated concentrations of these markers reflect activation of both inflammatory and tumor-specific pathways, highlighting their potential utility in improving diagnostic accuracy, prognostic assessment, and monitoring of disease progression. Integrating these biomarkers into clinical practice could enhance risk stratification and guide more informed management decisions for patients with prostate cancer.

Author Contribution Statement

Mustafa H. Ghazi contributed to study conception and design. Elaaf Fadhil Hassan and Noora Hamid Ibrahim performed data collection and laboratory analyses. Osama A. Mohsein supervised the study and provided critical revisions. All authors read and approved the final manuscript.

Acknowledgements

Scientific Approval

The study was approved by the Human Ethics Committee of the Thi-Qar Health Directorate, Al-Habbobi Teaching Hospital, Thi-Qar, Iraq (Approval No. 422, January 2024). This work forms part of an approved research project conducted by the authors.

Ethical Considerations

The study protocol was reviewed and approved by the Human Ethics Committee of the Thi-Qar Health Directorate, Al-Habbobi Teaching Hospital, Thi-Qar, Iraq (Approval No. 422, January 2024). All participants provided written informed consent after being fully informed about the study purpose and procedures. Confidentiality of participants' personal data was strictly maintained throughout the research.

Availability of Data

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Study Registration

This observational case-control study was not registered in any public clinical trial registry.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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