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Study the association of interleukins-8 and 39 with some biochemical variables in prostate cancer patients

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ABSTRACT

Prostate cancer (PC) is a disease that primarily affects older men, and nearly one in eight men will develop it during their lifetime. The most common form occurs after the age of 50. We assessed whether interleukin-8 (IL-8) and interleukin-39 (IL-39) are associated with selected biochemical parameters in Iraqi patients with PC. This investigation included 42 patients with PC from the oncology center in Ramadi and 42 healthy controls (HCs). Serum levels of IL-8, IL-39, and prostate-specific antigen (PSA) were measured using the enzyme-linked immunosorbent assay (ELISA) method. Urea, creatinine, total bilirubin (TBIL), total calcium (TCa), and zinc (Zn) were determined using enzymatic colorimetric methods. PC patients had significantly higher serum IL-8 and IL-39 levels than HCs ($p < 0.0001$). IL-39 showed a significant correlation with IL-8, hemoglobin (Hb), PSA, and urea, while IL-8 and IL-39 showed no significant association with the other measured parameters. The analyzed parameters showed the following descending order for the area under the receiver operating characteristic (AUROC) curve; PSA (1.0), hemoglobin (Hb) (0.9802), urea (0.9572), TCa (0.7577), IL-39 (0.7321), TBIL (0.7271), IL-8 (0.6706), creatinine (0.6670), red blood cells (RBCs) (0.6440), and white blood cells (WBCs) (0.6301). Serum IL-8 and IL-39 levels were significantly correlated with each other. IL-8 showed a weak and non-significant correlation with the other measured parameters, whereas IL-39 showed a significant association only with PSA and Hb.

Keywords: *Hemoglobin , PSA, Urea, WBCs, Zinc.*

1 INTRODUCTION

After lung and breast cancer, prostate cancer (PC) is the third most common cancer diagnosed globally and the fifth leading cause of cancer-specific mortality among men [1]. The most prevalent form occurs after the age of fifty. It occurs in males and affects the prostate gland, which protects the function of sperm by producing semen [2]. PC usually presents as a localized tumor that is managed by observation, prostatectomy, or radiation therapy. For advanced tumors, the mainstay of treatment consists of hormonal therapy [3].

Immunotherapy using cytokines has made progress in recent years. These molecules can either promote tumor development and inhibit anti-tumor responses or they can strengthen anti-tumor defense. Treatment results can be greatly affected by the cytokine dose used in cancer immunotherapy, as well as adverse effects. Other immunotherapy strategies used in PC are also influenced by cytokines [4].

As cancer progresses, the expression of several cytokines and chemokines increases in patient serum, metastatic sites, and primary tumor tissues. Studies have shown correlations between tumor progression, metastasis, and disease outcome [5, 6]. The prevalence and severity of prostate cancer are linked to SNPs in cytokine genes, and inflammatory cytokines may encourage inflammation-related prostate carcinogenesis [7, 8]. Interleukin-8 is a proinflammatory chemokine expressed in cancer cells that is generated by neutrophils, monocytes,

endothelium, and epithelial cells [9]. The induction of chemo taxis is IL-8's primary action on neutrophils. Furthermore, IL-8 triggers the oxidative burst by priming it, upregulating adhesion molecules, releasing lysosomal enzymes, and increasing intracellular calcium [10]. IL-8 is an IL-12 family member, a heterodimer glycoprotein made up of two covalently joined α and β chains [11].

IL-8 has been shown to influence the biology of several types of cancer, including melanoma, prostate, colon, pancreatic, breast, and lung cancer [12]. Tumor-associated macrophages and cancer cells have been shown to express IL-8 at higher levels than normal, indicating that IL-8 may play a major regulatory role in the tumor microenvironment. Because of the variety of downstream targets, IL-8 signaling may enhances angiogenesis, cancer cell proliferation and survival, cancer cell migration, and neutrophil infiltration at the tumor site [13]. A study conducted on PC patients indicated that IL-8 was increased in the serum of men with PC and was linked to less favorable outcomes [14]. IL-8 expression was assessed in a study of PC patients, and the results showed that IL-8 was the most highly expressed cytokine in each case [15].

Pro-inflammatory IL-39 is a heterodimer that belongs to the interleukin-12 family. IL-39 is produced by various types of immune cells, including B cells, dendritic cells, and macrophages. It is crucial in inflammatory responses by regulating immune cell function and inflammation [16]. The interleukin-12 cytokine IL-39 is known to mediate inflammatory responses and is implicated in the immune pathogenesis of diseases, including psoriasis, systemic lupus erythematosus, myocardial infarction, and hepatocyte necrosis [17]. Additionally, investigators reported that individuals with acute coronary syndrome had considerably higher serum levels of IL-39, and they proposed that IL-39 might be an indicator of systolic dysfunction [18]. Various Iraqi studies have explored the association between interleukins and many diseases [19,20]. While the present study is the first to assess the correlation of IL-8 and IL-39 with other biochemical parameters in Iraqi patients with PC. The aim of this study was to determine whether there was any association of IL-8 and IL-39 with age, W/H, W/T, W/N, urea, creatinine, TBIL, TCa, WBCs, RBCs, Hb, Zn, and PSA in Iraqi PC patients.

2 MATERIALS AND METHODS

The research participants ranged in age from 50 to 70 years and were randomly selected from patients visiting the oncology center in the city of Ramadi in Anbar Governorate between November 2023 and March 2024. Forty-two patients had PC, and forty-two apparently healthy individuals were included as the control group. Blood samples were collected at morning hours from 8:00 am to 12:00 pm from patients and healthy controls (HCs). Hip, waist, and thoracic circumferences were measured for all individuals. Commercial kits (Linear, Spain) were used to assess all biochemical parameters, whereas an ELISA kit (Bioassay Technology Laboratory, China) was used to detect serum levels of PSA, IL-8, and IL-39.

2.1 Exclusion criteria

Individuals with chronic or immune-related conditions such as diabetes, infections, or inflammation were excluded from the study. Individuals with another type of cancer, kidney disorders, or thyroid disorders were also excluded.

2.2 Statistical analysis

The statistical analysis of the study data was conducted using GraphPad Prism 8.02 (GraphPad Software, La Jolla, CA, USA). The results are reported as the mean, median, and standard deviation (SD). Statistical significance was evaluated using the independent samples t-test between patients with and without prostate cancer. Bivariate relationships were tested using two-tailed Pearson correlations. Sensitivity (sen%), specificity (spec%), a cut-off value, and likelihood ratio (LHR) were calculated for each parameter. The area under the receiver operating characteristic (ROC) curve was used to evaluate the validity of the investigation. A p-value of less than 0.05 was designated as the significance level.

2.3 Ethical considerations

The study was conducted in accordance with the ethical values outlined in the Declaration of Helsinki, and the protocol was approved by the institutional Ethics Committee of Tikrit University. All patients provided verbal and analytical agreement before samples were taken.

3 RESULTS

Table 1 shows the results for the patients and control groups, which are described as the mean, standard deviation (SD), and median. The mean ages (years) of patients with PC and healthy controls (HCs) were 60.50 and 59.52,

respectively ($p > 0.05$). Among anthropometric measures (AMs), W/H and W/T were lower in PC patients (1.054 and 1.008) than in HCs (1.054 and 1.028), but these differences were not significant ($p > 0.05$). In contrast, W/N was significantly lower in PC patients (2.541) than in HCs (2.647) ($p < 0.05$).

Urea (mg/dL) and creatinine (mg/dL) levels were higher in PC patients (46.10 and 1.100) than in HCs (31.02 and 0.8874), with p-values less than 0.05 for both. Total bilirubin (T.BIL, mg/dL) concentration was significantly lower in PC patients (0.6551) than in HCs (0.8055), while total calcium (T.Ca, mg/dL) was significantly higher in PC patients (9.398) than in HCs (8.939). However, WBCs ($\times 10^3$/mL), RBCs (cells/µL), Hb (g/dL), and Zn (µg/dL) were lower in PC patients (7.915, 4.319, 11.67, and 61.88, respectively) than in HCs (8.406, 4.628, 14.91, and 71.23, respectively), Table 1.

Table 1 Comparisons of Parameters Between PC patients and HCs

Parameter	Healthy Controls			PC Patients			p-value
	Mean	SD	Median	Mean	SD	Median	
Age years	59.52	6.050	58.50	60.50	6.177	60.00	0.4664
W/H	1.054	0.0677	1.057	1.030	0.0932	1.047	0.1812
W/T	1.028	0.0658	1.028	1.008	0.1289	1.031	0.3916
W/N	2.647	0.1684	2.650	2.541	0.2743	2.561	0.0356
Urea mg/dL	31.02	5.476	31.00	46.10	9.987	42.00	<0.0001
Creatinine mg/dL	0.8874	0.1791	0.9000	1.100	0.3165	1.100	0.0003
T.BIL mg/dL	0.8055	0.1587	0.8000	0.6551	0.1622	0.6800	<0.0001
T. Ca mg/dL	8.939	0.5615	8.950	9.398	0.4075	9.400	<0.0001
WBCs * 10^3/mL	8.406	1.163	8.620	7.915	1.488	7.800	0.0956
RBCs*10^6/mL	4.628	0.6671	4.775	4.319	0.5297	4.375	0.0212
Hb g/dL	14.91	0.8627	15.00	11.67	1.402	11.50	<0.0001
Zn µg/dL	71.23	12.28	71.13	61.88	14.62	61.72	0.0021

Table 2 indicates the results of PSA, IL-8, and IL-39 in the patient and control groups, which are expressed as the median. PSA (ng/mL) levels were significantly higher in PC patients (23.15) than in HCs (0.9350). IL-8 and IL-39 were also significantly higher in patients with PC (286.0 and 204.9, respectively) compared to HCs (229.3 and 125.3, respectively) ($p < 0.05$), as shown in Table 2 and Figure 1.

Table 2 Comparisons of Parameters PC Patients and HCs

Parameters	Groups	1st Quar.	Median	3rd Quar.	Min.	Max	Range	p-value
PSA ng/mL	Controls	0.3000	0.9350	1.525	0.100	2.200	2.100	<0.0001
	PC Patients	12.15	23.15	50.60	8.000	75.17	67.17	
IL-8 ng/L	Controls	202.6	229.3	324.1	105.3	621.6	516.3	0.0126
	PC Patients	247.2	286.0	346.0	196.3	669.6	473.3	
IL-39 ng/L	Controls	101.9	125.3	203.1	73.14	381.6	308.5	0.0008
	PC Patients	153.7	204.9	289.0	45.71	482.3	436.6	

Table 3 displays IL-8, which showed a significant positive correlation with IL-39. No observations of any association between IL-8 and the other studied parameters were detected. However, IL-39 showed a significant positive correlation with IL-8, PSA and urea; and a significant negative association with Hb ($p < 0.05$). We did not observe any association between IL-39 and the other studied parameters (Table 4).

Table 3 Association of IL-8 with Examined Measurements

Parameter	R (IL-8 ng/L)	P-value
IL-8 ng/L	1.000	0.0000
IL-39 ng/L	0.504	<0.0001
PSA ng/mL	0.197	0.072
Creatinine mg/dL	0.023	0.833
Urea mg/d L	0.176	0.109
T.BIL mg/dL	-0.149	0.180
T. Ca mg/dL	-0.088	0.428
RBCs cells/µL	0.021	0.851
WBCs*10^6/mL	0.031	0.782
Hb g/dL	-0.073	0.511

Table 4 Association of IL-8 with Studied Parameters

Parameter	R (IL-39 ng/L)	P-value
IL-39 ng/L	1.000	0.0000
IL-8 ng/L	0.504	<0.0001
PSA ng/mL	0.237	0.030
Creatinine mg/dL	0.069	0.532
Urea mg/d L	0.229	0.036
T.BIL mg/dL	-0.082	0.463
T. Ca mg/dL	0.202	0.0656
RBCs cells/µL	-0.098	0.376
WBCs*10^6/mL	0.037	0.740
Hb g/dL	-0.287	0.008

Receiver operating characteristic (ROC) curve analysis demonstrated which biomarkers were most suitable for differentiating patients with PC from HCs. Table 5 and Figure 2 show the ROC analysis of the following variables, in descending order: PSA [AUC = 1.000, positive if COV > 5.100, 100% Sen, 100% Spec]; Hb [AUC = 0.9802, positive if COV < 13.75, 88.10% Sen, 85.71% Spec]; urea [AUC = 0.9572, positive if COV > 37.50, 88.10% Sen, 85.71% Spec]; and IL-39 [AUC = 0.7321, positive if COV > 167.4, 71.43% Sen, 71.43% Spec]. TBIL [AUC = 0.7271, positive if COV < 0.7150, 63.41% Sen, 59.52% Spec]; IL-8 [AUC = 0.6706, positive if COV > 265.3, 54.76% Sen, 54.76% Spec]; WBCs [AUC = 0.6301, positive if COV < 8.150, 61.90% Sen, 61.90%

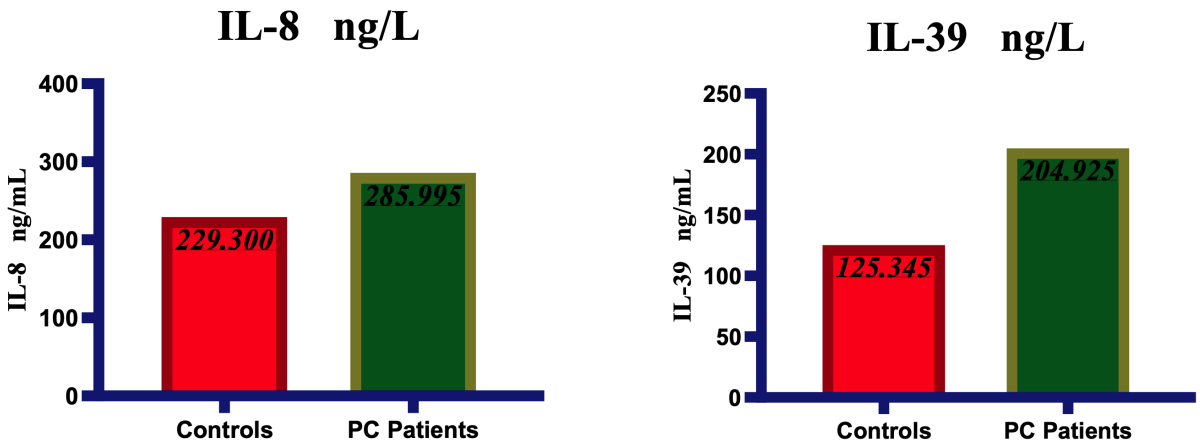

Fig. 1 Median of IL-8 in controls and PC patients (left), median of IL-39 in controls and PC patients (right)

Spec]; RBCs [AUC = 0.6440, positive if COV < 4.520, 57.14% Sen, 57.14% Spec]; creatinine [AUC = 0.6670, positive if COV > 0.9100, 59.52% Sen, 69.05% Spec]; W/N [AUC = 0.5918, positive if COV < 2.641, 52.38% Sen, 52.38% Spec]; age [AUC = 0.5485, positive if COV > 59.50, 52.38% Sen, 54.76% Spec]; W/H [AUC = 0.5377, positive if COV < 1.052, 52.38% Sen, 52.38% Spec]; and W/T [AUC = 0.5014, positive if COV < 1.029, 47.62% Sen, 45.24% Spec].

Table 5 Region Under ROC Curve for Every Parameter Analyzed in Studied Subjects

Parameter	AUC	Positive if COV	Sen%	Spec%	LHR
Age years	0.5485	>59.50	52.38	54.76	1.158
W/H	0.5377	<1.052	52.38	52.38	1.100
W/T	0.5014	<1.029	47.62	45.24	0.8696
W/N	0.5918	<2.641	52.38	52.38	1.100
PSA ng/mL	1.000	>5.100	100.0	100.0	
Urea mg/dL	0.9572	>37.50	88.10	85.71	6.167
Creatinine mg/dL	0.6670	>0.9100	59.52	69.05	1.923
T.BIL mg/dL	0.7271	<0.7150	63.41	59.52	1.567
T. Ca mg/dL	0.7577	>9.160	76.19	71.43	2.667
WBCs*106/mL	0.6301	<8.150	61.90	61.90	1.625
RBCs cells/µL	0.6440	<4.520	57.14	57.14	1.333
Hb g/dL	0.9802	<13.75	88.10	85.71	6.167
IL-8 ng/L	0.6706	>265.3	54.76	54.76	1.211
IL-39 ng/L	0.7321	>167.4	71.43	71.43	2.500

4 DISCUSSION

Prostate cancer (PC) is the second most frequent solid tumor in men and the fifth most common cause of cancer-related mortality [21]. Many men are diagnosed with PC through digital rectal examination, prostate-specific antigen (PSA) testing, magnetic resonance imaging (MRI), prostate biopsy and analysis, or general health screening. Factors that increase the risk of PC include age, weight, ethnicity, familial risk, and other environmental factors.

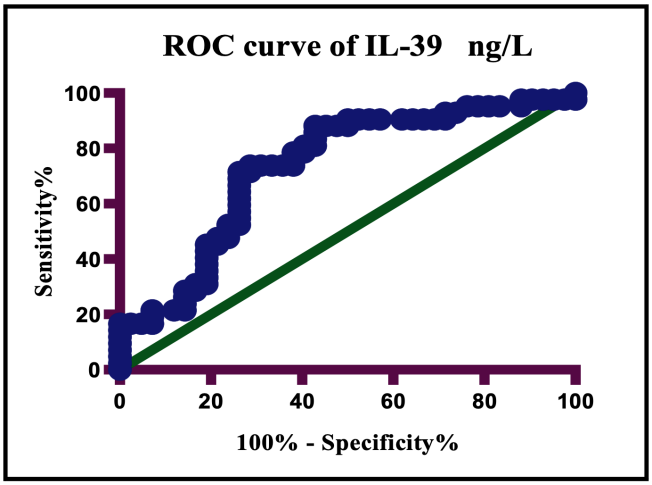

Fig. 2 Area under ROC curve for IL-39 in studied subjects

Prostate cancer is a complex disease from both an epidemiological and genetic perspective. The interaction between genetics, environment, and social factors influences race-specific survival estimates for PC and contributes to differences in its epidemiology between countries [22].

Tumor cells, stromal cells, and immune cells can express and produce cytokines and their receptors within the tumor microenvironment. This process alters the movement and function of different immune and non-immune cells in the tumor microenvironment. Together, these changes affect immune responses and tumor cell behavior [23].

IL-8 acts as a chemoattractant and stimulator for

neutrophils. It can also enhance cell growth, infiltration, viability, and resistance to chemotherapy [24]. IL-8 levels were higher in PC patients than in HCs. The results of our study align with earlier findings showing that IL-8 modulates the proliferation and migration of tumor cells, including prostate cancer cells [25]. In individuals with PC, a previous study found a correlation between serum IL-8 and myeloid-derived suppressor cells (MDSCs). Serum IL-8 levels were also higher in these patients than in normal controls and in patients with benign prostatic hyperplasia, and the levels increased with clinical stage. Analysis of the Spearman association between MDSC percentages and IL-8 levels in patients with PC suggested that elevated serum IL-8 may contribute to MDSC accumulation [26]. Based on these findings, patients with PC may present with increased serum levels of proinflammatory IL-8 that could be partly responsible for MDSC accumulation [26].

Interleukins play a significant role in maintaining the balance of healthy cells and are involved in cancer development. IL-39 is a cytokine that has not yet been fully examined in cancer pathophysiology. In our study, PC patients showed significantly increased levels of IL-39 compared to HCs. However, a previous study in breast cancer reported reduced IL-39 levels compared to HCs [27]. In addition, IL-39 was reported to inhibit the development and survival of cancer by promoting the death of T24 bladder cancer cells and pancreatic cancer cells [28,29]. Increased expression of IL-39 was reported in acute coronary syndrome [20]. Recent work has also shown decreased expression of IL-39 in autoimmune thyroid disease [30].

This study showed that PSA levels were higher in PC patients than in HCs. This result corresponds to a previous study that reported increased PSA levels in patients compared to HCs [31]. Anthropometric measurements (AMs), including W/H and W/T, showed no significant differences between patients and HCs, except for W/N, which was notably lower in patients compared to HCs. A previous study did not find any relationship between AMs and PC outcomes after diagnosis [32]. The current research also showed that serum urea and creatinine levels were higher in PC patients than in HCs, which agrees with an earlier study that reported similar findings [33].

The current study showed that TBIL levels were lower in PC patients than in HCs. Another study reported a negative correlation between baseline bilirubin levels and the risk of cervical and lung cancer in males. However, extremely low or extremely high bilirubin levels may be linked to an elevated cancer risk, as suggested by the U-shaped correlation reported for breast and prostate cancer [34]. In contrast, another investigation found no significant association between serum bilirubin and prostate cancer risk [35]. Thus, the relationship between serum bilirubin and prostate cancer remains unclear. The current investigation also showed that calcium levels were higher in patients than in HCs. Laboratory research indicates that calcium interacts with parathyroid hormone to enhance the growth and dissemination of prostate cancer cells [36].

Although smaller red blood cell size may support the observed relationship between higher RBC counts and PC risk. RBC levels in our patients were lower than in HCs, consistent with findings in testosterone-induced prostate cancer [37]. While a prior study found that patients had higher WBC levels than HCs, our study indicated that PC patients had lower WBC levels than HCs. This pattern suggests that higher WBC and neutrophil counts are associated with a higher risk of PC mortality and may support the proposed role of chronic inflammation and infection in prostate cancer. Hb levels were lower in patients than in HCs. This corresponds with a previous study suggesting that the relationship between Hb and PC may be due to chronic blood loss in the urinary tract caused by PC, which can reduce Hb levels. PC treatments, such as radiation therapy or chemotherapy, can also affect bone marrow function and reduce red blood cell production, leading to anemia [37]. The present study also showed a decrease in Zn concentration in patients with PC compared to HCs. This finding is consistent with a previous study that reported a significant drop in prostate tissue zinc levels in PC relative to HCs, with zinc levels in malignant tissue reduced by 70-80% compared to normal tissue [38].

Study limitations: First, the sample size was not large, and future studies should include a larger sample size. Second, the analyses were performed in private laboratories, which may also be considered a limitation.

5 CONCLUSION

Serum IL-8 and IL-39 levels showed a significant correlation with each other. IL-8 displayed a weak and non-significant correlation with the other studied parameters, while IL-39 showed a significant association with PSA, urea, and Hb. IL-8 and IL-39 are therefore not good indicators for PC.

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DECLARATIONS

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Consent to publish

All authors consent to the publication of this work. Written informed consent for publication was obtained from the participants.

Ethical approval

The study was conducted in accordance with the ethical values outlined in the Declaration of Helsinki, and the protocol was approved by the institutional Ethics Committee of Tikrit University. All patients provided verbal and analytical agreement before samples were taken.

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