RESEARCH ARTICLE

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Association of *IL-1β* Gene Polymorphism with Prostate Cancer Severity, Prostate Volume, and PSA Levels: A Case-Control Study

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Abstract

Background: Prostate cancer (PCa) is the second leading cause of death from cancer among men. The development of prostate cancer depends on chronic inflammation and cytokines, including interleukin-1 beta (*IL-1β*). The objective of the research was to test the association between SNP (rs16944) in interleukin-1 β (*IL-1β*) gene and serum levels of Prostate Specific Antigen (PSA) and testosterone concentrations in patients with prostate cancer. **Methods:** This was a case-control study on 40 prostate cancer patients and 40 controls at Kirkuk City. The levels of serum prostate-specific antigen (PSA), prostatic acid phosphatase (PAP), testosterone, and prostate volume were determined by enzyme-linked immunosorbent assay. The ARMS-PCR was used to genotype the *IL-1β* , which was followed by statistical analysis of the association of genotypes with Gleason and clinical parameters with the help of Student's t-test, chi-square test, and correlation. The general significance level of the p-value is less than 0.05. **Results:** Significant differences were observed in PSA levels (36.4 ± 2.17 ng/ml in PCa vs. 0.91 ± 0.09 ng/ml in controls; P = 0.001), PAP levels (3.54 ± 1.51 IU/L vs. 0.87 ± 0.28 IU/L; P = 0.001), testosterone (6.54 ± 0.87 ng/ml vs. 3.27 ± 1.98 ng/ml; P = 0.011), and prostate volume (79.17 ± 6.26 cm³ vs. 23.21 ± 2.17 cm³; P = 0.001). *IL-1β* genotyping showed that the genotype AG and AA were more frequent among PCa patients than among the controls. The AA genotype was highly correlated with better Gleason scores (P = 0.021), increased prostate volume (P = 0.041), and increased levels of PSA (P = 0.034). **Conclusion:** *IIL-1β* polymorphism, particularly the AA genotype, is associated with increased PSA levels, larger prostate volume, and more aggressive prostate cancer phenotypes. These findings underscore the potential of *IL-1β* genotyping as a biomarker for prostate cancer severity and progression.

Keywords: Prostate cancer- *IL-1β*- single-nucleotide polymorphism- PSA- prostate volumeApitiate archil maio

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Introduction

Prostate cancer (PCA) ranks as the second leading cause of cancer-related mortality among males, with a death rate of 26.7% from 2001 to 2005 in the United States. Chronic inflammation is believed to substantially contribute to prostate cancer development [1]. PCA patients also have local and systemic immunosuppression[2]. Clarifying the molecular mechanisms behind these events may yield new insights into PCA genesis and progression, which could be of significant clinical importance[3]. Prostatic intraepithelial neoplasia (PIN) may act as a precursor to prostate cancer. It is responsible for the abnormal growth of epithelial cells that comprise the prostate gland. Prostate cancer is the most common malignancy in men, with approximately one in nine men receiving a diagnosis during their lifetime. It is recommended to make informed decisions on the screening of adults between the ages of 55 and 69 years [4]. Prostate cancer (PCa) can have a hereditary component, with 10% to 20% of patients exhibiting a familial cancer history, which is associated with an increased risk of mortality from the disease[5]. Cytokines serve as vital mediators of inflammation and play a crucial role in the interaction between the immune system and cancer. Numerous factors are associated with advanced-stage prostate cancer [6]. IL-4 and, specifically, IL-6 exhibit antiapoptotic impacts on PCA cells, while the proangiogenic characteristics of IL-8 have been validated [7]. Prostate cancer (PCa) is the second leading cause of mortality in men and the most commonly diagnosed non-cutaneous malignancy in the male population. Host genetic factors and inflammation-induced cytokines are crucial in prostate oncogenesis[8]. Single Nucleotide Polymorphisms (SNPs) in cytokine genes are posited to increase the risk of prostate cancer (PCa) onset and advancement [9]. This study aimed to examine the correlation between the SNP (rs16944) in the interleukin-1 β *(IL-1β)* gene and the serum levels of Prostate Specific

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Antigen (PSA) and testosterone in prostate cancer patients.

Materials and Methods

Study Design

This case-control study was conducted in Kirkuk City from November 1, 2021, to February 28, 2022, involving 40 male prostate cancer patients and 40 healthy male controls, aged 50–81 years. Inclusion criteria for patients required a histologically confirmed prostate cancer diagnosis from the Urology Consultation Unit at Azadi Teaching Hospital. Controls were healthy males with no personal or familial history of prostate cancer, verified by normal PSA levels (<4 ng/ml) and clinical evaluation. Exclusion criteria included prostatitis, sexually transmitted infections, chronic renal failure, or use of finasteride or dutasteride.

Data Collection and Measurements

Transabdominal ultrasound was used to estimate the volume of the prostate (Siemens, Germany) through the work of trained radiologists. The IPSS was evaluated in all the patients at the time of diagnosis. The questionnaire divided the symptoms under mild (IPSS ≤7), moderate (IPSS 8-19), and severe (IPSS 20-35) [10].

Laboratory Procedures

Each participant was sampled in the morning using disposable gel tubes and allowed to coagulate for 2 hours at room temperature. The samples were centrifuged at 6000 rpm and centrifuged over 10 minutes to extract the serum, which was then aspirated with a mechanical micropipette and put in the matching Eppendorf tubes. To enhance this safety and labeling (name, date, number), these tubes were put in urine cups and kept in -20 o C pending further analysis. PSA, PAP, and testosterone levels were assayed by using the serum of the patients and controls. Besides, the EDTA blood was utilized in the process of detecting polymorphism of the *IL-1β* gene through the following protocol [11].

Nucleic Acid Extraction

ZYBIO-B-200 kit (Zybio Inc., China) was used to extract the nucleic acid. The DNA or RNA isolation was performed using magnetic bead-based technology. Protein digestion, lysis, washing, and elution were incorporated into the process, and the extracted nucleic acids were stored at -20 °C for further analysis of the *IL-1β* gene polymorphism.

Primer Design and PCR Analysis

Single-nucleotide polymorphisms (SNPs) in the *IL-1β* gene were identified by the use of ARMS-PCR. Primer sequences were made in such a way that they would target a particular allele. The optimal PCR conditions were determined using different amounts of the primer, concentration of DNA, and different annealing temperatures. The amplification was done in a thermocycler, and the products were separated through agarose gel electrophoresis. Quality control was done by performing replicate PCR amplifications on 15 percent of the samples and by repeating patterns of restriction fragments on agarose gels to verify the accuracy of genotyping.

Gel Electrophoresis

Agarose gel (1.5%) was stained with ethidium bromide to view DNA in the UV light. Fragment sizes were determined by the use of DNA ladders.

Statistical Analysis

The descriptive statistics were used to describe the characteristics of the participants. Continuous variables were presented in terms of means plus standard deviations, whereas categorical variables were presented in terms of frequencies and percentages. The continuous variables were compared in the group by using the Student t-test, whereas the categorical variables were compared in the group by using of chi-square. Correlation was used to test the relationship between variables. A p-value of less than 0.05 was important. Minitab 23 and GraphPad Prism were used to do the statistics.

Results

Clinical Parameter Comparisons

A comparison of the clinical parameters of the prostate cancer patients and the control group was made in Table 1. The age and BMI of the two groups are similar, and there was no statistical significance between the two (P > 0.05). Other parameters, however, showed significant differences. The level of prostate-specific antigen (PSA) in prostate cancer subjects (36.4 ± 2.17 ng/ml) was significantly higher than relation of the control (0.91 ± 0.09 ng/ml), which depicts the diagnostic value of PSA. On the same note, prostatic acid phosphatase (PAP) level was also significantly greater in patients with prostate cancer (3.54± 1.51 IU/L) than in controls (0.87± 0.28 IU/L, P = 0.001), which supports its relevance in the progression of the disease. The prostate cancer patients

Table 1. Comparison of Clinical Parameters between Prostate Cancer Patients and the Control Group

Parameters	Prostate Cancer Patients (n : 40)	Control Group (n: 40)	P-value
Age (years)	59.41 ± 8.54	58.26± 8.11	>0.05
BMI (kg/m²)	25.13 ± 3.82	25.76 ± 3.91	>0.05
PSA (ng/ml)	36.4 ± 2.17	0.91± 0.09	0.001
PAP (IU/L)	3.54 ± 1.51	0.87 ± 0.28	0.001
Testosterone (ng/ml)	6.54 ± 0.87	3.27 ± 1.98	0.011
Prostate Volume (cm³)	79.17 ± 6.26	23.21 ± 2.17	0.001

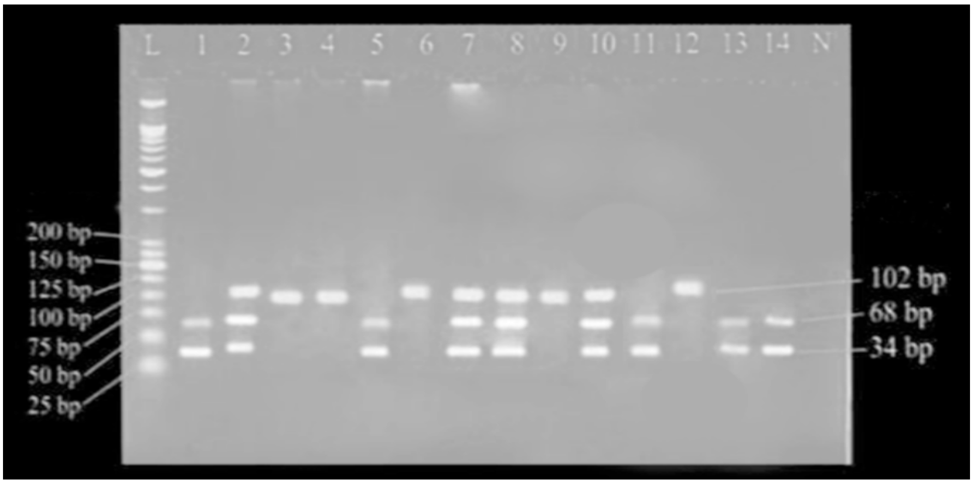

Figure 1. DNA image of *IL-1β* Fragments by Agarose Gel Electrophoresis after Restriction Enzyme Digestion

Table 2. Distribution of *IL-1β* Genotypes and Allele Frequencies in Prostate Cancer Patients and Controls

Genotype/Allele	Prostate Cancer Patients (n = 40)	Control Group (n = 40)	P-value
GG (homozygous wild type)	14 (35%)	19 (47.5%)	0.287
AG (heterozygous mutant)	20 (50%)	17 (42.5%)	
AA (homozygous mutant)	6 (15%)	4 (10%)	
Total	40 (100%)	40 (100%)	
Allele Frequency (G)	48 (60%)	55 (68.75%)	0.37
Allele Frequency (A)	32 (40%)	25 (31.25%)	

(6.54 ± 0.87 ng/ml) also had a significantly high level of testosterone in comparison with the controls (3.27 ± 1.98 ng/ml, P = 0.011), which may indicate that the disease has a possible hormonal factor. Finally, the patient group (79.17 ± 6.26 cm^3) had a much larger prostate volume than the controls (23.21 ± 2.17 cm^3, P = 0.001), thus demonstrating the relationship between this volume and prostate cancer pathology.

IL-1β Genotype and Allele Frequencies

In the case of PCa patients, the post-digestion of the *IL-1β* gene with the XagI restriction enzyme, the PCR-RFLP product was presented in the 4.1% agarose gel image in Figure 1. The gel was analyzed through the gel documentation system under the UV transilluminator, where it was stained with ethidium bromide. A 25/100 bp mixed DNA marker is contained in the L-strand. A single fragment band (102 bp) appears in the 3rd, 4th, 6th, 9th, and 12th strips, which is a trait of the AA genotype. The 1st, 5th, 11th, 13th, and 14th lanes indicate the presence of two fragment bands (68 bp and 34 bp) that are associated with the GG genotype. The 2nd, 7th, 8th, and 10th strands, however, show three fragment bands (102 bp, 68 bp, and 34 bp) which depict the AG genotype. The GG genotype (homozygous wild type) was relatively more common in the control group (47.5%) than in prostate cancer patients (35%), and did not differ significantly (P = 0.287), indicating that there is no significant protection in this sample. Conversely, the patients of prostate cancer had a greater prevalence of the AG genotype (heterozygous mutant) (50%), in comparison to controls (42.5%). Similarly, the AA genotype (homozygous mutant) was a bit higher among the patients of prostate cancer (15%) compared to the controls (10%). These results provide the clue of a possible linkage between the occurrence of mutant genotypes (AG and AA) and prostate cancer, but result was not found statistically significant when comparing the genotypes separately. In terms of allele frequencies, the G allele was more common with the controls (68.75%) than prostate cancer patients (60%), and the A allele was more common with prostate cancer patients (40%) than controls (31.25%). The variation in the allele frequencies was, however, not statistically significant (P = 0.37) Table 2.

Associations with Disease Severity

Table 3 indicates the association of genotypes of *IL-1β* and the distribution of Gleason Scores in patients with prostate cancer, and the association is statistically significant (P = 0.021). Gleason Scores (≤6) (57.1%)

Table 3. Gleason Score Distribution in Prostate Cancer Patients by *IL-1β* Genotypes

IL-1β Genotype	Low Gleason Score (≤6)	Intermediate Score (7)	High Gleason Score (≥8)	P-value
GG (Wild Type)	8 (57.1%)	4 (28.6%)	2 (14.3%)	0.021
AG (Heterozygous)	10 (28.6%)	12 (34.3%)	13 (37.1%)	
AA (Homozygous)	2 (33.3%)	1 (16.7%)	3 (50.0%)	

Table 4. Association of Prostate Volume with *IL-1β* Genotypes in Prostate Cancer Patients

IL-1β Genotype	Prostate Volume (cm³) Mean ± SD
GG (Wild Type)	76.12 ± 5.8
AG (Heterozygous)	82.45 ± 6.3
AA (Homozygous)	88.32 ± 7.2

P-value, 0.041

Table 5. Association of PSA Levels with *IL-1β* Genotypes in Prostate Cancer Patients

IL-1β Genotype	PSA Levels (ng/ml) Mean ± SD
GG (Wild Type)	28.5 ± 3.2
AG (Heterozygous)	36.7 ± 4.1
AA (Homozygous)	42.9 ± 5.6

P-value, 0.034

were low among patients with the GG genotype (wild type), and a small proportion of patients had high Gleason Scores (≥8) (14.3%). On the other hand, the AG genotype (heterozygous mutant) was more widely spread across Gleason Score categories, with a large proportion of patients (37.1%) exhibiting high Gleason Scores, which corresponds to high tumor aggressiveness. Interestingly, the largest proportion of patients with high Gleason Scores (50%) was of the AA genotype (homozygous mutant), which highlights an important role of the genotype in mediating more aggressive disease phenotypes. Such results indicate that *IL-1β* genotypes affect the severity of prostate cancer, the GG genotype is correlated with the milder forms of the disease, and the AG and AA genotypes are correlated with the aggressive forms of the tumor.

Table 4 provides the relationship between the genotypes of *IL-1β* and prostate volume in patients with prostate cancer. It exhibits a great variance among the genotypes (P = 0.041). It was also observed that the mean prostate volume of patients with the GG genotype (wild type) was the smallest (76.12±5.8 cm^3), and this could be linked to the milder severity of the disease. However, this is not the case with AG genotype patients (heterozygous), as they had a higher mean prostate volume (82.45 ± 6.3 cm^3) when compared to the patients with the AA genotype (homozygous), who had the highest mean prostate volume (88.32 ± 7.2 cm^3). The results indicate that there are sequential relative growths in prostate volumes, indicating that the alleles of the AA genotype might be connected to the development of more serious pathologies.

An interval between two characters depicts a gradual rise in the mutants of PSA through mutants. In addition, the genotype GG patients were generally the lowest mean PSA levels (28.5 ± 3.2 ng/ml), as in Table 5, indicating that they possessed less aggressive disease phenotype. AG heterozygous, in its turn, was more moderate in disease progression with the higher PSA (36.7 ± 4.1 ng/ml). Homozygous mutants of AA recorded the highest levels of PSA (42.9 ± 5.6 ng/ml), which are very much associated with the aggressiveness of the disease in patients. These give signs that the genotype of IL-1B influences the PSA expression where the mutant genotype (AG and AA) has been linked to the high level of PSA and probably more advanced diseases.

Discussion

The present case-control study shows evidence of associations between *IL-1β* gene polymorphisms (rs16944) and the severity of prostate cancer, as shown by clinical biomarkers (PSA, PAP, testosterone), prostate volume, and the Gleason scores. The results are added to the knowledge of the role of inflammation in the oncogenesis of prostate cancer and put forward *IL-1β* genotyping as a possible risk-stratification tool.

The high concentrations of PSA, PAP, and testosterone in patients with prostate cancer compared to healthy controls are another indication that the mentioned factors are diagnostic and prognostic markers [12, 13]. The use of the PSA as a diagnostic tool in the differentiation of prostate cancer and benign prostate hyperplasia (BPH) is not new, and Ferreira et al. [1] have observed the same levels of elevation of localized prostate cancer. The higher the level of PAP, the higher the disease progression as reported by Dahiya et al. [14], and the higher the levels of testosterone, the higher the level of androgen-driven tumor growth as reported by Kumar et al. [15]. These clinical variables give a solid basis on which the effect of *IL-1β* on the severity of the disease can be assessed.

The *IL-1β* genotype findings showed that AG (50%) and AA (15%) genotypes were more predominant in prostate cancer patients than in the controls (42.5% and 10% respectively), but also the difference was not significant (P = 0.287) [Table 2]. However, the GG genotype was more common in the control (47.5%) than in the patients (35 %), which indicated a possible protective effect, according to Abed et al. [3], (GG: 36 % in controls and 26 % in patients, OR 0.62, P = 0.254). The prevalence of alleles was higher in the patients (40%) than controls (31.25%), though no significant difference was found (P = 0.37). The results suggest that the AG and AA mutant genotypes can predispose individuals to prostate cancer, which is also consistent with Habanjar et al. [16], who also associated *IL-1b* solutions with tumor-stromal interactions that facilitate the progression of the disease. In our study, we employed the ARMS-PCR genotyping, a particular and cost-effective method to be used in the analysis of the IL-1B rs16944 variation. Despite the comprehensive coverage of the genome by such approaches as WGS or TaqMan assays [17].

ARMS-PCR provided the best balance of precision, speed, and affordability for our SNP research of interest [18]. It is important to note that ARMS-PCR allele-specific design minimizes the chances of cross-reactivity, which is a major drawback of RFLP-PCR, which depends on the effectiveness of restriction enzymes [19].

Significant correlation was found between the *IL-1β* genotypes and disease severity markers. AA had higher Gleason scores (half of AA patients scored 50% had scores ≥8, P = 0.021), increased prostate volume (88.3272 cm^3, P = 0.041), and higher levels of PSA (42.956ng/ml, P = 0.034) in comparison to taxon GG and AG (Tables 3-5).

These findings indicate the role of the AA genotype in aggressive phenotypes, which might be mediated by the increased production of IL-1B. NF-8 -inflammatory cytokine, *IL-1β* 2 activates NF-8 -signaling, leading to tumor proliferation, angiogenesis, and PSA secretion [20, 21]. Lower Gleason scores (57.1% ≤6) and smaller prostate size (76.12 =5.8 cm³) are associated with the GG genotype and suggest a protective potential, perhaps because of a decreased level of inflammatory activity [22].

IL-1β polymorphisms have a broader application with prostate cancer, with identical results reported in breast [23], lung [24], and gastric cancer [25, 26]. As an example, Liu et al. [27] discovered that the *IL-1β* variants augment the risk of breast cancer due to the augmentation of the microenvironment of inflammation. These similarities highlight the very general role of *IL-1β* that affects oncogenesis brought about by inflammation [28], but the standard hormonal and stromal environment of prostate cancer should be studied specially. The current study on the topic of rs16944 is more specific in these general observations by demonstrating its significance in the severity of prostate cancer.

What is interesting is the clinical implications of these findings. It is possible to combine *IL-1β* genotyping, which is effective with the AA genotype, with PSA-based screening to determine the individuals at risk of developing aggressive disease [29]. This stratification can inform initial interventions, including anti-inflammatory treatments or *IL-1β* inhibitors, which have demonstrated efficacy in preclinical models [30]. In addition, the *IL-1β* genotyping could be used together with other genetic markers to increase the level of personal risk assessment, which has been limited by the fact that PSA is specific to risk [31]. This research is weak due to its small sample size, which could diminish the statistical power and extrapolation of the results. To confirm the connections between *IL-1β* polymorphisms and prostate cancer severity, a larger multicenter cohort study is required in the future.

Conclusion: The polymorphism of *IL-1β* and especially genotype AA is linked to high levels of PSA, higher volume of the prostate gland, and a more aggressive prostate cancer phenotype. These results highlight the possibility of *IL-1β* genotyping being a biomarker of prostate cancer severity and progression.

Author Contribution Statement

Study conception and design by (Ayad Abdulkhaleq Ismael) and (Ahmed Mahmood Hussein); data collection by (Alan Adnan Sabe) and (Ahmed Mahmood Hussein); evaluation and comprehension of results by (Ayad Abdulkhaleq Ismael) and (Alan Adnan Sabe). All authors reviewed the work and approved the final version of the publication.

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If it was approved by any scientific Body/ if it is part of an approved student thesis

The manuscript received approval from the scientific committee of the College of Medicine, Kirkuk University, and is not associated with any student thesis.

Availability of data

All data generated in this study were published in this article.

Was the study registered in any registration dataset

The study was not registered in any clinical trial, guideline, or meta-analysis dataset, per the manuscript provided.

Ethics Statement

The ethical issue was handled by the Research Ethics Committee of Kirkuk University-College of Medicine, which approved the research in August 2021

Conflict of Interest

The authors declare that they have no conflicts of interest.

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