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Original Article

Plasma Interleukin-6 as a Biomarker of Disease Progression in Prostate Cancer: Association with Metastasis, PSA Levels, and Gleason Score

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Abstract

Background: Prostate cancer (PC) remains one of the most commonly diagnosed malignancies among men worldwide, characterized by heterogeneous clinical behavior ranging from indolent disease to aggressive metastatic progression. Conventional biomarkers such as prostate-specific antigen (PSA) have limitations in accurately predicting disease progression, necessitating the identification of additional reliable biomarkers. Interleukin-6 (IL-6), a pro-inflammatory cytokine, has emerged as a potential indicator of tumor progression due to its role in cancer biology and metastasis.

Objective: To evaluate the association of plasma IL-6 levels with prostate cancer progression, specifically in differentiating metastatic from non-metastatic disease, and to assess its correlation with PSA levels and Gleason scores.

Methodology: A cross-sectional study was conducted including 50 histopathologically confirmed PC patients, categorized into metastatic (n = 25) and non-metastatic (n = 25) groups. Plasma IL-6 levels were measured using enzyme-linked immunosorbent assay (ELISA), while PSA levels were determined via chemiluminescent microparticle immunoassay. Gleason scores were recorded based on histopathological evaluation.

Results: Plasma IL-6 levels were significantly elevated in metastatic patients (28.9 ± 5.4 pg/mL) compared to non-metastatic patients (2.3 ± 1.2 pg/mL; $p < 0.001$). A moderate positive correlation was observed between IL-6 and PSA levels ($r = 0.512$, $p = 0.029$), and a significant positive correlation was found between IL-6 and Gleason score ($r = 0.431$, $p = 0.042$).

Conclusion: Plasma IL-6 is significantly associated with prostate cancer progression and demonstrates strong correlations with established clinical parameters such as PSA and Gleason score. These findings suggest that IL-6 may serve as a complementary biomarker for assessing disease severity and aggressiveness.

Keywords: Biomarker, Gleason Score, Interleukin-6, Metastasis, Prostate Cancer, PSA.

Introduction

Prostate cancer (PC), the second most commonly diagnosed cancer among men globally, represents a major public health challenge due to its increasing incidence and complex clinical behavior [1, 2]. Despite significant advances in diagnosis and management, the mechanisms underlying disease progression, particularly the transition from localized to metastatic stages, remain incompletely understood [3]. PC is a highly heterogeneous disease, with some patients experiencing slow, indolent progression, while others develop aggressive forms that rapidly metastasize and lead to increased mortality [4].

The prostate-specific antigen (PSA) test is widely used as a screening and monitoring tool; however, it has well-recognized limitations, particularly in distinguishing aggressive disease from indolent cases and predicting metastatic progression [5]. This limitation underscores the need for additional biomarkers that can provide more precise prognostic and diagnostic information. In recent years, attention has shifted toward inflammatory mediators, especially cytokines, due to their critical roles in tumor biology, immune regulation, and cancer progression [6].

Among these, interleukin-6 (IL-6) has emerged as a key cytokine implicated in the pathophysiology of several malignancies, including prostate cancer [7,8]. IL-6 is produced by various cell types, including immune cells, stromal cells, and tumor cells, and functions through both autocrine and paracrine signaling mechanisms. It contributes to tumor proliferation, survival, angiogenesis, and metastasis. Elevated IL-6 levels have been consistently associated with poor prognosis and advanced disease stages in multiple cancers, including PC [9].

Furthermore, IL-6 has been implicated in the development of castration-resistant prostate cancer (CRPC), an advanced and treatment-resistant form of the disease [10]. Mechanistically, IL-6 activates key signaling pathways such as the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway, which promotes tumor cell survival, proliferation, and resistance to apoptosis. These molecular insights highlight the potential of IL-6 not only as a biomarker but also as a therapeutic target.

In addition to molecular markers, histopathological grading using the Gleason score remains a cornerstone for assessing tumor aggressiveness. Higher Gleason scores are indicative of poorly differentiated tumors with greater metastatic potential. When combined with PSA levels, the Gleason score provides important clinical insights into disease severity and progression risk [11].

Given the limitations of current biomarkers and the emerging role of inflammatory mediators in cancer progression, this study was designed to evaluate the association between plasma IL-6 levels and prostate cancer progression. Specifically, it aims to determine whether IL-6 can effectively differentiate metastatic from non-metastatic disease and to assess its correlation with PSA levels and Gleason scores. By integrating biochemical and clinical parameters, this study seeks to explore the potential of IL-6 as a complementary biomarker for improving prognostic accuracy and guiding clinical decision-making.

Methodology

Study Design

This study was designed as a non-randomized cross-sectional analytical investigation aimed at evaluating the association between plasma interleukin-6 (IL-6) levels and prostate cancer (PC) progression. The primary objective was to compare IL-6 levels between metastatic and non-metastatic PC patients, while the secondary objective focused on examining the correlation of IL-6 with prostate-specific antigen (PSA) levels and Gleason scores to assess its prognostic utility.

Ethics

Ethical approval for the study was obtained from the Institutional Review Board (IRB) under reference number F-39/NHRC/IRB/237. All procedures were conducted in accordance with ethical standards for human research. Written informed consent was obtained from all participants prior to enrollment, ensuring voluntary participation and confidentiality of data.

Setting

The study was conducted in collaboration with the Urology Department at Shaikh Zayed Hospital, Lahore, a tertiary care center with a high volume of prostate cancer patients, allowing for appropriate recruitment and clinical evaluation of both metastatic and non-metastatic cases.

Participants

The study included male patients aged 50–85 years with histopathologically confirmed prostate cancer. Participants were categorized into metastatic and non-metastatic groups based on clinical and diagnostic findings. Patients with coexisting inflammatory or autoimmune diseases, obesity, or other active malignancies were excluded to minimize confounding factors affecting IL-6 levels.

Variables

The primary independent variable was plasma IL-6 level, while dependent variables included disease status (metastatic vs. non-metastatic), PSA levels, and Gleason scores. Additional variables included demographic factors (age, BMI) and clinical characteristics relevant to prostate cancer progression.

Data Sources/Measurement

Data were collected using a structured checklist capturing demographic information, clinical history, PSA levels, Gleason scores, and imaging findings. Venous blood samples (5 mL) were collected in EDTA tubes, centrifuged to separate plasma, and stored at −80 °C until analysis. Plasma IL-6 levels were measured using a commercially available ELISA kit (Thermo Fisher Scientific, USA), while PSA levels were determined using a chemiluminescent microparticle immunoassay. PSA values were categorized as elevated (≥20 ng/mL) or lower (<20 ng/mL) based on established high-risk thresholds supported by previous studies [13, 14].

Bias

To reduce selection bias, a non-probability purposive sampling technique was used, with an additional step of applying a computer-generated random list when multiple eligible patients presented simultaneously. Confounding bias was minimized by excluding patients with conditions known to influence inflammatory markers. Standardized laboratory procedures were used to reduce measurement bias.

Study Size

The sample size was calculated for comparison of two independent means using the formula:

$n \text{ per group} = (Z\alpha/2 + Z\beta)^2 \times (\sigma_1^2 + \sigma_2^2) / \Delta^2$.

Using $Z\alpha/2 = 1.96$ (95% confidence level), $Z\beta = 0.84$ (80% power), σ_1^2 and $\sigma_2^2 = 36$, and $\Delta = 5$ pg/mL (clinically meaningful difference based on prior literature [12]), the calculated sample size was approximately 23 participants per group. To account for potential attrition, 25 patients were recruited in each group, resulting in a total sample size of 50 participants.

Quantitative Variables

IL-6 levels were expressed in pg/mL, PSA levels in ng/mL, and Gleason scores were categorized into low-grade (≤6), intermediate [7], and high-grade [8–10]. Continuous variables were summarized using means and standard deviations, while categorical variables were presented as frequencies and percentages.

Statistical Methods

Data analysis was performed using SPSS version 25. Descriptive statistics were used to summarize baseline characteristics. Differences in IL-6 levels between metastatic and non-metastatic groups were assessed using the independent-samples t-test or its non-parametric equivalent where appropriate. Correlations between IL-6 and PSA levels, and between IL-6 and Gleason scores, were evaluated using Pearson's correlation coefficient or Spearman's rank correlation depending on data distribution. A p-value of <0.05 was considered statistically significant.

Results

Participants

A total of 50 patients diagnosed with prostate cancer (PC) were included in the study, comprising 25 metastatic and 25 non-metastatic cases. All participants met the predefined inclusion criteria and were successfully evaluated for biochemical and clinical parameters. There were no reported exclusions after enrollment, and complete datasets were available for all participants included in the final analysis (Table 1).

Descriptive Data

Baseline demographic and clinical characteristics of the study population are presented in Table 1. The mean age of patients in the metastatic group was 70.5 ± 6.8 years, compared to 66.2 ± 7.3 years in the non-metastatic group, with no statistically significant difference ($p = 0.121$). Similarly, body mass index (BMI) did not differ significantly between the two groups (27.8 ± 3.1 kg/m² vs. 26.5 ± 2.9 kg/m²; $p = 0.256$). However, marked differences were observed in key disease-related parameters. Metastatic patients exhibited significantly higher PSA levels (410.5 ± 92.4 ng/mL) compared to non-metastatic patients (45.8 ± 18.7 ng/mL; $p < 0.001$). Additionally, Gleason scores were significantly elevated in the metastatic group (7.8 ± 0.6) relative to the non-metastatic group (6.4 ± 0.5; $p = 0.011$), indicating more aggressive tumor characteristics (Table 1).

Outcome Data

The primary outcome variable, plasma IL-6 level, demonstrated a substantial difference between the two groups. Metastatic PC patients showed markedly elevated IL-6 levels (28.9 ± 5.4 pg/mL) compared to non-metastatic patients (2.3 ± 1.2 pg/mL), with this difference being highly statistically significant ($p < 0.001$). Furthermore, correlation analyses revealed meaningful associations between IL-6 and established clinical markers. A moderate positive correlation was observed between IL-6 and PSA levels (r =

0.512, p = 0.029), suggesting that higher inflammatory activity is associated with increased tumor burden. Similarly, IL-6 demonstrated a significant positive correlation with Gleason score (r = 0.431, p = 0.042), indicating its relationship with tumor aggressiveness (Table 2).

Main Results

The findings of this study highlight a strong association between elevated plasma IL-6 levels and prostate cancer progression. Specifically, IL-6 levels were significantly higher in metastatic patients compared to non-metastatic cases, reinforcing its potential role as a biomarker of advanced disease. In addition, the observed positive correlations of IL-6 with both PSA levels and Gleason scores further support its clinical relevance in reflecting tumor burden and histopathological severity. These results suggest that IL-6 may serve as a complementary biomarker alongside PSA and Gleason score for improved assessment of disease progression and aggressiveness (Tables 1 and 2).

Table 1: Demographic and Clinical Characteristics of Metastatic and Non-Metastatic Prostate Cancer Patients

Variable	Metastatic (n = 25)	Non-Metastatic (n = 25)	p-value
Age (years)	70.5 ± 6.8	66.2 ± 7.3	0.121
BMI (kg/m²)	27.8 ± 3.1	26.5 ± 2.9	0.256
PSA (ng/mL)	410.5 ± 92.4	45.8 ± 18.7	< 0.001
Gleason Score	7.8 ± 0.6	6.4 ± 0.5	0.011

Table 2: Correlation of Plasma IL-6 Levels with PSA and Gleason Score in Prostate Cancer Patients

Variables Compared	Correlation Coefficient (r)	p-value
IL-6 vs. PSA	0.512	0.029
IL-6 vs. Gleason Score	0.431	0.042

Discussion

The present study investigated the role of plasma interleukin-6 (IL-6) as a biomarker of prostate cancer (PC) progression by comparing its levels between metastatic and non-metastatic patients and evaluating its association with established clinical parameters [12,13]. The findings demonstrated a significant elevation of IL-6 levels in metastatic PC, supporting its potential role as an indicator of advanced disease and tumor aggressiveness.

The observed increase in IL-6 levels among metastatic patients is consistent with previous studies that have highlighted the role of inflammatory cytokines in cancer progression [14-16]. IL-6 has been shown to promote tumor growth, angiogenesis, and metastatic spread through activation of key intracellular signaling pathways. In particular, the IL-6/JAK/STAT3 signaling axis has been implicated in enhancing tumor cell proliferation, survival, and resistance to apoptosis [17]. These mechanisms provide a biological basis for the elevated IL-6 levels observed in patients with advanced disease and support its potential utility as a biomarker of progression.

In addition to group differences, the present study identified a moderate positive correlation between IL-6 and PSA levels. This finding suggests that IL-6 may reflect tumor burden and disease activity alongside PSA. While some studies have reported similar associations [16], others have found inconsistent or non-significant relationships between IL-6 and PSA [18]. Such variability may be attributed to differences in study populations, disease stages, and methodological approaches. Nevertheless, the current findings contribute to the growing body of evidence supporting the complementary role of IL-6 in conjunction with PSA.

Furthermore, a significant positive correlation between IL-6 and Gleason score was observed, indicating that higher IL-6 levels are associated with increased tumor aggressiveness. This aligns with findings from meta-analyses and clinical studies demonstrating the prognostic value of IL-6 in predicting tumor grade, metastasis, and overall disease severity [19]. Given that Gleason scoring reflects histopathological differentiation, the association with IL-6 underscores the link between systemic inflammation and tumor biology.

Despite these promising findings, it is important to recognize that IL-6 is a non-specific inflammatory marker influenced by various physiological and pathological conditions. Previous studies have reported variability in IL-6 levels across different populations and clinical contexts [20, 21]. Therefore, its use as a standalone biomarker may be limited. However, when integrated with established parameters such as PSA and Gleason score, IL-6 has the potential to enhance diagnostic and prognostic accuracy. This combined biomarker approach may improve patient stratification, facilitate early identification of aggressive disease, and support personalized clinical decision-making.

Limitations

Several limitations of this study should be acknowledged. First, the relatively small sample size (n = 50) may limit the generalizability of the findings and reduce statistical power for detecting subtle associations. Second, the cross-sectional study design precludes the establishment of causal relationships and limits the ability to assess longitudinal changes in IL-6 levels over the course of disease progression. Third, although efforts were made to minimize confounding by excluding patients with inflammatory and autoimmune conditions, residual confounding factors cannot be entirely ruled out. Additionally, IL-6 levels may be influenced by subclinical inflammation or other unmeasured variables.

Another limitation is the reliance on a single-center study setting, which may introduce selection bias and limit external validity. Variability in laboratory techniques and assay sensitivity may also affect the reproducibility of IL-6 measurements across different settings. Finally, the study did not evaluate additional inflammatory or molecular biomarkers, which could have provided a more comprehensive understanding of the tumor microenvironment and strengthened the biomarker model.

Future studies should involve larger, multi-center cohorts with longitudinal follow-up to validate these findings and explore the dynamic role of IL-6 in disease progression. Integration with other biomarkers and advanced molecular profiling may further enhance its clinical applicability.

Conclusion

This study demonstrates that plasma IL-6 levels are significantly elevated in metastatic prostate cancer and show positive correlations with PSA levels and Gleason scores. These findings highlight the potential of IL-6 as a complementary biomarker for assessing disease progression and tumor aggressiveness. While IL-6 alone may lack specificity, its integration with established clinical parameters could improve prognostic accuracy and support more informed clinical decision-making.

Authors' Contributions:

All authors meet the ICMJE criteria for authorship.

Author 1: Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 2: Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 3: Analysis and interpretation of data, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 4: Analysis and interpretation of data, critical revision, final approval, agreed to be accountable for all the work.
Author 5: Substantial contribution to conception and design, drafting the manuscript, final approval, agreed to be accountable for all the work.
Author 6&7: Substantial contribution to conception and design, data acquisition, drafting the manuscript, final approval, agreed to be accountable for all the work.

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