Association of some immunological indicators in patients with prostate cancer and UTI

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ABSTRUCT
Prostate cancer is the most common cancer among men in many countries. Urinary tract infections and chronic inflammation can accelerate prostate carcinogenesis. These disorders are caused by important microorganisms that are linked to carcinogenesis. This leads to the stimulation of inflammatory cytokines resulting from exposure to microbial agents. According to the study's findings, all of the markers—CXCL12, TLR-4, IL-6, and IL-8—were significantly higher in prostate patients than in controls, with the greatest levels seen in individuals who had urinary tract infections and prostate disorders. Given their critical involvement in inflammation and immune cell recruitment during infection, they direct attention to the possible application of these proteins in the detection of infection in prostate disorders. Additionally, they highlight how these indicators may be used in clinical diagnosis, particularly in the categorization of prostate illnesses according to the degree and condition of infection.
According to these results, These findings suggest that the combination of these immune markers could be very useful in distinguishing between simple prostate problems and those aggravated by infection.

Introduction

One of the most common causes of mortality and morbidity amongst men is prostate cancer (Ou etal.,2018). Prostate cancer incidence varies among populations, with higher rates in developed countries. Risk increases with age, family history, genetic mutations, and race. (Litwin and Tan,2017; Rawla,2019).

Prostate cancer can remain within the prostate gland for years and grow slowly, but in some cases, it may spread to nearby tissues and distant organs. Advanced or metastatic disease results. Prostate cancer can manifest in various ways, including issues with urination, blood in urine or semen, and sexual performance issues like impotence (Rawla,2019; Taitt,2018).

The urinary microbiota, a unique community of microbial species, is influenced by host genetics, immune responses, and environmental factors, potentially affecting disease processes in the bladder and surrounding tissues (Colella *et al.*,2023; Perez-Carrasco *et al*.2012). Studies show dysbiosis in urine can be linked to urological diseases like urinary tract infections and prostate cancer, with variations in urine microbe composition potentially affecting disease pathogenesis and clinical outcomes (Choi *etal*.,2023).

Factors like autoimmune diseases, infections, obesity, smoking, asbestos exposure, and excessive alcohol consumption also increase cancer risk (Zhao *et al*.,2021) .

The immune system uses pattern recognition receptors (PRRs) to identify and prepare for infection, binding pathogens and initiating inflammation in macrophages, neutrophils, and dendritic cells. (Al-Wazni *etal*.,2021). In response to infections, TLR4 and its signaling pathways trigger the host's innate immune system , leading in the production of pro-inflammatory cytokines including IL-6, TGF-β1, TNF-α, and IL-1β as well as the expression of antiapoptotic proteins (Kim *etal*.,2013). Both healthy and cancerous prostate epithelial cells express Toll-like receptor (TLR) 4 (Ou *etal*.,2018).

Cytokines, small messengers secreted by immune and tumor cells, are crucial in host defense and cancer development. They influence immune function, cell damage, inflammation, angiogenesis, metastasis, and tumor survival, impacting the tumor environment (Morris. *etal*.,2022).

Chemokines play a crucial role in tumor development, influencing immune cell infiltration, growth, angiogenesis, and metastasis (Chow *etal*.,2014) by controlling tumor cell proliferation, invasiveness, and metastasis, they alter tumor progression and metastasis. (Nagarsheth *etal*.,2017). In prostate cancer, cytokines and chemokines, including IL-6, CXCL8, and CXCL12, significantly influence tumor growth, invasiveness, and metastasis (Vindrieux *etal*.,2009). Stromal and endothelial cells release CXCL12, which modulates tumor adhesiveness and motility and is crucial for prostate tumor cell homing, re-establishment, and proliferation in metastatic sites. (Gladson and Welch,2008).

The aim of this study was to investigate the relationship between some variation of Immunological indicators and development of prostate cancer in patients with urinary tract infection .

MATERIALS AND METHODS

This study included collecting 120 blood samples from men over 45 years of age. The samples were distributed among 30 patients with prostate cancer , 30 patients with prostate cancer and UTI , 30 patients with urinary tract infections only in addition to 30 samples from healthy men as control group collected from Imam Hassan Al-Mujtaba and Imam Zain Al-Abidin Hospital during the period from January 7th (2024) to the end of October (2024) .

Venous blood samples (5 ml) were taken from all patients and controls using disposable syringes. Five milliliters of blood were drawn from each subject's vein and placed in disposable tubes with gel. The blood was left in the tubes to clot at room temperature for ten to fifteen minutes before being centrifuged at 4000 rpm for four to five minutes. Serum was stored at −70°C until needed for immunological studies.

The levels of PSA, HKLK2, IL-6, IL-8, CXCL12, and TLR4 in the patients' serum were determined according to the manufacturer's instructions (bioassay) using enzyme-linked immunosorbent assay.

Ethics statement :

The Imam Hassan Al-Mujtaba and Imam Zain Al-Abidin Hospital in the Iraqi region of Karbala provided the ethical and scientific committee. Additionally, each patient and control group provided written informed consent before a blood sample was drawn.

Questionnaire

From the patients' case sheets, the following data was obtained: name, age, other diseases and medication.

Inclusion criteria

Patients who had just been diagnosed with prostate cancer diagnosis with or without urinary tract infection were included in the study groups and were asked to complete a questionnaire.

Exclusion criteria

Exclusion criteria included previous treatment for prostate cancer and patients with other autoimmune disease and acute infection.

Statistical Analysis

The study used IBM SPSS for statistical analysis, evaluating data normality and variance homogeneity using the Shapiro-Wilk and Levene tests. Chi-square tests and Pearson's correlation analyses were used to investigate relationships between categorical and numerical variables. Differences between independent groups were evaluated using Mann-Whitney U and Independent T-tests. ANOVA and Duncan's post-hoc tests were used for comparisons. ROC curve analysis was used to determine critical cut-off points and label significant findings.

Results and Discussion

Distribution of study groups by age

As shown in Table, the study found that the age group over 70 years old has the highest incidence of prostate cancer (51.9%), (48.5%), followed by the age group (61–70) years old (29.6%), (36.4%) and then the age group (45–60) years old (18.5%), (15.2%) for both groups of prostate cancer (1).

Table 1: Distribution of study groups According to the Age.

Age Group	Control	Prostate without UTI	Prostate with UTI	UTI	Total	P. value
45 - 60	33.3%	18.5%	15.2%	43.3%	27.5%	0.0796
61 - 70	40.0%	29.6%	36.4%	33.3%	35.0%	
> 70	26.7%	51.9%	48.5%	23.3%	37.5%	

The study's findings demonstrated that elderly males are primarily affected by prostate cancer, rarely affecting those under the age of 45, and the age group most affected by prostate cancer was the age group over 70 years. This is in agreement with findings made by Cao *et al*. (2021) that the incidence of prostate cancer rises significantly with aged and although it is a very rare disease in men under the age of 45 years, its incidence increases significantly after that . This has been confirmed by Ferrlay *et al.* (2015). Males under 40 are rarely affected by prostate cancer, however the prevalence increases dramatically beyond the age of 55. This is also in line with Belkahla *et al*. (2022) findings that the risk of prostate cancer rises rapidly beyond the age of fifty and that men over 65 account for around half of all cases, with a more severe overall survival rate. The high incidence of cancer in the elderly have lately been linked to aging as a chronic, systemic, low-grade inflammatory process (inflammation) (Franceschi et al., 2018; Nagai et al., 2021). Numerous factors are linked to age-related inflammation and, consequently, the development of cancer, including immunosenescence, cellular senescence, and long-term lifestyles. Aging-related senescent cells release inflammatory proteins that promote tumor growth, known as senescence-associated secretory phenotype (SASP) factors, which include IL-6 and IL-8 (Faget et al., 2019).

Level of PSA in study groups

The current study's findings showed that the serum PSA level had significantly increased at the probability level (0.0005) in individuals with prostate cancer in both groups (82.21±74.50) ng/ml and (99.10±76.82) ng/mL respectively in comparison to healthy individuals (0.99±0.58) ng/ml and the urinary tract infection group (1.39±1.08) as indicated in table (2):

Table (2): level of Prostate-Specific Antigen (PSA) in patients and their controls.

Groups	Mean	Std. Deviation	P. value	Duncan Post hoc Test
Control	0.99	0.58	0.0005	a
Prostate without UTI	82.21	74.50		b
Prostate with UTI	99.10	76.82		b
UTI	1.39	1.08		a

PSA values in those with prostate problems were significantly higher in the prostate groups than in the UTI and control. These findings are in line with those of Youssef *et al.* (2023), who discovered that serum PSA levels in patients with prostate cancer were (67.52 ± 123.66), and Ahmed *et al.* (2017), who discovered a significant difference in mean serum PSA levels between the patient group (25.7 ± 21.6) and control group (12.7 ± 6.9) ng/mL (P = 0.01). This is linked to the abnormal PSA flow into the bloodstream, which is caused on by the malignant epithelium's high PSA expression level and the structural abnormality of the prostate gland (Williams *et al*., 2007). The PSA test, which is among the most widely used laboratory tests, yields data that help identify prostate cancer early on. Prostate-specific antigen (PSA) is a protein that is only produced in very high amounts by the prostate gland.

Level of HK-2 in study groups

According to the table (3): The current study's findings demonstrated that both groups of prostate cancer patients had significantly higher levels of human kallikrein-2 (HK-2), those with prostate cancer without UTI and those with UTI (695.76 ± 210.24) (973.29 ± 249.98) respectively compared with the control group (13.37 ± 9.31) and the UTI group (137.61± 49.86).

Table(3) level of Human Kallikrein-2 (HK-2) in patients and their controls.

Groups	Mean	Std. Deviation	P. value	Duncan Post hoc Test
Control	13.37	9.31	0.0008	a
Prostate without UTI	695.76	210.24		c
Prostate with UTI	973.29	249.98		d
UTI	137.61	49.86		b

The prostate gland produces the majority of the human kallikrein 2 (KLK-2) that is then expelled from the body as a proenzyme and outside the cell is activated into active enzymes, making (Balk *et al*.,2003).

According to the study's findings, patients with prostate cancer had significantly greater HK-2 levels than those in the control groups. It can be utilized as a marker for prostate cancer as this is in line with earlier research that demonstrated that KLK-2 is markedly elevated in this form of cancer. Timirmand *et al*. (2014), Youssef *et al*. (2023), Stefan *et al*. (2004). Our findings also align with studies by Skorella *et al.* (2003) and Bashour and Dalla Maria *et al*. (2015), who

discovered that some kallikreins are high in several tumors, especially hK2, which is elevated in prostate cancer and can serve as a marker for this condition.

Level of TLR-4 in study groups

As shown in Table (4):): TLR-4 levels were consistently elevated in patients with prostate problems, with the highest levels in the group with a UTI (P = 0.0003) compared to those in the healthy group (0.93 ± 0.45). The study results also showed significant differences between patient groups, between prostate cancer patients alone (1.57 ± 0.39), prostate cancer patients with UTIs (1.65 ± 0.54), and prostate cancer patients with UTIs (2.72 ± 0.56).

Table(4): level of Toll Like Receptors (TLR-4) in patients and their controls.

Groups	Mean	Std. Deviation	P. value	Duncan Post hoc Test
Control	0.93	0.45	0.0003	a
Prostate without UTI	1.57	0.39		b
Prostate with UTI	2.72	0.56		c
UTI	1.65	0.54		a

The findings revealed a significant difference between patients with prostate cancer and those with UTI in prostate cancer, as well as a substantial increase in TLR4 concentration in prostate cancer patients compared to healthy individuals (P value = 0.0003). According to Zhao *et al*. (2014), functional expression of TLRs has been linked to the progression of prostate cancer. TLRs may play a dual role in the development of prostate cancer by either promoting the growth of tumors and the malignant transformation of epithelial cells or, on the other hand, inducing apoptosis and preventing the progression of tumors. This was demonstrated by Ou *et al.* (2018), who found that the expression was elevated in prostate tissues.

One of the main sensors of Gram-negative bacterial LPS is the TLR4 complex, which can also be triggered by different endogenous danger-associated molecules (DAMPs) that are generated from lytic cells in response to viral infection or host tissue damage (Heine etal., 2022).Both normal and cancerous prostate epithelial cells express TLR4. Innate immune responses to invasive infections are triggered by prostate cells' activation of TLR4 signaling. Prostate epithelial cells' long-term stimulation of the TLR4 cell signaling pathway, however, may encourage the activation, growth, survival, and transformation of tumor cells. Oncogenic herpesvirus infection is facilitated by the microbial products lipoteichoic acid and LPS from pathogenic bacteria (Dai *etal*.,2014; Gonzalez-Reyes S *etal*.,2011).

This is what Gatti et al. (2006) pointed out.The complicated situation that results from TLR activation in tumor cells and its activation in the tumor microenvironment, such as in normal

innate immune cells, establishes the part that TLRs play in the development of prostate cancer. Th1 and T cytotoxic responses or Th2 and Treg responses can result from TLR activation in antigen-presenting cells such DCs, macrophages, and B cells. Prostate cancer cells' TLR2, 4, and 9 activations tend to encourage the formation of tumors.

Level of in IL-6 and IL-8 study groups

As shown in table (5), IL-6 levels are significantly greater in patients with prostate problems, especially those who also have an accompanied UTI than in the control group (55.95± 4.99). IL-6 levels were highest in the prostate with UTI group (116.43±44.06), followed by the prostate without UTI group (76.54±13.64) and the UTI group (65.46±6.35).

Table(5): level of Stratified by Interleukin 6 (IL-6) in patients and their controls.

Groups	Mean	Std. Deviation	P. value	Duncan Post hoc Test
Control	55.95	4.99	0.0003	a
Prostate without UTI	76.54	13.64		b
Prostate with UTI	116.43	44.06		c
UTI	65.46	6.35		ab

According to Table (6), the results of the study showed that the concentration of IL-8 was significantly higher in patients with prostate cancer compared to the groups with urinary tract infections (94.33±8.73) and healthy individuals (48.97±16.98) at the probability level (0.0003). It also showed significant differences between the patient groups, especially between those with prostate cancer and urinary tract infections (172.11±41.00) and those with prostate cancer only (125.76±38.23).

Table (6) level Interleukin 8 (IL-8) in patients and their controls.

Groups	Mean	Std. Deviation	P. value	Duncan Post hoc Test
Control	48.97	16.98	0.0003	a
Prostate without UTI	125.76	38.23		c
Prostate with UTI	172.11	41.00		d
UTI	94.33	8.73		b

The results of the study showed that the p-value (0.0003) for IL-6 and IL-8 was higher in prostate cancer patients than in controls. The study results are consistent with the study conducted by Katongole *etal.* (2022) were showed that Prostate cancer patients had significantly higher levels of the cytokines IL-6 and IL-8. Elevations of plasma prostate-specific antigen were substantially correlated with rising IL-6 and IL-8 levels ($p < 0.05$). A study by Ma *et al*. (2015) found that serum levels of the cytokines TNF-α, IL-6, and IL-8 were greater in prostate cancer patients than in controls. The occurrence of metastases, PSA level, and disease stage were all

associated with this. Further studies have shown that elevated pre-operative blood PSA levels are associated with advanced clinical stage and elevation of TNF-α, IL-1, IL-6, and IL-8 Murphy *et al*. (2005) Rodriguez-Berriguete *et al*. (2013). Tissue growth depends on IL-6, which also makes it more likely for cancer cells to spread. (Weber *et al*., 2021).

Level of CXCL12 in study groups

According to table (7), the study's findings showed that the prostate with UTI group (79.75±29.04) and patients with prostate only (62.12±24.46) had higher levels of the chemokine CXCL12 at the probability level (0.0002) than the control group (30.42±4.19) and UTI groups (34.87±5.01).

Table(7) level Chemokine (CXCL12) in patients and their controls.

Groups	Mean	Std. Deviation	P. value	Duncan Post hoc Test
Control	30.42	4.19	0.0002	a
Prostate without UTI	62.12	24.46		b
Prostate with UTI	79.75	29.04		c
UTI	34.87	5.01		a

According to the present investigation, prostate cancer cells have higher levels of the chemokine CXCL12. Elevated levels of CXCL12 were also observed by Sun et al. (2003), Mochizuki et al. (2004), and Xing et al. (2008). Prostate cancer overexpresses CXCL12 and CXCR4, and through its modulatory effects on tumor adhesion and migration, CXCL12 plays an important role in the homing, repopulation, and dissemination of prostate tumor cells to metastatic areas (Gladson et al., 2008). The homing of cancer cells from the breast and prostate to bone has been linked to the CXCL12/CXCR4 axis because of aberrant expression of the CXCR4 receptor for the CXCL12 chemokine. In contrast to normal tissue, PC metastatic tissue has an overexpression of the chemokine CXCL12. It has been demonstrated that the CXCL12/CXCR4 axis is crucial for PC cell invasion, migration, and proliferation(Singareddy *etal*., 2013; Cojoc, Monica, *etal*.,2013 ;Conley-LaComb *etal*.,2016). The results of the current investigation showed Our findings support the previously proposed theory that increased expression of CXCL12 and CXCR4 is linked to a higher risk of cancer.

Correlations of immunological marker in patients

Age and vital signs: Table (8) shows that there is no statistically significant correlation between age and other markers such as PSA, TLR-4, IL-6, and IL-8 ($P > 0.05$), but there is a weak positive correlation between age and the chemokines CXCL12 ($r = 0.218$, $p = 0.039$) and human

kallikrein 2 (HK-2) (r = 0.284, p = 0.007), suggesting that the levels of these markers rise slightly with age. Although some biomarkers might change as people age, others might not be as impacted, suggesting that they could be used as indications that are not influenced by age.

Table(8): Correlation Coefficient Among Research Parameters of **all Patients**

Parameters	Value	Prostate-Specific Antigen (PSA)	Human Kallikrein-2 (HK-2)	Chemokine (CXCL12)	Toll Like Receptors (TLR-4)	Interleukin 6 (IL-6)	Interleukin 8 (IL-8)
Age	R value	0.173	0.284**	0.218*	0.090	0.119	0.124
	P. value	0.103	0.007	0.039	0.399	0.266	0.246
Prostate-Specific Antigen (PSA)	R value	1	0.469**	0.324**	0.165	0.405**	0.361**
	P. value		0.000	0.002	0.121	0.000	0.000
Human Kallikrein-2 (HK-2)	R value		1	0.772**	0.643**	0.689**	0.828**
	P. value			0.000	0.000	0.000	0.000
Chemokine (CXCL12)	R value			1.000	0.514**	0.655**	0.732**
	P. value				0.000	0.000	0.000
Toll Like Receptors (TLR-4)	R value				1	0.611**	0.607**
	P. value					0.000	0.000
Interleukin 6 (IL-6)	R value					1	0.703**
	P. value						0.000

Pearson and Spearman's correlations were performed to assess the association strength and direction between the two continuous variables.
**. Correlation is significant at the 0.01 level
. *. Correlation is significant at the 0.05 level.

PSA Correlations: Many markers show relatively favorable correlations with PSA, including HK-2 (r = 0.469, p < 0.001), CXCL12 (r = 0.324, p = 0.002), IL-6 (r = 0.405, p < 0.001), and IL-8 (r = 0.361, p < 0.001). Since there is no discernible correlation between PSA and TLR-4, it is possible that TLR-4 functions independently of PSA levels in these patients. These correlations indicate that when PSA levels increase, correspondingly rise levels of these indicators. Since PSA and TLR-4 do not significantly correlate, it is possible that TLR-4 functions in these patients irrespective of PSA levels. According to Katongole *et al*. (2020), prostate cancer patients had significantly higher plasma levels of the proinflammatory cytokines IL-6 and IL-8 compared to controls. High levels of prostate plasma were significantly associated with elevated levels of IL-6 and IL-8.

Human Kallikrein-2 (HK-2) Correlations: With p values less than 0.001, human kallikrein 2 exhibits a strong connection with TLR-4 (r = 0.643), IL-6 (r = 0.689), IL-8 (r = 0.828), and CXCL12 (r = 0.772). Human kallikrein 2 exhibits a high correlation with TLR-4, IL-6, IL-8, and CXCL12, among other indicators. Given its close association with markers linked to

immunological and inflammatory responses, this strong correlation pattern highlights the relevance of human kallikrein 2 as a key biomarker associated with prostate disorders.

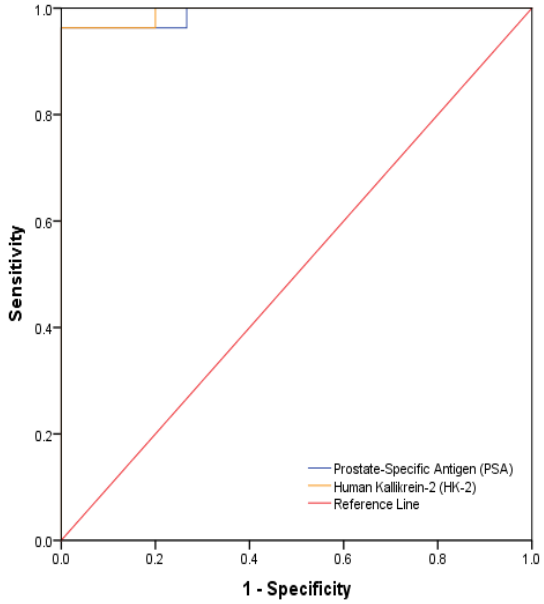
Chemokine (CXCL12) Correlations: At the 0.01 level, CXCL12 had statistically significant correlations with TLR-4 (r = 0.514), IL-6 (r = 0.655), and IL-8 (r = 0.732). This suggests that CXCL12 may be involved in pathways associated with immune signaling, as reflected by its association with markers such as IL-6 and IL-8, which are known to play a role in inflammation and cellular immune responses.

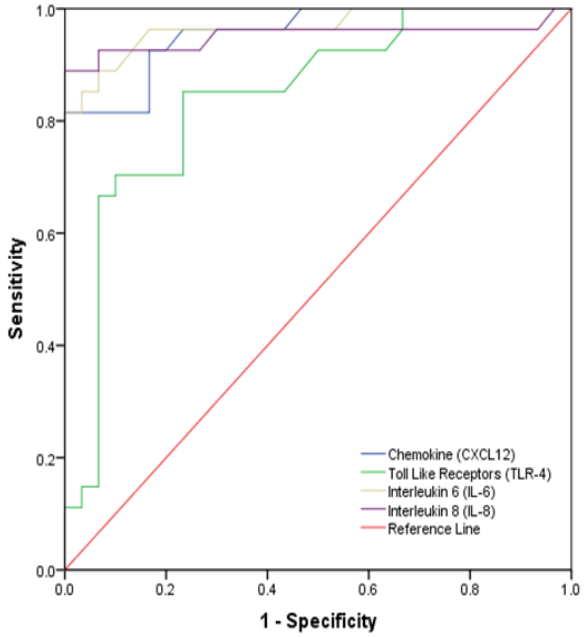
Associations of interleukin markers (IL-6, IL-8) and TLR-4: there is a strong association between IL-6 and IL-8 (r = 0.703), and both IL-6 and IL-8 exhibit significant affinity with TLR-4 receptors (r = 0.611 and 0.607, respectively) which strengthens the association between these cytokines and innate immune response mechanisms, as TLR-4 are key receptors involved in cell activation . The strong correlation of IL-6 and IL-8 suggesting that these interleukins may act in tandem within inflammatory pathways associated with prostate disease. This is what (Nunzio *et al*., 2011) suggested. The development and spread of prostate cancer are mediated by the TLR cytokines IL-6, IL-8, and IL-10. Furthermore, through enhanced TLR4 expression and the production of pro-inflammatory mediators, prostate epithelial cells respond to TLR4 ligand activation by upregulating NF-κB, TGF-β1, and VEGF (Gonzalez-Reyes *et al*., 2011). Certain TLR4 cytokines (like IL-8) were discovered to be more abundant in prostate cancer tissues than in non-tumor control tissues. This implies that prostate cells suffer from persistently elevated levels of inflammation due to endogenous TLR4 ligands produced by injured cells and bacterial byproducts like LPS (Hochreiter *etal*., 2000; Ou *etal*.,2018)..

HK-2 shows promise as a reliable measure of immunological activity and illness severity due to strong associations with other indications. The somewhat positive correlations between PSA and other markers such as HK-2, CXCL12, IL-6, and IL-8 suggest that PSA may be a part of a broader inflammatory response associated with prostate disease. However, there is no significant correlation between PSA and TLR-4. These findings provide valuable guidance for understanding the use and interactions of biomarkers in the diagnosis and treatment of prostate disease and suggest that a multi-marker approach may increase the precision of disease .

The model predicts the working characteristic curves of the subjects based on the immunological indicators for the prostate group.

As show in figure (1) and figure (2)





The exceptionally high AUCs of PSA and HK2 (99.000% and 99.300%, respectively), IL-6 (96.605%), IL-8 (95.185%), and CXCL12 (95.670%) are strong predictors. The 95% CIs provide a level of confidence in each marker's predictive power. Notably, a high degree of diagnostic accuracy is demonstrated by the upper limits of 1.000 for PSA, HK2, IL-6, and IL-8. TLR-4's broader confidence interval (0.737 to 0.948) indicates that it is less predictive than other markers, despite having a lower AUC (84.259%).It is still predictably within a reasonable range.

PSA and HK2 are the most effective markers for prognosticating prostate disease, with near-perfect AUC, high sensitivity, and specificity, making them excellent tools for initial detection and confirmation. CXCL12, IL-6, and IL-8 also provide strong predictive ability and maintain high accuracy and PPV/NPV values. Although TLR-4 is statistically significant, it shows slightly lower reliability compared to the other markers due to its lower specificity and wider confidence intervals. These results underscore the potential of a multi-marker approach to improve diagnostic accuracy, especially when markers such as PSA, HK2, and CXCL12 are used in combination.

Conclusion

According to the study, PSA and HK2 tests are a common test for diagnosing prostate cancer since they are easy to use and non-invasive. While IL-6 ,IL-8 and CXCL12 concentrations are promising biomarkers more research is needed to validate their predictive usefulness. Prostate cancer is diagnosed early using a variety of indicators. The ability to improve diagnostic accuracy by combining multiple markers demonstrates the potential of a multi-marker approach.

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