RESEARCH ARTICLE

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Evaluation of S100A4, CA-12, CA-9, Annexin A1/A2, and Galectin-3 in Prostate Cancer: Diagnostic and Prognostic Implications

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Abstract

Objective: The limited specificity of prostate-specific antigen (PSA) increases the risk of unnecessary biopsies and overtreatment. This study aimed to evaluate the diagnostic and prognostic value of serum S100A4, along with CA-9, CA-12, Annexin A1/A2, and Galectin-3, in prostate cancer. **Methods:** This prospective case–control study, conducted between July 2024 and September 2025, included 80 patients with histopathologically confirmed prostate cancer and 40 age-matched healthy controls. Patients were stratified into low-risk (ISUP grades 1–2) and high-risk (ISUP ≥3) groups. Serum biomarker levels were measured using ELISA. Diagnostic and prognostic performance was assessed by receiver operating characteristic (ROC) analysis, with cut-off values determined using the Youden index. Logistic regression analyses were performed to identify independent biomarkers. **Results:** Serum CA-12 and CA-9 levels were significantly higher in prostate cancer patients than in controls ($p = 0.004$ and $p = 0.032$, respectively). Although S100A4 levels were lower in prostate cancer patients compared with controls, they were significantly higher in high-risk patients within the cancer cohort ($p = 0.002$). Logistic regression identified S100A4 ($p = 0.032$) and CA-12 ($p = 0.004$) as independent predictors of prostate cancer diagnosis. ROC analysis demonstrated excellent diagnostic accuracy for CA-12 (>52.9 ng/mL; AUC = 0.99) and S100A4 (<9.96 ng/mL; AUC = 0.98). For prognostic stratification, S100A4 (>8.27 ng/mL; AUC = 0.97) and CA-12 (>72.8 ng/mL; AUC = 0.91) effectively distinguished high-risk from low-risk disease. **Conclusion:** S100A4 and CA-12 exhibit strong diagnostic and prognostic performance in prostate cancer. When used alongside PSA, S100A4 and CA-12 may improve risk stratification in patients with suspected prostate cancer and help reduce unnecessary prostate biopsies.

Keywords: Annexin A1, Annexin A2, Biomarkers, Tumor, Carbonic Anhydrases, Prostatic Neoplasms, S100A4 Protein

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Introduction

Prostate cancer is one of the most commonly diagnosed malignancies in men worldwide and remains a leading cause of cancer-related mortality [1]. Prostate-specific antigen (PSA) testing is widely used for screening and early detection; however, its limited specificity results in false-positive findings in benign conditions such as benign prostatic hyperplasia and prostatitis, leading to unnecessary biopsies and potential overtreatment [2]. Therefore, there is an ongoing need for novel biomarkers that can improve diagnostic accuracy and better distinguish clinically significant disease.

Recent research has focused on molecular biomarkers reflecting key biological processes involved in prostate cancer progression, including hypoxia, tumor invasion, and metastatic potential. S100A4 is a calcium-binding protein associated with epithelial–mesenchymal transition and tumor aggressiveness, and increased expression has been linked to poor prognosis in prostate cancer [3, 4]. Carbonic anhydrase isoenzymes, particularly CA-9 and CA-12, are induced under hypoxic conditions and play a role in intracellular pH regulation and tumor cell survival [5, 6]. Annexin A1 and Annexin A2 participate in membrane organization and inflammatory signaling and have been implicated in prostate cancer biology with variable expression according to disease stage [7, 8]. Galectin-3 is involved in cell adhesion and immune modulation, but its role as a reliable serum biomarker in prostate cancer remains controversial [9].

We aimed to evaluate the diagnostic and prognostic value of serum S100A4, CA-9, CA-12, Annexin

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A1, Annexin A2, and Galectin-3 in patients with prostate cancer. Specifically, we sought to determine whether S100A4 and CA-12 provide additional clinical information beyond PSA and whether these biomarkers could contribute to improved risk stratification between low-risk and high-risk disease.

Materials and Methods

Study Design and Ethical Approval

This prospective case–control study was conducted after approval by the Clinical Research Ethics Committee of Van Yüzüncü Yıl University Faculty of Medicine (Decision No: 001, April 17, 2024). Written informed consent was obtained from all participants prior to enrollment. The reporting of this study was guided by the REMARK recommendations for tumor biomarker studies.

Study Population and Risk Stratification

Between July 2024 and September 2025, 80 patients aged 45–70 years with histopathologically confirmed prostate cancer were prospectively enrolled. Patients were stratified according to the International Society of Urological Pathology (ISUP) grading system. Those with ISUP grades 1–2 were classified as the low-risk group, while patients with ISUP ≥3 were categorized as the high-risk group. A flow diagram summarizing patient selection and study design is provided in Figure 1.

The control group consisted of 40 age-matched healthy volunteers without a history of prostate cancer. All controls underwent PSA testing, digital rectal examination, urinary system ultrasonography, and urinalysis; individuals with abnormal findings were excluded. Participants with diabetes mellitus, chronic kidney disease, chronic inflammatory or rheumatologic disorders, cardiovascular disease, any malignancy other than prostate cancer, or use of immunosuppressive medications were excluded from the study.

Clinical and Pathological Evaluation

Prostate cancer diagnosis was established by transrectal ultrasound-guided prostate biopsy. Tumor staging and grading were performed in accordance with the European Association of Urology (EAU) and World Health Organization (WHO) guidelines. Clinical and pathological data were prospectively recorded.

Serum Sample Collection and Storage

Peripheral venous blood samples (5 mL) were obtained from all participants under fasting conditions in the morning and collected into standard biochemical tubes. Samples were centrifuged at 3500 × g for 10 minutes, and separated serum aliquots were stored at −80 °C until analysis.

Biomarker Measurements (ELISA)

Serum CA IX, CA XII, Annexin A2, S100A4, and Galectin-3 levels were measured in duplicate using commercially available human enzyme-linked immunosorbent assay (ELISA) kits. All assays were performed according to the manufacturers' instructions. To ensure reproducibility, the specific catalog and lot numbers for the kits were as follows: CA IX (Cat. No: YLA3010HU, Lot: YL0129NG), CA XII (Cat. No: YLA4583HU, Lot: YL1738395), Annexin A2 (Cat. No: YLA0058HU, Lot: YLOWKMC), and S100A4 (Cat. No: YLA4563HU, Lot: YL182NV8) from Shanghai YL Biotech Co., Ltd (Shanghai, China); and Galectin-3 (Cat. No: ABT1857Hu, Lot: KD724450107821) from Atlas Biotechnology (Ankara, Turkiye).

Statistical Analysis

Statistical analyses were performed using SPSS software (version 26.0; SPSS Inc., Chicago, IL, USA). Normality of continuous variables was assessed using the Shapiro–Wilk test, and homogeneity of variances was evaluated by Levene's test. Descriptive statistics are presented as mean ± standard deviation.

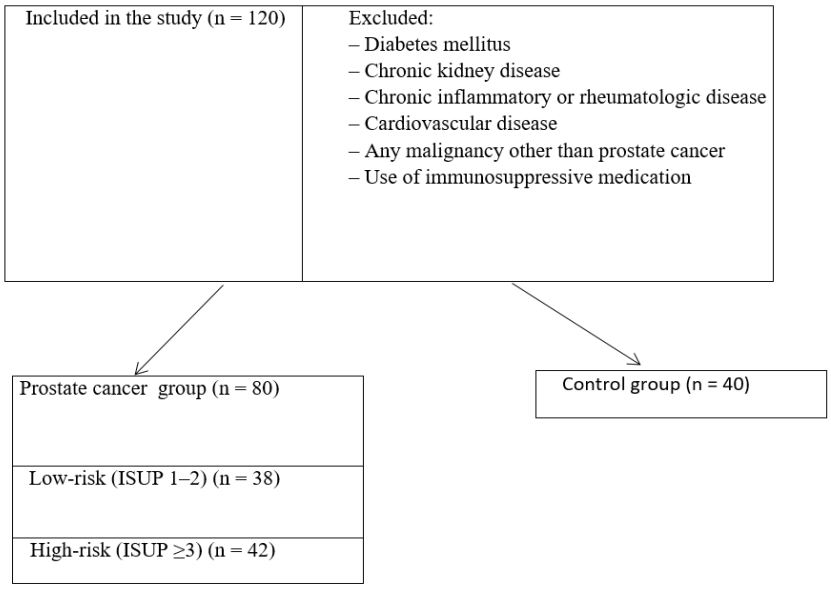

Figure 1. Flow Diagram of Patient Selection and Study Design

Group comparisons were conducted using one-way analysis of variance (ANOVA). Tukey HSD or Games–Howell post-hoc tests were applied when appropriate. Effect size (η^2) was estimated based on pilot data, and power analysis was reported with $\alpha=0.05$ and $1-\beta=0.95$. This study was designed as an exploratory biomarker investigation.

Logistic regression analyses were performed to identify independent biomarkers associated with prostate cancer diagnosis and risk stratification. Age, PSA level, tumor size, and tumor stage were included as covariates in multivariable models due to their clinical relevance. Multicollinearity was assessed using variance inflation factor (VIF), with all variables demonstrating VIF values below 2. Model fit was evaluated using the Hosmer–Lemeshow test, and results were reported as adjusted odds ratios (ORs) with 95% confidence intervals.

Receiver operating characteristic (ROC) analysis was used to assess diagnostic and prognostic performance. Cut-off values were determined using the Youden index. Area under the curve (AUC), sensitivity, and specificity were calculated. A two-sided p value <0.05 was considered statistically significant.

Results

No significant differences were observed between prostate cancer patients (n=80) and healthy controls (n=40) with respect to age, body mass index, or smoking status (all p>0.05). Demographic characteristics are presented in Table 1.

Clinicopathological features of low-risk (ISUP 1–2) and high-risk (ISUP ≥3) prostate cancer patients are summarized in Table 2. Patients in the high-risk group had significantly higher PSA levels, larger tumor size, and a greater number of tumor foci compared with the low-risk group (p<0.001, p=0.012, and p=0.008, respectively).

Comparisons of serum biomarker levels among study groups are shown in Table 3 and Figure 2. Annexin A1 and Annexin A2 levels were significantly higher in the low-risk prostate cancer group than in both the high-risk group and controls (p<0.001). No significant differences

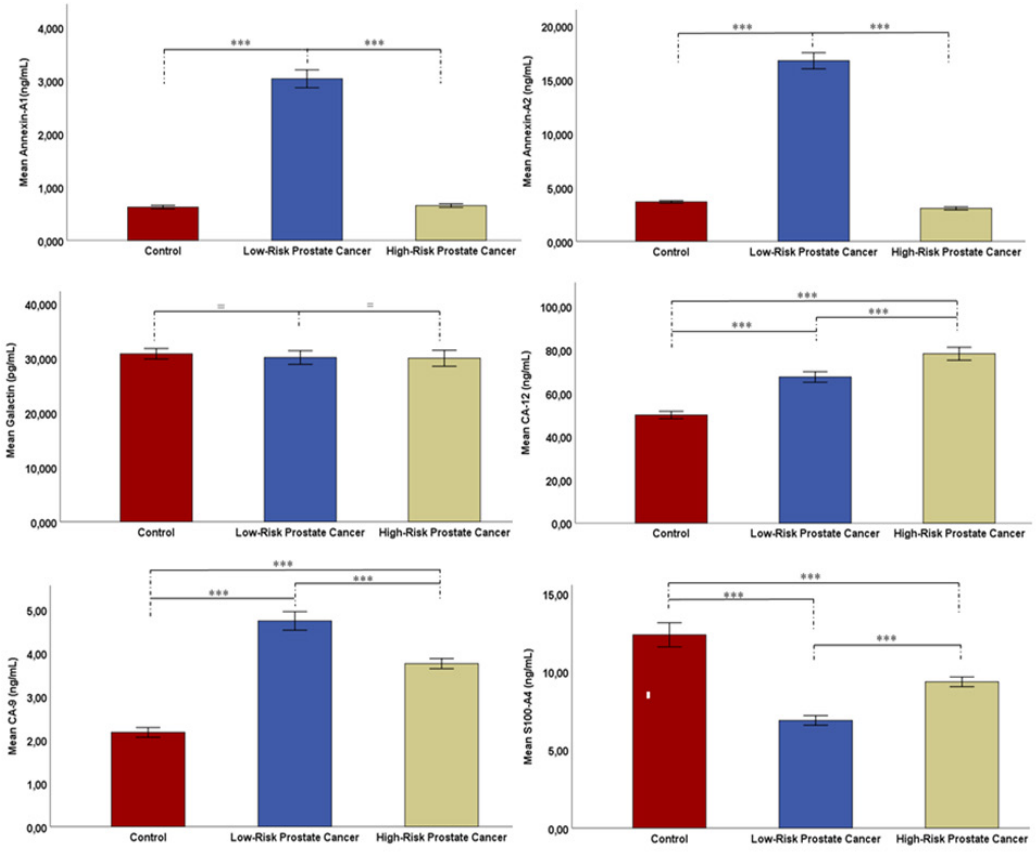

Figure 2. Distribution of Mean Serum Biomarker Levels (± SD) among the Control Group, Low-Risk Prostate Cancer Group, and High-Risk Prostate Cancer Group, Including Post-hoc Pairwise Comparisons. Abbreviations: SD, standard deviation; ISUP, International Society of Urological Pathology.

Table 1. Demographic and Clinical Characteristics of Prostate Cancer Patients and Control Subjects

Variables	Prostate Cancer (n=80)	Control (n=40)	p-value
Age (years, mean ± SD)	62.8 ± 6.4	61.9 ± 5.8	0.512
Smoking Status (%)	46 (57.5)	18 (45.0)	0.218
Body mass index (kg/m², mean ± SD)	26.2 ± 3.1	25.7 ± 2.9	0.374

p-values were calculated using the independent samples t-test for continuous variables and the chi-square test for categorical variables..

Table 2. Pathological Characteristics of Patients with Prostate Cancer

Variables	Low-risk (ISUP 1–2) (n=38)	High-risk (ISUP ≥3) (n=42)	p-value
Age (years, mean ± SD)	61.7 ± 6.1	63.8 ± 6.7	0.264
PSA (ng/mL, mean ± SD)	7.2 ± 3.5	12.6 ± 5.8*	<0.001
Tumor size (cm, mean ± SD)	2.8 ± 1.1	4.1 ± 1.5*	0.012
Number of tumor foci (mean ± SD)	1.4 ± 0.6	2.2 ± 0.8	0.008

* Significantly higher compared with the low-risk group ($p < 0.05$); p-values were calculated using the independent samples t-test.

Table 3. Comparison of Descriptive Biochemical Parameters between Prostate Cancer Patients and Healthy Controls

Biomarkers/ Parameters	Control		Low-Risk Prostate Cancer		High-Risk Prostate Cancer		*p-value
	Mean	St D	Mean	St D	Mean	St D	
Annexin-A1 (ng/mL)	0.627	0.071	3.037	0.377	0.655	0.076	<.001
Annexin-A2 (ng/mL)	3.66	0.23	16.748	1.67	3.056	0.328	<.001
Galectin-3 (pg/mL)	30.791	2.16	30.101	2.795	29.968	3.28	0.607
CA-12 (ng/mL)	49.9	3.84	67.46	5.46	78.19	6.71	<.001
CA-9 (ng/mL)	2.17	0.25	4.74	0.48	3.75	0.26	<.001
S100-A4 (ng/mL)	12.36	1.73	6.89	0.69	9.35	0.7	<.001

p-values were calculated using one-way analysis of variance (ANOVA) followed by post-hoc Tukey or Games–Howell tests, as appropriate.

Table 4. Variables Associated with Prostate Cancer Diagnosis and Corresponding Odds Ratios

Parameters	Univariate Logistic regression OR (95%CI)	p-value
Annexin-A1 (ng/mL)	4.71 (0.821-7.654)	0.232
Annexin-A2 (ng/mL)	1.316 (1.056-1.641)	0.014
Galectin (pg/mL)	0.898 (.728-1.109)	0.318
CA-12 (ng/mL)	1.669 (1.182-2.357)	0.004
CA-9 (ng/mL)	5.71(1.025-9.25)	0.994
S100-A4 (ng/mL)	0.028 (0.001-0.729)	0.032

OR, Odds-Ratio; CI, Confidence interval; p-values were calculated using univariate logistic regression analysis

were observed between the high-risk group and controls for Annexin A1 or Annexin A2 (p>0.05).

Serum CA-9 and CA-12 levels were markedly elevated in both prostate cancer groups compared with healthy controls (p<0.001). When the cancer cohorts were compared, CA-9 levels were lower, whereas CA-12 levels were higher in the high-risk group (both p<0.001). Although S100A4 levels were significantly lower in prostate cancer patients than in controls (p<0.001), they were significantly higher in high-risk patients compared with low-risk patients within the cancer cohort (p<0.001). No significant differences in Galectin-3 levels were detected among the three groups (p>0.05).

Logistic regression analysis identifying biomarkers associated with prostate cancer diagnosis is presented in Table 4. Annexin A2, CA-12, and S100A4 were significantly associated with prostate cancer. Increases in Annexin A2 and CA-12 levels were associated with higher odds of prostate cancer, whereas lower S100A4 levels were associated with disease presence. Diagnostic performance was evaluated using ROC analysis (Table 5, Figure 3).

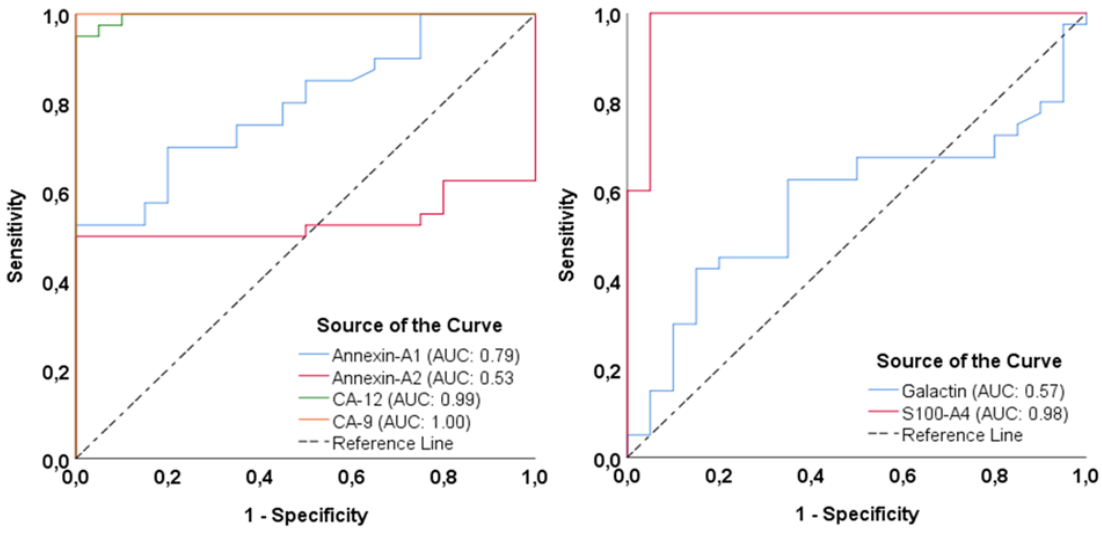

Figure 3. Receiver Operating Characteristic (ROC) Curves Demonstrating the Diagnostic Performance of Independent Serum Biomarkers in Distinguishing Prostate Cancer Patients from Healthy Controls. Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval.

Table 5. Diagnostic Performance of Independent Biomarkers for Distinguishing Prostate Cancer Patients from Healthy Individuals based on ROC-Derived Cut-off Values

Biomarkers/ Parameters	Cut-off values	AUC (%95 CI)	Std. Error	Asymptotic Sig.	Sensitivity	Specificity
Annexin-A1	> 0.668 (ng/mL)	0.796 (0.685-0.906)	0.056	<.001	0.7	0.8
Annexin-A2	- (ng/mL)	0.534 (0.385.-0.683)	0.076	0.672	-	-
Galectin-3	- (pg/mL)	0.573 (0.426-0.721)	0.075	0.359	-	-
CA-12	> 52.927 (ng/mL)	0.996 (0.988-1.000)	0.004	<.001	1	0.9
CA-9	> 2.935 (ng/mL)	1.000 (1.000-1.000)	<.001	<.001	1	1
S100-A4	< 9.960 (ng/mL)	0.980 (0.940-1.000)	0.02	<.001	1	0.95

AUC, Area under the curve; CI, Confidence. p-values were calculated using receiver operating characteristic (ROC) curve analysis

CA-12 (>52.927 ng/mL), CA-9 (>2.935 ng/mL), and S100A4 (<9.960 ng/mL) demonstrated high AUC values. Notably, CA-12 and S100A4 showed excellent sensitivity and specificity in discriminating prostate cancer patients from healthy individuals.

Logistic regression analyses for distinguishing high-risk from low-risk prostate cancer are summarized in Table 6. Increased CA-12 and S100A4 levels and decreased CA-9 levels were significantly associated with high-risk disease.

Prognostic performance assessed by ROC analysis is shown in Table 7 and Figure 4. CA-12 (>72.830 ng/mL), CA-9 (<4.077 ng/mL), and S100A4 (>8.275 ng/mL) demonstrated high accuracy in differentiating high-risk from low-risk patients. Although Annexin A1 and Annexin A2 exhibited mathematically high AUC values, they were not identified as independent predictors in regression analyses and were therefore considered of limited clinical utility.

Table 6. Variables associated with Prognosis (High-Risk vs. Low-Risk Prostate Cancer) and Corresponding Odds Ratios

	Univariate Logistic regression	
Biomarkers/ Parameters	OR (95%CI)	p-value
Annexin-A1 (ng/mL)	0.025 (0.000-0.107)	0.996
Annexin-A2 (ng/mL)	0.214 (0.041-0.753)	0.854
Galectin-3 (pg/mL)	0.985 (0.799-1.214)	0.887
CA-12 (ng/mL)	1.482 (1.148-1.914)	0.003
CA-9 (ng/mL)	0.020 (0.000-0.044)	0.006
S100-A4 (ng/mL)	201.136 (3.109- 13014.2)	0.002

OR, Odds-Ratio; CI, Confidence interval

Discussion

Prostate cancer exhibits marked biological heterogeneity, resulting in highly variable clinical behavior and outcomes. Although prostate-specific antigen (PSA) remains the cornerstone of prostate cancer screening, its limited specificity restricts its utility as a standalone diagnostic and prognostic tool [1, 2]. In this study, we evaluated multiple serum biomarkers and demonstrated that S100A4 and CA-12 provide meaningful diagnostic and prognostic information in prostate cancer.

S100A4 is a key regulator of epithelial–mesenchymal transition, cellular motility, and metastatic dissemination. Previous studies have linked increased S100A4 expression with aggressive tumor phenotypes and adverse outcomes in prostate cancer and other solid malignancies [3, 4, 8]. In the present study, serum S100A4 levels were lower in prostate cancer patients than in healthy controls, yet

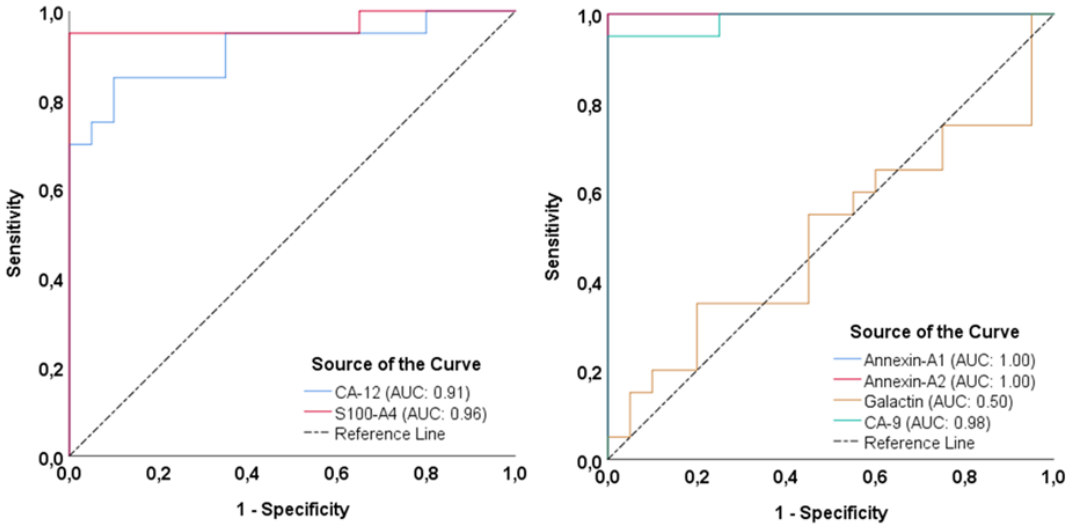

Figure 4. Receiver Operating Characteristic (ROC) Curves Showing the Prognostic Performance of Independent Serum Biomarkers in Distinguishing High-Risk Prostate Cancer Patients from Those with Low-Risk Disease. Abbreviations: ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; ISUP, International Society of Urological Pathology.

Table 7. Prognostic Performance of Independent Biomarkers in Distinguishing High-Risk Prostate Cancer Patients from Low-Risk Cases (ROC Analysis)

Biomarkers/ Parameters	Cut-off values	AUC (%95 CI)	Std. Error	Asymptotic Sig.	Sensitivity	Specificity
Annexin-A1	< 1.502 (ng/mL)	1.000 (1.000-1.000)	<.001	<.001	1	1
Annexin-A2	< 8.196 (ng/mL)	1.000 (1.000-1.000)	<.001	<.001	1	1
Galectin-3	- (pg/mL)	0.50 (0.316-0.684)	0.094	1	-	-
CA-12	>72.830 (ng/mL)	0.912 (0.818-1.000)	0.048	<.001	0.85	0.9
CA-9	< 4.077 (ng/mL)	0.988 (.960-1.000)	0.014	<.001	0.95	1
S100-A4	>8.275 (ng/mL)	0.967 (0.904-1.000)	0.033	<.001	0.95	1

AUC, Area under the curve; CI, Confidence; p-values were calculated using receiver operating characteristic (ROC) curve analysis.

significantly higher in high-risk patients within the cancer cohort. This bidirectional pattern suggests that S100A4 may reflect disease biology and risk status rather than serving as a simple presence marker. The strong diagnostic and prognostic performance observed in ROC analyses supports its potential clinical relevance for both disease detection and risk stratification.

CA-12 emerged as one of the most informative biomarkers in our analysis. Its excellent diagnostic and prognostic accuracy underscores the importance of hypoxia-related metabolic adaptation in prostate cancer progression. Carbonic anhydrase isoenzymes have been shown to facilitate tumor cell survival under hypoxic conditions and to contribute to tumor aggressiveness [5,6]. Although data regarding serum CA-12 levels in prostate cancer remain limited, our findings indicate that CA-12 may represent a clinically applicable biomarker that complements established diagnostic tools.

The findings related to CA-9 are consistent with previous reports suggesting a stronger association with early-stage or less aggressive disease [5]. Despite its high discriminatory performance in ROC analysis, CA-9 did not retain independent prognostic significance in regression models, limiting its value as a standalone biomarker. Annexin A1 and Annexin A2 levels were higher in low-risk patients, indicating a possible association with early tumor biology; however, their lack of independent predictive value suggests limited clinical applicability [7]. Serum Galectin-3 levels did not differ significantly among study groups, consistent with recent studies reporting conflicting or negligible associations with prostate cancer outcomes [2, 12].

In recent years, several biomarker strategies have been developed to overcome the limitations of PSA testing and improve prostate cancer detection and risk stratification. Urinary markers such as PCA3 and TMPRSS2–ERG fusion transcripts have demonstrated higher specificity than PSA, particularly in repeat biopsy settings [9]. Blood-based panels, including the 4Kscore and the Prostate Health Index (PHI), have shown improved accuracy in identifying clinically significant prostate cancer and reducing unnecessary biopsies, with multiple studies published between 2020 and 2024 reporting area under the curve values exceeding 0.70 [10- 12]. However, these assays are associated with increased cost and logistical complexity, and their availability varies across clinical settings. Compared with these approaches, our results indicate that combined assessment of serum S100A4 and CA-12 achieves comparable discriminative performance for identifying high-risk prostate cancer while also providing insight into underlying tumor biology. These findings suggest that S100A4 and CA-12 may serve as complementary biomarkers within existing risk assessment frameworks rather than as replacements for currently validated tests [13].

Several limitations of this study should be acknowledged. This was a single-center investigation with a relatively limited sample size. Biomarker measurements were restricted to serum samples, and tissue-based validation was not performed. Furthermore, long-term oncological outcomes and treatment response were not assessed. Therefore, the generalizability of these findings remains limited, and larger multicenter prospective studies are required to confirm the clinical utility of these biomarkers.

In conclusion, this study demonstrates that serum S100A4 and CA-12 exhibit strong diagnostic and prognostic performance in prostate cancer. When applied with appropriate cut-off values, these biomarkers may complement PSA, potentially reducing unnecessary biopsies and improving risk stratification. However, multicenter validation studies are required before these biomarkers can be incorporated into routine clinical practice.

Author Contribution Statement

Study design: R. Aslan, Z. Huyut, M.F. Keleş; Data collection: Data collection: M.F. Keleş, R. Eryılmaz, N. Bedir; Laboratory analysis: Z. Huyut, M. Saygın; Statistical analysis: M.T. Huyut; Manuscript drafting: M.F. Keleş; Critical revision and approval: All authors

Acknowledgements

Ethics Approval

Ethics approval was obtained from the Van Yüzüncü Yıl University Clinical Research Ethics Committee (Decision No: 001, Date: 17 April 2024).

Conflict of Interest

The authors declare no conflict of interest.

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