



The Prognostic Value of a Composite Score in Predicting Mortality Among Metastatic Castration-resistant Prostate Cancer Patients Treated with Enzalutamide

İlker Nihat ÖKTEN¹, Tuba BAYDAŞ¹, İbrahim ÇİL², Mehmet BEŞİROĞLU¹, Sinan KOCA¹

¹Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Medical Oncology, İstanbul, Türkiye

²University of Health Sciences Türkiye, Ümraniye Training and Research Hospital, Department of Medical Oncology, Ümraniye, İstanbul, Türkiye

ABSTRACT

Objective: This study aimed to develop a composite prognostic score using prostate-specific antigen (PSA) elimination rate, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), and albumin derived from routine blood biochemistry tests in patients with castration-resistant prostate cancer and to evaluate the prognostic value of this index for overall survival.

Material and Methods: This multicenter retrospective cohort study included 173 patients receiving enzalutamide treatment. The performance of PSA elimination rate, albumin/ALP ratio, and LDH/ALP ratio in mortality classification was evaluated using receiver operating characteristic analysis. The composite prognostic score was created by summing indices with significant area under the curve values. An increase in the score was interpreted as an increased mortality risk. The role of the composite score in predicting mortality was investigated.

Results: The mean age of the patients included in the study was 68.61±8.57 years (range: 43-87). PSA elimination rate, LDH/ALP ratio, and albumin/ALP ratio were found to be lower in the mortality group. The 10-year survival rate was 16.3% for patients with a composite prognostic score of 3, 32.3% for those with a score of 2, 46.5% for those with a score of 1, and 70.4% for those with a score of 0. The mean overall survival was 64.6 months for score 3, 99.6 months for score 2, 134.4 months for score 1, and 205 months for score 0 (p<0.001). Mortality risk was 2.85-fold lower in patients with a score of 1 [hazard ratio (HR): 0.35, p=0.001] and 2.56-fold lower in those with a score of 0 (HR: 0.39, p=0.036). In the Fagan nomogram, the post-test probability for the combined prognostic score was calculated as 68.1%.

Conclusion: Based on our findings, the developed composite prognostic score demonstrated significant potential for predicting mortality. The combined use of PSA elimination rate, LDH/ALP ratio, and albumin/ALP ratio improved mortality prediction accuracy. This composite prognostic score may assist clinicians in decision-making regarding treatment strategies.

Keywords: Prostate cancer; enzalutamide; biomarker

INTRODUCTION

Prostate cancer is the most common cancer in men and the second leading cause of cancer-related mortality. Approximately 27% of all new annual cancer cases and 11% of cancer-associated deaths in men are attributed to prostate cancer.¹ While the five-year survival rate exceeds 90% in localized prostate cancer, it decreases to 31% in advanced and metastatic stages.² Androgen deprivation

therapy (ADT) forms the basis of prostate cancer treatment. Currently, chemotherapy (docetaxel) and androgen receptor-targeted agents such as abiraterone acetate, enzalutamide, apalutamide, and darolutamide are used in combination with ADT.³ However, many patients eventually develop metastatic castration-resistant prostate cancer (mCRPC), which is associated with a poorer prognosis. Although most patients initially respond to ADT, progression to castration-resistant disease is common.⁴ Patients with high tumor burden

Correspondence: İlker Nihat ÖKTEN MD;

Göztepe Prof. Dr. Süleyman Yalçın City Hospital, Clinic of Medical Oncology, İstanbul, Türkiye

E-mail: ilkernihat@gmail.com

ORCID ID: orcid.org/0000-0003-2360-3392

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progress more rapidly to castration-resistant prostate cancer and have lower survival rates.⁵ Prognostic variables such as Gleason score or clinical stage may be used in mCRPC, but reliable and accurate prediction tools are still lacking.⁶

Recent studies have shown that routinely used diagnostic biomarkers such as serum alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and albumin have prognostic value in several cancer types.⁷⁻¹⁰ These markers are readily obtained from routine blood biochemistry tests and are currently evaluated as standard parameters for some cancer patients. Serum ALP is primarily secreted by osteoblasts, kidneys, the gastrointestinal tract, and other organs, and is considered an important indicator of bone metastases in cancer patients.¹¹ Serum albumin functions in maintaining plasma colloid osmotic pressure, nutrient transport, and antioxidant activity.¹² Studies have demonstrated that malnutrition may promote tumor growth and progression and negatively affect treatment response and survival. Reduced serum albumin levels are closely associated with poor prognosis in malignancies.^{13,14} LDH is an enzyme responsible for converting pyruvate to lactate during glycolysis. LDH levels are increased in tumor cells as a result of a metabolic shift toward anaerobic glycolysis and an adaptation to hypoxic conditions. Additionally, cancer cells rely on glucose to produce metabolites required for growth, invasion, angiogenesis, and metastasis. These mechanisms contribute to elevated serum LDH levels, making LDH a potential prognostic marker for tumor progression.¹⁵

Although these biomarkers have been widely investigated in malignant tumors, their prognostic value in castration-resistant prostate cancer has not been adequately explored.¹⁶ The aim of this study was to develop a composite prognostic score based on LDH, ALP, and albumin derived from routine blood biochemistry tests in patients with castration-resistant prostate cancer and to evaluate its prognostic significance for overall survival.

MATERIAL AND METHODS

This multicenter retrospective cohort study was conducted among patients receiving enzalutamide treatment for metastatic prostate cancer between 2017 and 2021 across twelve tertiary healthcare centers.

In the sample size analysis, assuming a Type I error of 0.05, a power of 95%, and an effect size $d=0.5$ with $N2/N1=1$, the minimum sample sizes required were calculated as $N1: 88$ and $N2: 88$, totaling 176 participants. Because no reference study was available for direct comparison in the literature, the effect size was considered moderate (0.5) according to Cohen's guidelines. During the study period, 320 patients

with prostate cancer were screened across 12 centers; 173 who met the inclusion and exclusion criteria were enrolled (Figure 1).

Inclusion criteria were as follows:

- Patients aged ≥ 18 years with histopathologically confirmed prostate adenocarcinoma.
- Patients meeting the diagnostic criteria for mCRPC, defined as biochemical and/or radiological progression despite continuous androgen suppression (luteinizing hormone-releasing hormone analog/antagonist or orchiectomy) with serum testosterone <20 ng/dL.
- Patients who received enzalutamide as first-line systemic therapy during the mCRPC stage.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 at treatment initiation.
- Availability of baseline prostate-specific antigen (PSA), Gleason score, complete blood count, ALP and LDH values, and adequate follow-up data for survival analysis at the start of enzalutamide therapy.

Exclusion criteria were as follows:

- Non-metastatic disease or non-mCRPC prior to developing castration resistance.
- Prior treatment during the mCRPC stage with second-generation androgen receptor pathway inhibitors (e.g., abiraterone, apalutamide, darolutamide) or chemotherapy before starting enzalutamide.

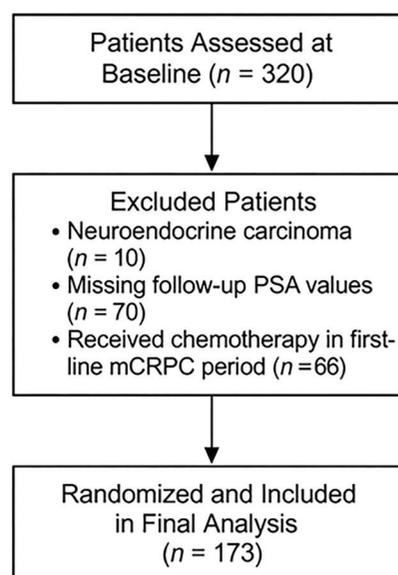


FIGURE 1: Consort diagram.

PSA: Prostate-specific antigen; mCRPC: Metastatic castration-resistant prostate cancer.

- Presence of small-cell/neuroendocrine morphology or dominant neuroendocrine component on pathology.
- History of another active malignancy (excluding non-melanoma skin cancers and appropriately treated *in situ* cancers with no recurrence).
- Missing baseline laboratory or follow-up data required for enzalutamide initiation, insufficient follow-up duration to allow survival evaluation, or restricted access to patient files.

The demographic and clinical characteristics of each patient were recorded retrospectively, including age, dates of diagnosis and metastasis, Gleason score, metastatic sites, ECOG performance status, treatment response, progression status, and survival outcomes. Laboratory parameters were obtained from measurements performed within 14 days prior to initiation of enzalutamide therapy. Baseline PSA, PSA nadir, LDH, ALP, and serum albumin levels were evaluated in all patients. Three biochemical indices—PSA ratio (baseline PSA/nadir PSA), albumin/ALP ratio, and LDH/ALP ratio—were calculated and used in prognostic analyses. The primary endpoint of the study was overall survival. Secondary endpoints included progression-free survival, treatment response, and the prognostic impact of the composite score. All data were anonymized, and the study was conducted in accordance with the Declaration of Helsinki after approval was granted by Marmara University Faculty of Medicine, Istanbul, Türkiye, number: 09.2024.911, date: 19.07.2024. Treatment protocol: Enzalutamide was administered orally at a dose of 160 mg daily.

Histopathological grading of prostate adenocarcinoma was performed using the Gleason scoring system, which is accepted as the gold standard for assessing tumor biology and prognosis. Specimens from all patients, obtained by biopsy or radical prostatectomy, were reviewed by experienced genitourinary pathologists. In the Gleason system, tumor architecture is classified into histological patterns graded from 1 to 5 based on their deviation from normal glandular architecture. For each case, the primary pattern, representing the most dominant tumor area, and the secondary pattern, representing the next most prevalent component, were identified. The Gleason score was calculated by summing

these two grades (e.g., 3+4=7). In the presence of high-grade components (grade 4 or 5), these were incorporated into scoring even if not predominant, in accordance with the International Society of Urological Pathology recommendations.

Gleason scores were further categorized according to widely accepted literature classifications:

- 6 (3+3): low-grade tumor
- 7 (3+4 or 4+3): intermediate-grade tumor, with prognostic differences depending on pattern distribution
- 8-10: high-grade tumors with aggressive biological behavior

Patients were considered to have mCRPC if biochemical and/or radiological progression occurred while maintaining serum testosterone levels below 20 ng/dL under continuous androgen suppression.¹⁷

PSA progression: At least three consecutive PSA elevations (measured ≥ 1 week apart) with an increase of ≥ 2 ng/mL

Radiological progression: Appearance of new lesions or enlargement of existing metastases

In the receiver operating characteristic (ROC) analysis evaluating the performance of PSA elimination rate (calculated as the ratio of baseline to nadir PSA), albumin/ALP ratio, and LDH/ALP ratio for mortality classification, all three indices demonstrated statistically significant area under curve (AUC) values, though with modest discriminatory power. The optimal cut-off values were determined to be 6.94 for PSA ratio (sensitivity 60%, specificity 73%, AUC: 0.688), 0.03 for albumin/ALP ratio (sensitivity 65%, specificity 74%, AUC: 0.703), and 1.95 for LDH/ALP ratio (sensitivity 60%, specificity 73%, AUC: 0.634). Values below these thresholds were associated with higher mortality risk (Table 1, Figure 2).

The composite score was generated by summing the indices that showed significant AUC values. For each marker, values below the determined cut-off were assigned 1 point (indicating higher mortality risk), whereas values above the cut-off were assigned 0 points. The total composite score ranged from 0 to 3. Higher scores reflected a greater mortality risk (Table 2).

TABLE 1: ROC analysis.

	Cut-point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Youden's index	AUC	p	DeLong test
1. PSA elimination ratio	<6.94	60	72.73	68	65.31	0.327	0.688	<0.001	1 vs. 2 p=0.785
2. Albumin/ALP	<0.03	64.71	73.86	70.51	68.42	0.386	0.703	<0.001	1 vs. 3 p=0.352
3. LDH/ALP	<1.95	62.35	61.36	60.92	62.79	0.237	0.634	<0.001	2 vs. 3 p=0.006

ROC: Receiver operating characteristic; PSA: Prostate-specific antigen; PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under the curve; ALP: Alkaline phosphatase; LDH: Lactate dehydrogenase.

Statistical Analysis

Statistical analyses were performed using JAMOVI software (version 2.6.17). Normality was assessed using the Kolmogorov-Smirnov test. Pearson chi-square test, Fisher's exact test, t-test, Kaplan-Meier survival analysis, and Cox regression analysis were used to evaluate the data. ROC analysis was used to assess the mortality classification performance of the indices, and the optimal cut-off value was determined using the Youden index and AUC. The DeLong test was applied to compare AUC values. A p-value <0.05 was considered statistically significant.

RESULTS

The mean age of patients included in the study was 68.61±8.57 years (range: 43-87). The proportion of patients

with disease progression and the proportion of those without pathological response were significantly higher in the deceased group. When index values were compared by survival status, baseline PSA, nadir PSA, and neutrophil-to-lymphocyte ratio were higher in the mortality group, whereas the baseline PSA/nadir PSA ratio, LDH/ALP ratio, and albumin/ALP ratio were lower (Table 3).

Analysis of survival durations and 1-, 3-, 5-, and 10-year survival rates, stratified by composite scores, revealed statistically significant differences between groups. Patients with a score of 3 had significantly shorter mean survival than those with scores of 0 and 1, and patients with a score of 2 had shorter mean survival than those with a score of 0. Ten-year survival rates were 16.3% for score 3, 32.3% for score 2, 46.5% for score 1, and 70.4% for score 0. Mean overall survival times were 64.6, 99.6, 134.4, and 205 months for scores 3, 2, 1, and 0, respectively (Table 4, Figure 3).

A Cox regression analysis created to predict mortality was statistically significant (p<0.001). Variables found to be significant in the model included Gleason score, composite score, and presence of progression. Patients with a Gleason score of 9-10 had a 1.69-fold higher mortality risk, while those with progression had a 4.69-fold higher mortality risk. Mortality risk was 65% lower in patients with a composite score of 1 [hazard ratio (HR): 0.35] and 61% lower in those with a score of 0 (HR: 0.39). In the Fagan nomogram, the post-test probability for the combined prognostic score was calculated as 68.1%. The pre-test mortality probability of 49% increased to 68.1% following the application of the model (Table 5, Figure 4).

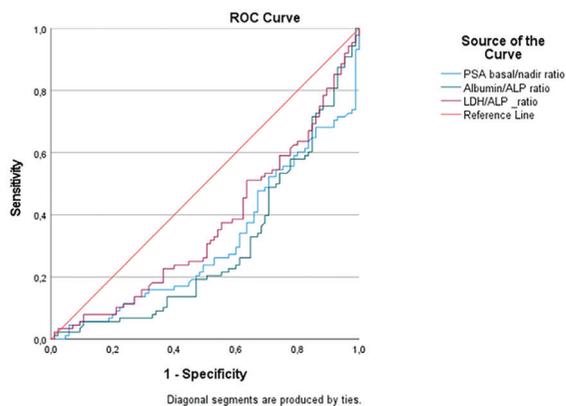


FIGURE 2: ROC analysis.

ROC: Receiver operating characteristic; LDH: Lactate dehydrogenase; ALP: Alkaline phosphatase; PSA: Prostate-specific antigen.

TABLE 2: Composite score calculation.

Composite score	If value is below cut-off → score 1, If value is above cut-off → score 0		Score
PSA elimination ratio	<6.94 = 1 point	>6.94 = 0 points	
Albumin/ALP	<0.03 = 1 point	>0.03 = 0 points	
LDH/ALP	<1.95 = 1 point	>1.95 = 0 points	
			Total

PSA: Prostate-specific antigen; ALP: Alkaline phosphatase; LDH: Lactate dehydrogenase.

TABLE 3: Sociodemographic and clinical characteristics according to survival status.

	Mortality		
	Mean ± SD or median (IQR) or n (%)		
	Absent (n=85)	Present (n=88)	
Age	67.33±8.57	69.85±8.44	0.053
PSA (baseline)	27 (79.34)	52.09 (155.35)	<0.001
PSA (nadir)	3 (17.96)	46.57 (60.05)	0.001
PSA elimination ratio	10.41 (29.69)	2.72 (9.40)	<0.001
NLR	2.91 (1.97)	3.49 (3.02)	0.027
LDH/ALP ratio	2.37 (2.15)	1.70 (1.49)	0.002
Albumin/ALP ratio	0.038 (0.04)	0.022 (0.02)	<0.001

	Mortality Mean \pm SD or median (IQR) or n (%)		
	Absent (n=85)	Present (n=88)	
Gleason score			
6-8	43 (50.6)	40 (45.5)	0.499
9-10	42 (49.4)	48 (54.5)	
Metastasis			
Bone	40 (47.1)	28 (31.8)	0.087
Lymph node	4 (4.7)	3 (3.4)	
Bone + lymph node	41 (48.2)	57 (64.8)	
Visceral metastasis			
Absent	66 (77.6)	67 (76.1)	0.954
Liver	9 (10.6)	10 (11.4)	
Lung	7 (8.2)	9 (10.2)	
Other	3 (3.5)	2 (2.3)	

PSA: Prostate-specific antigen; SD: Standard deviation; IQR: Interquartile range; NLR: Neutrophil-to-lymphocyte ratio; LDH: Lactate dehydrogenase; ALP: Alkaline phosphatase.

Score	Time (month)	Number at risk	Number of events	Survival (%)	95% confidence interval		Mean (month)
					Lower (%)	Upper (%)	
3	12	49	1	98.0	94.2	100.0	64.6
3	36	25	22	53.9	41.7	69.7	
3	60	15	7	37.7	26.0	54.7	
3	120	2	6	16.3	7.0	38.1	
2	12	43	0	100.0	100.0	100.0	99.6
2	36	30	10	76.1	64.2	90.2	
2	60	16	8	54.4	40.7	72.7	
2	120	6	5	32.3	18.5	56.5	
2	240	1	3	8.6	1.5	49.6	
1	12	43	0	100.0	100.0	100.0	134.4
1	36	34	5	87.9	78.4	98.4	
1	60	21	3	77.9	65.1	93.1	
1	120	7	6	46.5	28.6	75.6	
0	12	37	0	100.0	100.0	100.0	205.0
0	36	34	2	94.5	87.4	100.0	
0	60	17	3	84.1	71.8	98.5	
0	120	7	2	70.4	51.9	95.4	

Dependent		All	HR (univariable)	HR (multivariable)
Gleason category	6-8	83 (48.0)	-	-
	9-10	90 (52.0)	1.94 (1.25-3.01, p=0.003)	1.69 (1.06-2.69, p=0.026)
Composite prognostic score	3	50 (28.9)	-	-
	2	43 (24.9)	0.56 (0.34-0.94, p=0.028)	0.63 (0.36-1.09, p=0.095)
	1	43 (24.9)	0.32 (0.18-0.57, p<0.001)	0.35 (0.19-0.66, p=0.001)
	0	37 (21.4)	0.15 (0.07-0.35, p<0.001)	0.39 (0.16-0.94, p=0.036)

TABLE 5: Continued

Dependent		All	HR (univariable)	HR (multivariable)
Progression	No	74 (42.8)	-	-
	Yes	99 (57.2)	6.29 (3.34-11.85, p<0.001)	4.69 (2.34-9.38, p<0.001)
Bone-lymph node metastasis	Bone	68 (39.3)	-	-
	Lymph node	7 (4.0)	0.98 (0.30-3.23, p=0.975)	2.35 (0.67-8.25, p=0.183)
	Bone + lymph node	98 (56.6)	1.43 (0.90-2.25, p=0.126)	1.15 (0.71-1.88, p=0.567)
Visceral metastasis	No	133 (76.9)	-	-
	Liver	19 (11.0)	1.13 (0.58-2.20, p=0.720)	1.08 (0.53-2.23, p=0.826)
	Lung	16 (9.2)	1.18 (0.59-2.38, p=0.636)	0.75 (0.35-1.58, p=0.446)
	Other	5 (2.9)	0.96 (0.23-3.94, p=0.957)	1.10 (0.26-4.65, p=0.900)

HR: Hazard ratio

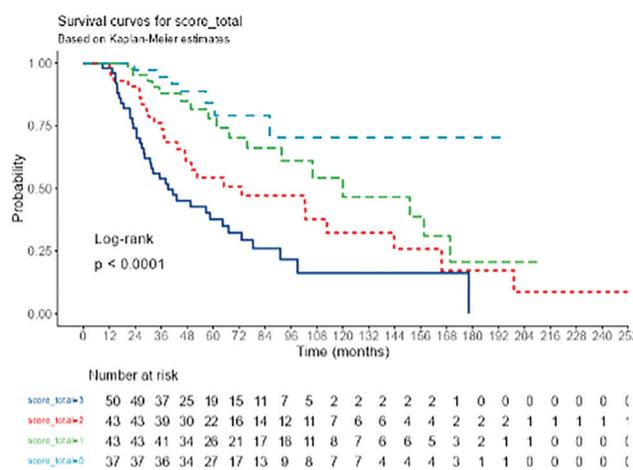


FIGURE 3: Overall survival by total composite score.

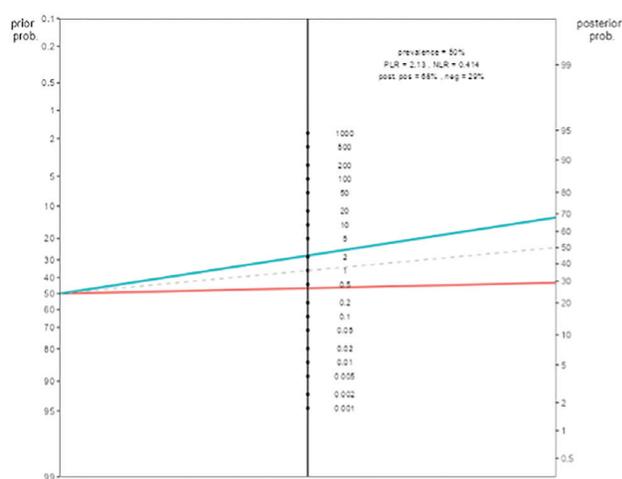


FIGURE 4: Fagan nomogram.

NLR: Neutrophil-to-lymphocyte ratio; PLR: Platelet-to-lymphocyte ratio.

DISCUSSION

Castration-resistant prostate cancer represents an advanced stage of prostate cancer characterized by disease progression despite ADT.¹⁸ Owing to its distinct biological behavior, resistance mechanisms, and therapeutic limitations, its management requires a differentiated approach compared to hormone-sensitive disease.¹⁸ Prognosis in castration-resistant prostate cancer is heterogeneous, and reliable prognostic biomarkers are needed to estimate survival risk more accurately. Despite the widespread use of biomarkers such as PSA and other clinical parameters, achieving high predictive accuracy in prognosis remains challenging.¹⁹

In our study, we evaluated the prognostic value of a composite score developed for castration-resistant prostate cancer with respect to survival. Gleason score, the composite index score, and the presence of progression were identified as independent predictors of mortality. When survival groups were compared, baseline PSA, nadir PSA, PSA elimination rate, LDH/ALP ratio, and albumin/ALP ratio were lower in patients who died than in those who survived. The 10-year survival rates were 16.3% for score 3, 32.3% for score 2, 46.5% for score 1, and 70.4% for score 0. Mortality risk was 2.85-fold lower in patients with a score of 1 (HR: 0.35) and 2.56-fold lower in those with a score of 0 (HR: 0.39).

In a study by Huo et al.²⁰, a cohort of 703 patients with mCRPC was evaluated using a comprehensive set of 41 clinical and demographic variables to predict 24-month mortality, and machine-learning models were compared. PSA, albumin, and LDH were among the identified predictive variables. These findings support the effective use of clinical markers in machine-learning-based mortality prediction. In our study, ROC analysis demonstrated that PSA elimination rate, albumin/ALP ratio, and LDH/ALP ratio each had significant AUC values and acceptable classification performance. The optimal cut-off values showed sensitivities of 60%, 65%, and

60% and specificities of 73%, 74%, and 73% for PSA ratio, albumin/ALP, and LDH/ALP, respectively. The composite score created from these markers was a significant predictor of mortality, increasing the estimated probability of mortality at presentation from 49% to 68%.

In a study by Chen et al.²¹, factors associated with progression in castration-resistant prostate cancer were evaluated, and albumin, PSA, ALP, and LDH were identified as independent risk factors. A model incorporating albumin, PSA, ALP, LDH, Gleason score, and perineural invasion achieved a discrimination power of 77.82%. ROC analysis demonstrated strong predictive performance, with an AUC of 0.845 for predicting progression. The model was later validated in an external cohort, confirming high net clinical benefit. In a meta-analysis by Mori et al.²², elevated LDH levels were associated with worse survival [HR: 2.07; 95% confidence interval (CI): 1.75-2.44] and increased progression risk (HR: 1.08; 95% CI: 1.01-1.16) in metastatic prostate cancer. Subgroup analyses in both castration-resistant and hormone-sensitive disease demonstrated that LDH remained prognostic (HR: 2.02 and HR: 2.25, respectively). High LDH levels were associated with an increased risk of mortality and disease progression. Researchers suggested that LDH may be incorporated into prognostic tools to guide treatment decision-making. Consistent with these findings, our study shows that combining LDH, albumin, and PSA into a composite score improves mortality prediction.

In a study by Whitney et al.²³, factors associated with mortality in non- mCRPC were evaluated, and PSA doubling time was found to be significant. Patients with PSA doubling time ≥ 9 months had a 50% lower mortality risk compared to those < 9 months (HR: 0.5). Similarly, in our study, the PSA elimination rate was identified as a significant independent predictor of mortality in both univariate and multivariate analyses, with slower elimination associated with an increased risk.

In the study by Schlack et al.²⁴, the prognostic value of ALP-flare, LDH, PSA, and their combination after initiating enzalutamide was evaluated. More than 50% reduction in PSA, LDH normalization, and ALP flare were associated with longer median progression-free survival. When the combined dynamics of ALP-flare, LDH normalization, and PSA reduction were compared to PSA reduction alone, patients with all three favorable markers demonstrated significantly longer progression-free and overall survival. Consistent with these findings, our results show that combining biomarkers significantly enhances predictive performance and that favorable biomarker dynamics correlate with longer survival. Available evidence and our study indicate that LDH, albumin, and ALP are associated with progression and mortality and that combining them may improve risk stratification.

These easily accessible parameters may alert clinicians to high-risk patients and contribute to clinical decision-making.

Study Limitations

The retrospective design of our study and the possibility of missing data may have introduced information bias, while the limited number of participating centers could have led to selection bias. Despite these limitations, the development of a new model by combining routinely available parameters is a key strength of our study.

CONCLUSION

Our findings demonstrate that the composite prognostic score, developed using PSA elimination rate, LDH/ALP ratio, and albumin/ALP ratio, has significant potential to predict mortality in castration-resistant prostate cancer. Combined evaluation of decreasing trends in these biomarkers improved the accuracy of mortality estimation. This composite score may aid in identifying high-risk patients and guiding treatment decisions. Further validation through prospective cohort studies is recommended.

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Ethics

Ethics Committee Approval: This study was conducted in accordance with the principles of the Declaration of Helsinki. Approval was granted by Marmara University Faculty of Medicine, İstanbul, Türkiye, number: 09.2024.911, date: 19.07.2024.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: İ.N.Ö., T.B., İ.Ç., M.B., S.K., Design: İ.N.Ö., S.K., Data Collection or Processing: İ.N.Ö., T.B., İ.Ç., M.B., S.K., Analysis or Interpretation: İ.N.Ö., T.B., İ.Ç., M.B., Literature Search: İ.N.Ö., T.B., Writing: İ.N.Ö., T.B.

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