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AI-Driven Insights Identify PSA, Frailty, and Comorbidities as Key Survival Predictors in mCRPC

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Abstract

Metastatic Castration-Resistant Prostate Cancer (mCRPC) presents significant therapeutic challenges and requires data-driven strategies to enhance patient outcomes. This study compared and analyzed the efficacy of two second-generation androgen receptor inhibitors, enzalutamide and abiraterone, and identified the key predictors of mortality. Models such as logistic regression, Random Forest, and support vector machine (SVM) were evaluated using patient-level data, with Random Forest achieving the highest accuracy (96.7%) and demonstrating strong generalizability across cross-validation folds (mean score: 0.972). Comorbidity scores, Prostate-Specific Antigen (PSA) levels, and frailty indices were consistently found to be the best indicators of death, highlighting the importance of systemic health over treatment choice in determining survival. While logistic regression provided interpretability and SVM showed competitive accuracy, Random Forest proved to be the most effective for risk stratification and personalized treatment planning. These findings demonstrate the potential of machine learning models for mortality risk stratification in mCRPC and highlight the importance of incorporating systemic health indicators into predictive oncology models.

Keywords

Metastatic Castration, Resistant Prostate Cancer, Prostate-Specific Antigen, Comorbidity Scores, Support Vector Machine, Logistic Regression, Random Forest

1. Introduction

Prostate cancer is one of the most common causes of tumor-related deaths among men worldwide. Advanced and highly aggressive mCRPC develops during ongoing ADT, showing how ADT eventually fails to suppress disease progression; hence, other treatment modalities must be sought. Second-generation androgen receptor inhibitors such as Abiraterone and Enzalutamide have shown promise in improving survival. However, identifying the best treatment for specific subgroups of patients remains a major challenge in ongoing studies.

The following objectives will be pursued in this study by analyzing the clinical and demographic data of patients with mCRPC: Identification of critical determinants of death, such as frailty, comorbidities, and clinical signs; comparison of the effectiveness of Abiraterone and Enzalutamide in real-world settings, develop predictive models to improve risk stratification and guide therapeutic decisions. Metastatic castration-resistant prostate cancer (mCRPC) management has evolved significantly with the introduction of second-generation androgen receptor (AR) inhibitors, such as abiraterone acetate and enzalutamide. These therapies have transformed the treatment landscape by targeting androgen receptor-axis signaling pathways, which are essential factors in the development of prostate cancer [1]. Despite their efficacy, therapeutic challenges such as treatment resistance and the need for personalized therapeutic approaches exist. Both enzalutamide and abiraterone were shown to be effective in landmark clinical trials. In post-chemotherapy settings, abiraterone plus prednisone demonstrated improved overall survival compared to placebo (15.8 vs 11.2 months; HR 0.74) in the COU-AA-301 trial [2], and comparable populations exhibited similar benefits from enzalutamide (18.4 vs 13.6, and 0.63, respectively) [3]. Among chemotherapy-naïve patients, the COU-AA-302 validated abiraterone's survival benefit (34.7 vs 30.3 months, HR 0.81) [4]. Enzalutamide also significantly extended radiographic progression-free survival (rPFS) and reduced the risk of death by 29% (HR 0.71) [5].

Comparative analyses of these therapies have yielded variable outcomes. La *et al.* found that enzalutamide improved prostate-specific antigen (PSA) response rates and provided modest survival benefits (0.90 additional months > four years), especially in patients who never received chemotherapy [6]. Despite enzalutamide's benefit in delaying the disease progression and PSA elevation. However, Tan *et al.* found no significant difference in overall survival despite the advantage of enzalutamide in delaying disease progression and PSA elevation. Tan *et al.* did not find any significant differences in overall survival [7]. The average survival benefit of enzalutamide over abiraterone was shown by Gopukumar *et al.* using a causal survival forest analysis in a veteran cohort. The treatment effect heterogeneity was influenced by age, BMI, PSA levels, and comorbidities [8].

Clinical factors such as disease presentation and patient characteristics were considered when choosing treatment. Although statistical significance favored non-visceral disease subgroups, Goodman *et al.* observed that abiraterone was efficacious across visceral disease subgroups [9]. The similar efficacy and safety pro-

files of both drugs in elderly populations were validated by age-related analyses [10] [11].

The interplay between frailty, comorbidities, and survival has been well established in mCRPC research. Frailty and baseline comorbidities had a substantial impact on therapy outcomes, with cardiovascular events being more common in patients treated with abiraterone, according to Lin *et al.*'s investigation of treatment-emergent comorbidities and survival outcomes in mCRPC patients receiving abiraterone or enzalutamide [12]. These findings emphasize the importance of individualized treatment plans that account for patient health profiles.

Fiala *et al.* conducted a long-term evaluation of mCRPC patients treated with enzalutamide or abiraterone in a real-world clinical context, emphasizing the heterogeneity in medication efficacy based on patient characteristics, such as baseline performance status and previous treatment history [13]. Despite the efficacy of both medications and patient-specific factors affecting survival rates, suggesting the need for structured treatment approaches.

With sequencing studies showing decreased efficacy in subsequent treatment lines, cross-resistance among these therapies poses a serious challenge. Loriot *et al.* and Noonan *et al.* reported modest progression-free survival with abiraterone after enzalutamide failure (2.7 months and 15.4 weeks, respectively) [14] [15], while Bianchini *et al.* and Brasso *et al.* observed limited PSA responses (≤13.3% achieving ≥50% PSA decline) when enzalutamide followed abiraterone [16] [17]. Similar findings by Thomsen *et al.* and Badrising *et al.* in heavily pretreated patients underscore the need for optimized sequencing strategies [18] [19]. Recent technological advances have reshaped the management of prostate cancer. Although issues with data quality and standardization still exist, artificial intelligence has demonstrated potential for enhancing diagnosis, risk assessment, and treatment selection [20]. Machine learning algorithms for predicting survival outcomes in bone-metastatic disease have achieved promising predictive performance, with AUC values up to 0.78 for overall survival [21].

Phan *et al.* proposed incorporating androgen-to-PSA ratios into predictive models to account for androgen dependency in PSA expression, potentially improving assessment accuracy during disease progression and treatment resistance development [22]. For nonmetastatic castration-resistant prostate cancer (nmCRPC), Ni *et al.* developed a machine learning-based prognostic model using data from phase III clinical trials and identified eight key prognostic factors, including novel hormone therapy application, Gleason score, previous treatments, race, PSA doubling time, hemoglobin levels, and PSA values. Their model demonstrated robust predictive performance with a C-index of 0.724 in internal validation and good calibration in external testing [23].

Nakata *et al.* developed a deep learning model for metastatic hormone-sensitive prostate cancer (mHSPC) using biopsy images to estimate time-to-resistance to hormone therapy before progression to castration-resistant disease. Their research demonstrated a strong correlation between this predicted time-to-re-

sistance and overall survival, achieving nearly 80% accuracy in identifying patients likely to benefit longer from standard hormone therapy [24].

Integrating predictive modeling with clinical datasets offers new opportunities for personalized mCRPC management. Lin *et al.* and Jarimba *et al.* emphasized the potential of data-driven approaches to refine treatment decisions, improve risk stratification, and enhance survival [12] [25]. The use of predictive analytics aligns with these findings by identifying key predictors, such as frailty, PSA levels, and systemic health markers, paving the way for precision oncology. These technological developments collectively suggest an emerging paradigm shift toward personalized treatment selection through advanced computational approaches across the spectrum of prostate cancer from hormone-sensitive to castration-resistant stages.

2. Data Description

The project's data was collected by Dr. Martin Schoen's lab. The dataset contains patient-level data on 32 features and is grouped as follows.

- **Demographics: Age (0% missing), sex (0% missing), and race (6 patients; <0.1% missing).**
- **Clinical Data: PSA levels (1481 patients; 5.9% missing), albumin (1571 patients; 6.3% missing), hemoglobin (1253 patients; 5.0% missing), and Gleason score (0% missing).**

Treatment Details: Administration of Abiraterone (0% missing), Enzalutamide (0% missing), and docetaxel therapy (0% missing).

- **Indices: Charlson Comorbidity Index (4599 patients; 18.4% missing), frailty scores (0% missing), and Elixhauser groups (0% missing).**

Data Preprocessing:

- **Missing Data:** Addressed using predictive modeling techniques.
- **Scaling:** The Standard Scaler ensured that no feature dominated the others during model training.

Preprocessing procedure: Missing continuous variables were imputed using median imputation, while categorical and binary variables were imputed using the most frequent (mode) value. To prevent data leakage, imputation and z-score standardization were performed independently within each training fold of the five-fold cross-validation procedure, and the learned parameters were subsequently applied only to the corresponding validation fold. This preprocessing pipeline was identical for all machine learning models (**Table 1**).

Cohort Construction: This retrospective cohort study included 25,070 Veterans with metastatic castration-resistant prostate cancer (mCRPC) who received care within the Veterans Health Administration (VHA) between 2011 and 2022. Eligible patients had confirmed mCRPC and available baseline demographic, clinical, and treatment information. Baseline variables included demographics (age, sex, and race), clinical characteristics (prostate-specific antigen [PSA], albumin, hemoglobin, and Gleason score), treatment history (abiraterone, enzalutamide,

and docetaxel), and comorbidity measures, including the Charlson Comorbidity Index, frailty scores, and Elixhauser comorbidity groups. Patients with insufficient baseline information or missing outcome data were excluded from the analysis. Missing predictor values were addressed using predictive imputation techniques, and continuous variables were standardized using the Standard Scaler before model development to ensure balanced feature contributions. Patients were followed from the index date until death or the end of follow-up. The primary outcome was all-cause mortality, which was evaluated over the entire follow-up period as well as at predefined 1-, 2-, 3-, 4-, and 5-year follow-up intervals.

Table 1. Missing data summary for variables included in the analysis.

Category	Variable	Missing (n)	Missing (%)	Imputation Method
Demographics	Age	0	0.0	None
	Sex	0	0.0	None
	Race	6	<0.1	Mode
Clinical Data	PSA	1481	5.9	Median
	Hemoglobin	1253	5.0	Median
	Albumin	1571	6.3	Median
	Bilirubin	1299	5.2	Median
	Creatinine	929	3.7	Median
	Gleason Score	0	0.0	None
Treatment Variables	Abiraterone	0	0.0	None
	Enzalutamide	0	0.0	None
	Docetaxel	0	0.0	None
Clinical Indices	Charlson Comorbidity Index	4599	18.4	Median
	Frailty Score	0	0.0	None
	Elixhauser Groups	0	0.0	None

The dataset integrates demographic, clinical, treatment, and comorbidity variables to enable development of predictive models for mortality risk assessment in patients with mCRPC by integrating demographic, clinical, treatment, and comorbidity data, the machine learning models provided improved risk stratification and individualized mortality prediction. These findings support the growing role of computational approaches in precision oncology and highlight a paradigm shift toward personalized treatment selection and clinical decision-making across the continuum of prostate cancer, from hormone-sensitive disease to metastatic castration-resistant prostate cancer.

3. Methodology

Model Development and Validation

The predictive modeling workflow followed a standardized machine learning pipeline for all evaluated algorithms to ensure fair model comparison and minimize bias. A total of 25,070 eligible patients were included in the analysis after applying the predefined inclusion and exclusion criteria (Figure 1). The study cohort was randomly partitioned into a training dataset (80%, n = 20,056) and an independent testing dataset (20%, n = 5014) using stratified sampling based on mortality outcome to preserve the class distribution in both datasets. Model development, data preprocessing, feature engineering, and hyperparameter optimization were performed exclusively on the training dataset, while the independent testing dataset was reserved for final model evaluation. For the final performance assessment, only 1165 patients from the testing dataset had complete data available for all predictors and outcomes required for model evaluation after preprocessing; therefore, the confusion matrix and associated performance metrics were calculated using this evaluable subset.

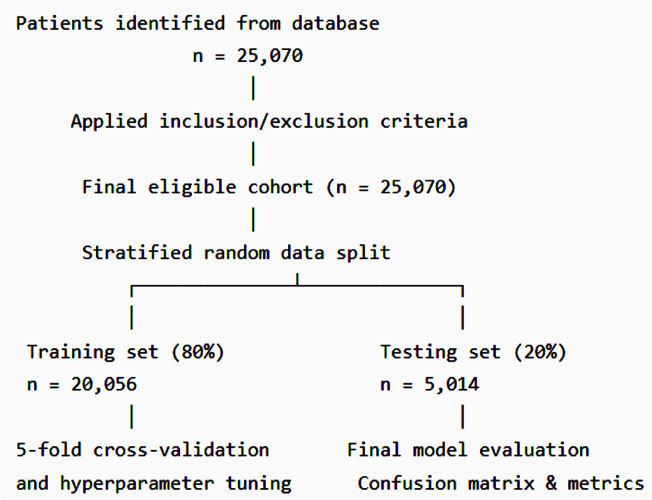

Figure 1. Patient selection flowchart.

Within the training dataset, five-fold cross-validation was employed for model training and hyperparameter optimization. During each fold, missing predictor values were imputed using predictive imputation methods, and continuous variables were standardized using the Standard Scaler. All preprocessing parameters were estimated solely from the training portion of each fold and subsequently applied to the corresponding validation fold, thereby preventing information leakage. The final optimized model was retrained using the complete training dataset and evaluated on the independent testing dataset, with the confusion matrix reported for the subset of 1165 evaluable patients.

Multiple supervised machine learning algorithms were evaluated, including logistic regression, random forest, gradient boosting, extreme gradient boosting (XGBoost), support vector machine, k-nearest neighbors, decision tree, and mul-

tilayer perceptron neural network. Hyperparameters for each algorithm were optimized using a grid-search strategy within the cross-validation framework. Representative hyperparameters included the number and depth of trees for ensemble methods, the regularization parameter (C) and kernel parameters for support vector machines, the number of neighbors for k-nearest neighbors, and learning rate and network architecture for neural networks.

Because mortality outcomes were imbalanced, model performance was assessed using multiple complementary metrics, including accuracy, sensitivity, specificity, precision, and F1-score. These measures were used to evaluate both overall predictive performance and the ability of models to correctly identify mortality and survival outcomes.

No explicit feature-selection algorithm was applied before model training. Instead, all 32 clinically relevant variables identified from demographic, clinical, treatment, and comorbidity domains were included in model development to preserve their potential prognostic value. Variable importance was subsequently evaluated using model-specific feature importance measures and SHapley Additive exPlanations (SHAP) analyses to identify the most influential predictors of mortality.

Outcome Definition: The primary outcome was all-cause mortality. Patients were classified into two groups: deceased patients (death = 1) and surviving patients (death = 0). The binary classification models were trained to predict mortality risk based on baseline demographic, clinical, treatment, and comorbidity features.

3.1. Statistical Analysis

- Heat Map;
- Box Plots.

3.2. Machine Learning

- **Logistic Regression Model:** Binary mortality outcomes were tested using cross-validation to validate performance robustness.
- **Support Vector Machine (SVM):** a supervised machine learning algorithm that finds the optimal hyperplane to separate data into classes with the maximum margin.
- **K-Nearest Neighbor (KNN):** a non-parametric algorithm that classifies data points based on the majority class among their closest neighbors in the feature space.
- **Random Forest:** Used to rank feature importance and enhance prediction accuracy.

4. Results

4.1. Statistical Analysis

Heat maps showed strong correlations between frailty indices, comorbidities, and

mortality. The confusion matrices from both models demonstrated their respective strengths and weaknesses in distinguishing the outcomes.

This analysis reveals that strong correlations exist among demographic factors, frailty scores, comorbidity indices, and mortality predictors in patients undergoing Abiraterone or Enzalutamide therapy. The heatmap shows clear clusters, particularly among age, frailty (fi_score_cat), comorbidity indices, and clinical markers like albumin levels, which are closely linked to mortality outcomes. In contrast, treatment type shows weak correlation with mortality, underscoring the greater importance of holistic patient assessment. Key predictors of mortality include frailty scores, albumin levels, creatinine clearance, and comorbidity burden, emphasizing the need to prioritize patient-specific health profiles over treatment choice in clinical decision-making and risk stratification.

Figure 2 highlights several critical predictors of mortality in patients, with strong associations observed between death and elevated PSA levels, low BMI (malnutrition), high comorbidity indices (Romano, Charlson, Elixhauser), prior Docetaxel use, and increased frailty scores. Patients with higher disease burden—reflected in the number of conditions, comorbidity scores, and frailty measures—consistently showed worse outcomes. Additionally, higher Gleason scores were strongly linked to mortality, emphasizing the role of tumor aggressiveness. Overall, these findings underscore the importance of integrating frailty, nutritional status, comorbidities, and cancer severity into risk assessment and clinical decision-making.

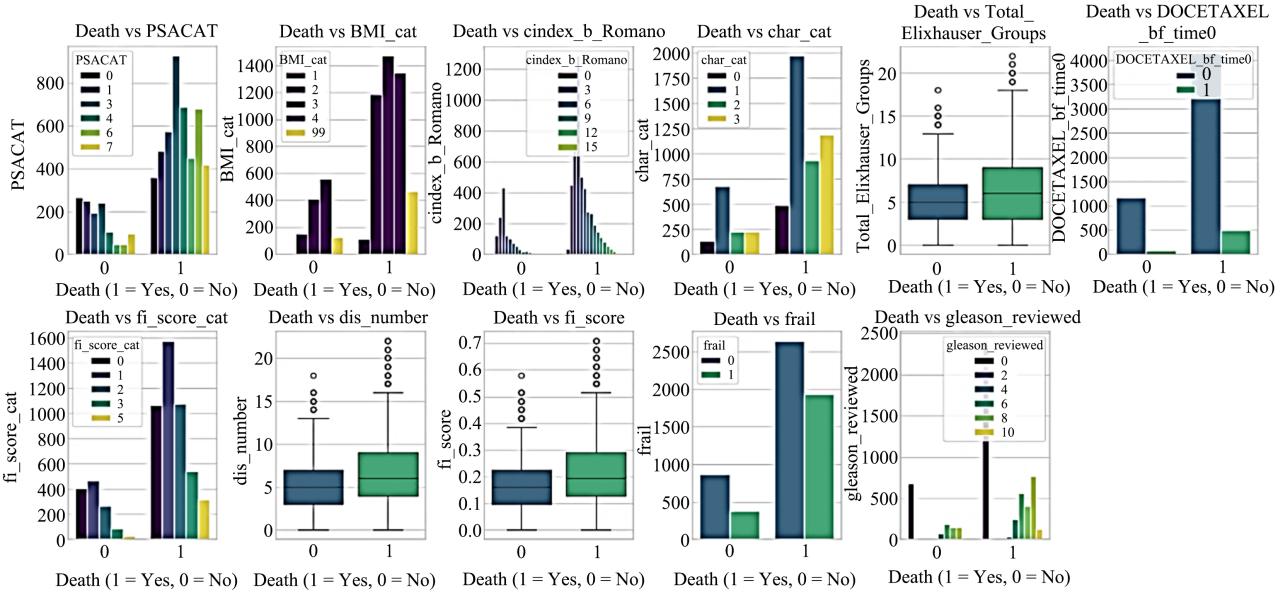

Figure 2. Association between clinical variables and mortality outcomes in mCRPC patients.

Key Features and Their Association with Mortality:

1) PSA Levels: Higher PSA categories (6 - 7) indicate greater disease burden and higher mortality.

2) BMI: A Lower BMI (malnutrition) was associated with increased mortality.

3) Comorbidity Index: Higher scores were strongly correlated with mortality risk.

4) Charlson/Elixhauser Groups: Greater comorbidities increase the mortality likelihood.

5) Docetaxel Use: Prior use of docetaxel suggests advanced disease and higher mortality.

6) Frailty: Higher frailty scores and status strongly predict mortality.

7) Gleason Score: Higher scores (8 - 10) reflect tumor aggressiveness and increased mortality.

Feature analysis identified frailty indices, PSA levels, albumin, hemoglobin, and comorbidity measures as the variables most strongly associated with mortality prediction. The graphs comprehensively illustrate the relationships between mortality (death: 1 = yes, 0 = no) and the key demographic, treatment, clinical, and laboratory features in the dataset. A thorough analysis reveals several critical patterns and insights that align with clinical understanding of metastatic castration-resistant prostate cancer (mCRPC).

Older age (particularly ≥74 years) is strongly associated with increased mortality, likely due to reduced physiological resilience and higher comorbidity burden. While race data hint at slightly lower mortality among Black patients compared to White patients, limited diversity restricts firm conclusions about racial disparities. Treatment patterns suggest that mortality was somewhat higher in patients initially treated with enzalutamide than abiraterone, possibly reflecting more advanced disease in the enzalutamide group. Prior use of docetaxel, often for severe cases, was also linked to higher mortality. Interestingly, enzalutamide treatment showed a reduction in mean death rate over time, suggesting potential survival benefits, while abiraterone was associated with a higher mean death rate—likely influenced by baseline differences in patient condition. Additionally, elevated PSA levels strongly correlated with increased mortality, reinforcing PSA as a key biomarker for disease severity and prognosis in prostate cancer.

4.2. Machine Learning

The predictors of mortality are:

- *Frailty*: strongly correlated with mortality and frail patients with a far higher death rate.
- *PSA Levels*: High PSA levels (≥50 ng/mL) are associated with increased mortality.
- *Albumin and Hemoglobin*: Low values of these factors indicate poor systemic health and significantly impact survival.

4.2.1. Logistic Regression Model

The logistic regression model was quite effective, achieving 89.37% training accuracy and 87.55% testing accuracy, indicating that the model generalizes well to the new data. It makes perfect predictions of mortality (death), especially for deceased patients Class 1, as shown by high precision (91%), recall (93%), and F1 score

(92%). Although the model yielded an overall good performance, it exhibited a slightly lower recall for survivors (Class 0) at 68%, which means that some survivors might be misclassified as dead. This indicates the need for possible modifications to improve Recall for Class 0 while maintaining high performance for Class 1, a critical clinical task for correctly identifying high-risk patients. Table 2 shows the confusion matrix.

Table 2. Confusion matrix of logistic regression classifier.

	Predicted Deceased (Class 0)	Predicted Survivor (Class 1)
Actual Deceased (Class 0)	True Positives (TP): 834	False Negatives (FN): 59
Actual Survivor (Class 1)	False Positives (FP): 86	True Negatives (TN): 186

4.2.2. Support Vector Machine (SVM)

The Support Vector Machine (SVM) model demonstrated a high training accuracy of 97.4% and a test accuracy of 96.8%, indicating solid predictive capabilities and generalization to unseen data. The confusion matrix highlights the model's ability to accurately classify outcomes, with 272 True Negatives, 856 True Positives, and 37 False Negatives. The classification report shows that Class 0 (non-survivors) had a precision of 0.88 and a perfect recall of 1.00, meaning that all actual non-survivors were correctly identified. For Class 1 (survivors), the model achieved perfect precision (1.00) and high recall (0.96), resulting in an F1-score of 0.98 for survivors, indicating a solid balance of Precision and Recall. The overall accuracy of 97% and balanced macro average Recall of 0.98 suggest that the SVM model is highly effective in predicting patient outcomes, making it a reliable tool for risk assessment and personalized treatment planning in a clinical setting for metastatic castration-resistant prostate cancer (mCRPC).

4.2.3. K-Nearest Neighbor (KNN)

The KNN model demonstrated robust learning with a training accuracy of 92.33% and robust prediction capabilities for unseen data, as evidenced by a test accuracy of 87.21%. The confusion matrix results indicate a reliable model performance in classifying both survivors and non-survivors, with 860 True Positives (860) and 156 True Negatives (156), while 116 False Positives (116) and 33 False Negatives (33) remained relatively low. In the classification report, the model effectively identified survivors with a precision of 0.88 and a recall of 0.96. While the performance for predicting non-survivors is somewhat lower, with a precision of 0.83 and a recall of 0.57, it still shows solid prediction results. The F1-scores of 0.92 for survivors and 0.68 for non-survivors highlight the model's better performance in identifying survivors.

4.2.4. Random Forest

The Random Forest model demonstrateda test accuracy of 96.7% and a mean cross-validation score of 0.972. It consistently achieved scores above 0.96 across multiple folds, indicating strong generalizability and low variability. This high

level of reliability, particularly in distinguishing between survivors and non-survivors, makes the model suitable for clinical decision-making in metastatic castration-resistant prostate cancer (mCRPC). The model's low false-positive rate minimizes unnecessary interventions, while its high recall ensures that high-risk patients are accurately identified, supporting risk stratification and personalized treatment planning.

Clinically, the model has strong potential to guide treatment strategies such as selecting between Enzalutamide and Abiraterone by identifying patients who may benefit from closer monitoring. Analysis of nature importance analysis revealed that PSA levels, frailty, and comorbidity indices were key predictors, aligning with known clinical risk factors. These insights offer valuable support for clinicians seeking to focus on the most impactful variables in patient care. Overall, this study highlights the value of machine learning in tackling complex clinical challenges, offering a robust and interpretable tool to enhance outcomes in mCRPC management.

5. Discussion

Table 3 shows the train and test accuracy of regression and classifiers. Based on this table, Random Forest and SVM had the best performance.

Table 3. Performance comparison of machine learning models for mortality prediction in mCRPC.

Model	Training Accuracy (%)	Testing Accuracy (%)	Sensitivity/ Recall (%)	Specificity (%)	Precision (%)	F1-score (%)
Logistic Regression	89.37	87.55	93.0	68.4	91.0	92.0
Support Vector Machine (SVM)	97.40	96.82	96.0	99.0	94.0	96.0
K-Nearest Neighbor (KNN)	92.33	87.21	96.0	57.3	88.0	92.0
Random Forest	97.20	96.70	97.0	96.0	96.0	96.0

5.1. Main Findings

This study developed and evaluated machine learning models for predicting mortality among patients with metastatic castration-resistant prostate cancer (mCRPC) using demographic, clinical, treatment, and comorbidity-related features. The results demonstrate that artificial intelligence approaches can effectively identify high-risk patients and reveal clinically relevant factors associated with survival outcomes. Among the evaluated algorithms, Random Forest demonstrated the strongest overall predictive performance, providing robust classification accuracy and consistent performance across cross-validation folds [26] [27].

Beyond predictive performance, feature importance analysis provided insights into the clinical factors contributing to mortality risk. PSA levels, frailty measures,

and comorbidity burden emerged as the most influential predictors across models. These findings suggest that overall patient health status and systemic disease burden may play a greater role in determining survival outcomes than treatment selection alone. The weaker association between androgen receptor-targeted therapy type (abiraterone versus enzalutamide) and mortality highlights the importance of considering patient-specific characteristics when evaluating treatment outcomes.

5.2. Comparison with Previous Studies

Previous clinical trials have established the survival benefits of abiraterone and enzalutamide in patients with mCRPC; however, differences in treatment response remain influenced by patient characteristics, disease severity, and prior therapies. The COU-AA-301, COU-AA-302, and AFFIRM trials demonstrated improved survival outcomes with these agents, but population-level treatment effects may not fully capture individual variations in prognosis.

Recent real-world studies have emphasized the heterogeneity of treatment response and the influence of baseline characteristics, including age, PSA levels, comorbidity burden, and prior treatment history. Consistent with these observations, our study identified systemic health indicators as important predictors of mortality. These findings complement previous work showing that treatment effectiveness in mCRPC depends not only on anticancer therapy but also on patient resilience, functional status, and underlying comorbid conditions.

The application of machine learning provides an additional approach for integrating multiple clinical factors simultaneously. Previous studies have demonstrated the ability of predictive models to estimate survival outcomes in prostate cancer; however, many models have focused primarily on tumor characteristics or treatment variables. Our study expands this approach by incorporating frailty, comorbidity indices, laboratory markers, and treatment information into a unified predictive framework.

5.3. Clinical Implications

The identification of frailty, PSA levels, and comorbidity burden as major predictors has important clinical implications. Traditional treatment decisions in mCRPC often emphasize tumor-related characteristics, but our findings suggest that comprehensive assessment of patient health status may improve risk stratification. Patients with increased frailty, elevated PSA levels, or substantial comorbidity burden may benefit from closer monitoring, supportive care interventions, and individualized treatment planning.

Machine learning models may serve as decision-support tools by identifying patients at elevated mortality risk who may require additional clinical attention. Importantly, these models are intended to complement—not replace—clinical judgment. Integration of predictive analytics with oncologist expertise may support more personalized approaches to treatment selection, follow-up intensity, and resource allocation.

5.4. Model Performance and Interpretability

Although Random Forest achieved the highest overall predictive performance, different models provided complementary advantages. Logistic regression offered greater interpretability and may be valuable when transparent associations between predictors and outcomes are required. SVM demonstrated strong predictive capability but requires careful parameter optimization and may be less interpretable in clinical settings. Random Forest provided a balance between predictive performance and interpretability through feature importance analysis, making it suitable for identifying clinically meaningful predictors.

The combination of predictive accuracy and explainability is particularly important in healthcare applications. Identifying the variables driving model predictions allows clinicians to understand and evaluate the factors contributing to patient risk assessment.

5.5. Limitations

Several limitations should be considered when interpreting these findings. First, this study used retrospective data from the Veterans Health Administration, which may limit generalizability to other healthcare systems and patient populations. External validation using independent cohorts from multiple institutions is necessary before clinical implementation.

Second, although the dataset included comprehensive clinical and comorbidity information, additional factors such as genomic characteristics, imaging findings, treatment adherence, patient-reported outcomes, and quality-of-life measures were not available. Incorporating these variables may further improve predictive performance and clinical relevance.

Third, while cross-validation and independent testing were used to reduce overfitting, machine learning models may still be influenced by dataset-specific patterns. Future studies should evaluate model calibration, prospective validation, and implementation feasibility in real-world clinical workflows.

5.6. Future Directions

Future research should focus on developing externally validated and clinically deployable predictive models for mCRPC management. Integration of longitudinal clinical data, real-time laboratory measurements, imaging biomarkers, and patient-reported outcomes may provide a more comprehensive representation of disease progression and treatment response.

Additionally, advanced approaches such as explainable artificial intelligence, causal machine learning, and multimodal modeling may help clarify treatment effects and identify patient subgroups most likely to benefit from specific therapies. These approaches may further support precision oncology by moving beyond population-based treatment strategies toward individualized risk assessment and therapeutic decision-making.

6. Conclusions

This study developed and evaluated machine learning models for mortality prediction in patients with metastatic castration-resistant prostate cancer using demographic, clinical, treatment, and comorbidity features. Among the evaluated algorithms, Random Forest demonstrated the strongest predictive performance and provided interpretable feature importance measures. PSA levels, frailty indices, and comorbidity burden emerged as consistent predictors of mortality, suggesting that systemic patient health plays an important role in survival outcomes.

The findings support the integration of machine learning approaches into mCRPC risk stratification by complementing traditional clinical assessment with data-driven prognostic insights. Future studies should focus on external validation, incorporation of longitudinal clinical information, and integration of patient-reported outcomes to further improve personalized oncology care.

Ethics Statement

This retrospective study was conducted using de-identified data from the Veterans Health Administration (VHA). The study was reviewed and approved by the appropriate Institutional Review Board (IRB). Because the study involved retrospective analysis of existing clinical data with minimal risk to participants, the requirement for informed consent was waived in accordance with applicable regulations and institutional policies.

Data Availability Statement

The data used in this study were obtained from the Veterans Health Administration (VHA) and are not publicly available because of institutional policies and patient privacy regulations. Access to the data may be granted to qualified investigators upon reasonable request and with approval from the Veterans Health Administration and the appropriate regulatory authorities.

Declaration of Generative AI and AI-Assisted Technologies in Manuscript Preparation

During manuscript preparation, the authors used Claude solely for limited language editing of selected sentences to revise to improve clarity. No AI tool was used to generate research content, analyze data, interpret results, or prepare references; the ideas, arguments, and intellectual contribution of the paper are entirely original. All AI-assisted suggestions were reviewed, revised where necessary, and approved by the authors, who take full responsibility for the final manuscript. We used AI to format references and find the doi numbers.

Author Contributions

Bahareh Rahmani: Supervision, Administration, Methodology, Review of the Paper;

Pavan Sai Gajula: Data Analysis, Methodology, Writing—Original Paper;
Mustaid Ahmed: Methodology, Writing—Original Paper;
Naga Pushpa Latha Ginni: Data Analysis, Visualization, Writing—Original Paper;
Vanitha Ajmeer: Visualization, Data Analysis;
Jason Doherty: Data Collection, Preprocessing, Review of the Paper;
Sailaja Vatsalya Madhurapantula: Literature Review, Visualization;
Payam Norouzzadeh: Validation, Methodology Advisor, Review of the Paper;
Leslie Hinyard: Validation, Review of the Paper;
Mostafa Yazdi: Funding, Review of the Paper;
Martin Schoen: Supervision, Data Collection, Review of the Paper.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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