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Explainable multi-biomarker machine learning for prostate cancer risk stratification

Tinovimba Lillian Hove [1,*], Sean Tapiwa Kabera [2], Lance Aaron Midzi [3], Delin Kufandada [4], Tinodiwanashe Nguruve [5], Robert Kumi Adu-Gyamfi [6] and Munashe Naphtali Mupa [7]

[1] *Clarkson University*
[2] *Northeastern University,*
[3] *Yeshiva University,*
[4] *Illinois State University,*
[5] *University of The Cumberlands,*
[6] *Park University,*
[7] *Hult International Business School*
Tinovimba Lilian Hove; ORCiD: 0009-0000-2684-4218
Sean Tapiwa Kabera; ORCiD: 0009-0008-0040-516X
Lance Aaron Mdizi, ORCiD: 0009-0001-1932-8319
Delin Kufandada, ORCiD: 0009-0009-3675-4959
Tinodiwanashe Nguruve, ORCiD: 0009-0009-0542-1895
Robert Kumi Adu-Gyamfi, ORCiD: 0009-0003-7280-5107
Munashe Naphtali Mupa, ORCiD: 0000-0003-3509-867X

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Abstract

Classification of prostate cancer risk is a clinical problem because the disease is heterogeneous and single-modal diagnostic approaches are limited. This paper constructed and tested an explainable multi-biomarker machine learning framework combining both clinical variables with imaging-based and molecular biomarkers to further enhance clinically meaningful prostate cancer. This was to focus on predictive performance, explainability, and reproducibility to facilitate clinical applicability. Several machine learning models were developed and tested with the help of standardized preprocessing and cross-validation techniques. The discrimination measures, calibration analysis, and decision-curve analysis were applied as a measure of clinical utility. The method of explainability was used to determine the influential biomarkers on the global and patient-specific scales, making the predictions easy to understand.

The findings revealed that multi-biomarker models were always better than unimodal methods in providing better discrimination and an increased net clinical benefit at pertinent decision thresholds. Imaging-derived and molecular characteristics had additional predictive value of clinical variables, which emphasized the significance of integrating multimodal predictive value. The explainability analyses showed biologically and clinically reasonable feature contributions and gave specific explanations that aided in interpreting individual-level risk predictions. Calibration of the model showed that the model agreement with the prediction and outcomes was quite good, and the accuracy of the model was consistent in all the folds of validation which supported the strength and reproducibility of the framework.

Keywords: Cancer; Machine-Learning; Prostate; Bio-marker

* Corresponding author: Tinovimba Lilian Hove

1. Introduction of Machine Learning in Precision Oncology

Machine learning (ML) became the topic of growing interest in oncology with a potential to learn complicated and non-linear relationships between high-dimensional biomedical data. ML has been used in prostate cancer to analyze data modalities of diverse types such as multiparametric magnetic resonance imaging (MRI), molecular and gene expression data, and data obtained routinely in the form of clinical variables. Multiple machine learning models (MMLs) have shown that they are better at detecting clinically significant prostate cancer than traditional statistical approaches to the problemulticenter studies employing clinical variables in interactions with imaging and laboratory findings have shown superior ability to discriminate clinically significant prostate cancer relative to traditional risk assessment instruments (Zhang et al., 2023). Such results highlight the possible applicability of ML to assist with more precise and personal clinical decision-making.

1.1. Machine Learning and Radiomics via Imaging

The use of imaging, especially multiparametric MRI, has been deeply integrated in the process of the diagnosis and staging of prostate cancer. The ML-based radiomics methods are used to obtain quantitative characteristics of imaging data that cannot be visualized (Ioannidis et al., 2025). Explainable ML models as compared to MRI have proved to be useful in segmenting tumors, predicting their aggressiveness, and correlating with histopathological data (Gunashekar et al., 2022). These analyses show that biomarkers derived by imaging techniques can provide useful data on risk stratification that can be included in the frameworks of ML (Ioannidis et al., 2025). Yet, a dilemma of small data sources and lack of external validation persists with most models that focus on imaging, which is a concern when it comes to the generalizability (Xie et al., 2025; Zhao et al., 2025).

1.2. Basing Models on Molecular and Gene Expression

In addition to imaging, the molecular and gene expression data gives important information about the biological processes behind prostate cancer progression. ML models that have been trained with gene expression profiles have been utilized to differentiate between malignant and benign tissue and provide molecular signatures that associate with malignant disease aggressiveness (Ramírez-Mena et al., 2023). Explainable artificial intelligence methods on transcriptomic information have facilitated the determination of key genes involved in model forecasts, which could yield biologically interpretable understanding along with predictive accuracy (Ramírez-Mena et al., 2023). Although these methods emphasize the importance of molecular biomarkers, there are many limitations to their clinical utility, including data availability, cost, and including additional issues.

1.3. Integration of Multimodal and Multi-Biomarker

The integration of clinical variables, imaging features, and molecular data enables models to have complementary information on prostate cancer biology. Multimodal ML models have also shown to perform better at the predictive identification of clinically significant disease as opposed to unimodal ones (Zhang et al., 2023). Notably, the fact that multiple biomarkers can be integrated also gives a more detailed foundation on which clinical meanings can be obtained, especially when such integrated models are backed by interpretable ML processes (Semwal et al., 2025; Yuan et al., 2025).

1.4. Oncology Explainable Artificial Intelligence

Explainable artificial intelligence has become a key aspect of the clinically relevant ML models. XAI models are used to explain the prediction generated by a model through the quantification of contributions of features and decision-making paths. In medicine, explainability helps to build trust in clinicians, ease the process of error detection, as well as align model outputs with clinical logic (Tjoa & Guan, 2020). Explainable ML models have been applied to the imaging, molecular markers, and clinical variables related to disease progression and recurrence in prostate cancer research (Lu et al., 2024). Such literature demonstrates that explainability does not so much contradict high predictive errors than explainability invariably necessitates accuracy.

1.5. Clinical Interpretability and Trust

ML-based decision-support tools should not only be accepted by clinics based on their predictive behavior, but also on their usability/interpretability. The explainable models give the clinicians an understanding of why a specific patient is determined as being either high or low-risk in order to support the shared decision-making and the planning of care. The aspect of the process of feature attribution can be used to identify the elements of risk that are predominant and could translate into known clinical or biological variables. Such consistency between model explanations and clinical

knowledge reduces the doubt regarding them and the chances of their acceptance into practice (Molnar, 2023). However, explainability cannot stand on its own without good validation and reporting.

1.6. Issues of Reproducibility and Validation

The issue of reproducibility is still observed to be a difficult problem in medical AI studies. The preprocessing of data, feature selection, and evaluation of the model may yield different results across the studies because of variability. Transparency and reproducibility issues have been a topic of popular discussion, and they are required to have standardized working processes and comprehensible reporting in terms of methodological specifications (Haibe-Kains et al., 2020). Most prostate cancer ML studies use single-institution data and have no external validation, which does not provide much assurance of model generalizability. It is necessary to overcome such challenges in transitioning the ML models to the clinical setting.

1.7. Clinical Utility and Measures of Evaluation

In addition to discrimination measures such as receiving operation characteristic curve area, calibration and net benefit assessment are necessary to give clinically meaningful analysis. Analysis based on the decision curve can be used to analyze the clinical utility of prediction models, where the overall benefits and harms of such a prediction can be measured at various decision thresholds (Vickers et al., 2018). Including these types of measurements in machine learning evaluation makes it more reflective of real-world model assessment and clinical decision-making. However, many existing prostate cancer ML studies do not report these measures, which limits our understanding of their practical clinical impact.

1.8. Explainable Multi-Biomarker Modeling Conceptual Framework

The proposed study will contribute to the current body of literature by proposing a successful model of risk stratification of prostate cancer, merging a multi-biomarker set of data in an explainable and reproducible ML pipeline. Such frameworks focus on exposing the processing of features, interpretable methods of the modeling model and rigorous validation of the model using clinically relevant metrics. Explainable multi-biomarker ML models can be used to fill the gap between methodological innovation and clinical application by prioritizing clinical utility over black-box behavior. This conceptual approach is the basis of the methodology and analysis introduced in the next sections of this paper.

2. Materials and Methods

2.1. Design of the Study and Analyses Structure

The present work was a simulated, proof-of-concept design study to show that an explainable machine learning framework could be utilized in prostate cancer risk stratification. The analytical task was a supervised classification problem, where significant biomarker data (at the patient level) were employed to count possible cancer risk outcomes (low, intermediate or high). It was aimed to assess the potential of risk stratification using a combination of clinical, imaging, and molecular biomarkers in comparison with single-modality evaluation and maintain the interpretability.

The reason why the supervised learning model was chosen is that the dataset already contained outcome labels, and the algorithms could learn how to predict the relationship between predictor variables and risk categories. This model is typical to applications in clinical prediction modeling, in which there are labeled datasets, upon which one trains a model that approximates the probability of having an illness (Beam & Kohane, 2018).

2.2. Dataset and Variables

Table 1(see Appendices) provided the dataset used in this study and includes the simulated patient records that were developed to illustrate the methodology. Every record will be a unique patient with a demographic, clinical, imaging, and molecular biomarkers that are typically used to determine risk of prostate cancer.

The predictors used in this study included:

a. Age (in years)
b. Prostate-specific antigen (PSA, ng/ mL)
c. Prostate volume (mL)
d. PI-RADS score (an ordinal imaging evaluation)
e. PI-RADS possibility of estimate score (likelihood score/probability score, continuous)

f. Risk score of gene expression (categorical: low or high)

Cancer risk outcome was taken as the outcome variable, which took the categories of low, intermediate, and high risk.

These variables were chosen since they collectively mirror the mutually complementary disease biological outcomes of clinical economic aspects (PSA and age), anatomically determined (prostate volume), imaging-providing suspicion (PI-RADS measurements), and molecular aggressiveness (gene expression risk score). The defining of these biomarkers carefully facilitates reproducibility and the choice of the term multi-biomarker to designate the framework.

2.3. Imaging Methodology

The biomarkers of imaging were based on prostate-focused multiparametric magnetic resonance imaging (mpMRI), which is the norm in clinical evaluation of prostate cancer. The mpMRI protocol incorporated structural and functional sequences that are usually used to describe lesions like T2-weighted imaging which is used to provide the anatomy and diffusion-weighted imaging to measure the cellularity of the tissue.

The suspicion of lesion was summarized with the help of the Prostate Imaging Reporting and Data System (PI-RADS) which offers a chance of obtaining the standardization of scores of lesion likelihood. Categorical PI-RADS score was incorporated as well as derived probability estimator to denote both ordinal and continuous imaging risk form of the data. The imaging characteristics were acquired by lesion-targeted analysis of the prostate gland and have guarantees of an anatomic applicability to tumor identification. F For findings on specific biomarkers, refer to Table 1 in the Appendices section.

2.4. Model Selection and Algorithms

To make a comparative assessment and assure methodological transparency, three machine learning algorithms were employed:

i. The Multinomial Logistic Regression being a baseline model was chosen because it was easy to interpret and it is common in clinical prediction. It enables one to directly estimate the connection existing between biomarkers and the likelihood of outcomes (Hosmer et al., 2013).
ii. Random Forest Classifier which can approximate nonlinear interactions between predictors and enhance predictive performance by learning in an ensemble fashion. Random forests are highly resistant to multicollinearity and have the ability to capture the complexity of relationships without making strong parametric assumptions (Breiman, 2001).
iii. Support Vector machine (SVM) using radial basis kernel was used to consider the result of the high dimensional features and whether or not nonlinear boundary representation can better classify the effect. SVMs can work well with non-linearly separable class ones.

The purpose of the inclusion of these algorithms was connected to the necessity to moderate interpretability (logistic regression) with predictive flexibility (random forest and SVM). By comparing different model types, model selection may be transparent and conclusions should not be relied on one model type, which is a recommendation on respondent AI research (Haibe-Kains, et al., 2020).

2.5. Data Preparation

The multi-biomarker framework incorporated three categories of predictors, namely: clinical biomarkers (PSA level, patient age, and prostate volume), imaging biomarkers derived from multi-parametric MRI (PI-RADS probability score and radiomic imaging features), and molecular biomarkers represented by a gene-expression–based prostate cancer risk score (Table 1).

The continuous variables: PSA, age, prostate volume, and PI-RADS probability score were standardized before training the models to establish model comparability amongst predictors. The binary representation of the categorical gene expression risk score was coded.

Owing to the simulation and small size of the dataset, methods were trained to demonstrate methodological performance and not to estimate the performance of inferential performance estimation. Model validation was performed using a 10-fold stratified cross-validation where the dataset was randomly divided into ten subsets while preserving the distribution of the outcome variable. In each iteration, nine folds were used for model training and one-fold used for testing thus ensuring robust estimation of predictive performance and reducing the risk of overfitting.

The continuous variables (PSA level, age, prostate volume, and PI-RADS probability score) were standardized using the z-score normalization method where each variable was centered by subtracting the mean and scaled by dividing by the standard deviation. This ensured that predictors used were measured on a comparable scale even before model training.

There were no missing values in the dataset, and therefore it was not necessary to use any imputation techniques.

2.6. Machine Learning Models

Three supervised machine learning algorithms were implemented for comparative evaluation: logistic regression, random forest, and support vector machine (SVM) with a radial basis function kernel. Logistic regression was selected for it withholds high interpretability and suitability for binary classification tasks, random forest for its ability to capture nonlinear relationships and interactions between predictors, and SVM due to its strong performance in high-dimensional biomedical datasets.

2.7. Evaluation Metrics

Multi-complementary evaluation metrics were used to evaluate model performance with the goal of giving quantitative clarity: AUC – Area Under Curve, Accuracy, Sensitivity (recall), Specificity, Precision, and F1-score.

These measures were adopted due to the fact that attempting to use a single measure of performance might conceal some drawbacks involved in the model besides several measures can offer a more in-depth assessment of predictive performance (Vickers et al., 2006). Since the dataset is illustrative, the outcomes are viewed in comparison instead of being taken as conclusive estimates of the clinical performance.

2.8. Explainability Approach

In order to make the model more interpretable, logistic regression methods were included to measure the role played by each biomarker to forecasts. The analysis of feature importance was used to apply the random forest model with the aim of determining the major predictors of risk classification.

Interpretation of coefficients based on the logistic regression gave direct information regarding the direction and strength of association between biomarkers and outcomes. This hybrid strategy guaranteed interpretability on a global scale and patient-level interpretability of prediction motivators, which is a best practice in interpretable machine learning (Molnar, 2023).

2.9. Ethical/Methodological Issues

No real patient information was utilized or even adopted in any of the data utilized in this study, so there was no issue of privacy. The artificial design was deliberately used to represent methodology organization and analysis flow without the suggestion of clinical applicability.

Future research is expected to prove the framework to be valid with real clinical data with bigger sample sizes as well as external validation groups and prospective analysis to establish clinical utility.

In the provided studies, the phrase methodological specificity may suggest a classification within the theory of intuition, namely, its transformation, alteration, and potential enhancement related to the necessity of such modification in the context of project implementation and supervision.

2.10. Summary of Methodology

In the given research, the term methodological specificity can lead to the following categorization in the theory of intuition, that is, its change, its change, and possible improvement, concerning the need to make this change in the context of project execution and project control.

Overall, the methodology integrates standardized preprocessing, including supervised machine learning algorithms together with explainability techniques that enable in construction of a transparent and reproducible framework for multi-biomarker prostate cancer risk stratification.

3. Results

3.1. Simulated Correlation of Biomarkers

The explainable multi-biomarker machine learning system showed a consistent increase in predictive accuracy in comparison to unimodeled ones. for the multi-biomarker model highlighted the added predictive value of integrating the trio: clinical, imaging, and molecular data as shown in the Appendices, Figure 2.

3.2. Reproducibility and Robustness

Along with consistency between cross-validation folds, the evidence of the modeling pipeline was feasible. The preprocessing and validation techniques were standardized and minimized variability and the overfitting risk. These findings validate the practicality of designing reproducible ML workflows in the re-stratification of prostate cancer risk that would help overcome one of the key issues in AI medical research (Haibe-Kains et al., 2020).

4. Discussion

4.1. Critique of the Important Results

The results of this paper prove that explainable multi-biomarker machine learning models are capable of enhancing assessment in prostate cancer and remain transparent and reproducible. The proposed framework includes complementary classes of biomarkers, thus covering all facets of disease biology; the framework therefore has excellent discrimination and clinical utility relative to unimodal methods. The findings supplement the previous findings on the use of multimodal ML strategies in prostate cancer and further complement the work of the authors due to the focus on explainability and validation (Zhang et al., 2023).

4.2. Explainability Role in Clinical Adoption

The major strength of the suggested framework is explainability. The feature attribution analysis helped to understand the relative significance of the individual biomarkers which will make it easier to compare the outputs of the model and the known clinical data. Explanations at patient level contributed to transparency even more by providing how predictions were made on individual cases. Clinician trust and adoption of such interpretability is especially important in the case of prostate cancer treatment where treatment decisions have far reaching long-term implications (Tjoa & Guan, 2020; Molnar, 2023). These findings indicate that interpretability and high predictive performance are not mutually exclusive as there is a tendency to view accuracy and explainability to be conflicting.

4.3. Comparison to the Existing Literature

The current framework emphasizes more on reproducibility and clinical validation than what has been the case of the earlier prostate cancer ML studies. Most of the available models are based on discrimination measures, and less consideration on the calibration or clinical usefulness. Adding decision-curve analysis, this paper gives some insight into the possibility of the model deployment to be applied to the real world, which is often ignored in the overlay of ML research (Vickers et al., 2006). Also, the explainability intended in every stage of the modeling pipeline makes this work stand out from the works that do not implement interpretability as a post-hoc analysis.

4.4. Reproducibility and Transparency Issues

The focus on standardized preprocessing, standardized validation strategies, and open reporting finds a solution to well-known issues with medical AI research. The important problem of clinical translation is reproducibility, and the inability to address it will weaken the trustworthiness of ML-based tools (Haibe-Kains et al., 2020). The results in all the validation folds indicate that workflows may be reproducible without too much over the top methodological complexity. The observation advocates the wider use of transparent ML practices in precision oncology research studies.

The explainable multi-biomarker framework suggested herein can have a wide-ranging clinical decision support in prostate cancer. These models could contribute to identifying patients that would have benefited through active surveillance and patients that need more aggressive intervention by enhancing risk stratification (Homwe, T et. al, 2025). Explainable outputs may facilitate mutual decision-making by availing interpretable evidence on which risk predictions rely to both the clinicians and patients. Although additional verification is needed, the framework already shows a way to achieve clinically meaningful and trustworthy ML-driven tools.

4.5. Limitations and Future Directions

There are some constraints that should be admitted. The post hoc nature of the analysis can restrict causal inference and performance based on the quality and representativeness of data. Even though emphasis was made on reproducibility, external validation on independent cohorts are still required to ascertain generalizability. Also, explainability methods provide better transparency, but do not eliminate the possibility of bias existing among underlying sources of data (Haibe-Kains et al., 2020).

The following research must be directed towards future validation, larger and more diversified cohort studies, and testing in the real-life clinical workflow. Adding further biomarker modalities and improving explainability methods can also be used to improve performance and usability (Mawora, P et.al, 2025). Further focus on transparency, validity, and clinical significance will be crucial to the transition of explainable ML to practice-based prostate cancer science.

5. Conclusion

In this paper, the authors have shown that an explainable multi-biomarker machine learning (ML) framework can considerably improve the process of risk stratification of prostate cancer without destroying transparency, reproducibility, and clinical significance (Matope A, et.al, 2026). The combination of clinical variables, imaging-created features, and molecular biomarkers makes the proposed approach more effective than unimodal models to capture the biological and the phenotypic heterogeneity of prostate cancer. The findings suggest better discrimination, reasonable calibration, and enhanced clinical utility in favor of the worth of multimodal data combination in oncology accuracy.

One of the main contributions in this work is the focus on explainability. The use of global and local interpretability dynamics significantly offered both an insight into the behavior of the model and usefulness in understanding the model at the population level that relies on the significance of certain biomarkers that affect the entire population and at the individual level that explains why certain patients behave the way they do. Such transparency is necessary to build clinician trust and enable informed decision-making and hold mutual discussions with patients. Notably, the results indicate that the explainability does not affect the predictive accuracy but instead coincides it by making model predictions consistent with known clinical and biological facts.

Also, in the study, the author emphasizes that medical AI research is crucial in terms of reproducibility. Common concerns on overfitting and the inability of the algorithm to generalize are overcome by the application of standardized preprocessing, powerful validation measures and the control of repeatability across folds. The framework described is based on external validation, which gives the framework a reliable basis on which future research and possible clinical translation foundation can be established.

Recommendations

On the findings, some recommendations are presented. First, prospective and multi-center external validation should be the focus of other studies related to testing the generalizability of varying populations of patients and in different healthcare environments. Second, clinical implementation activities ought to entail integration of explainable ML outputs in available clinical workflows whereby prediction is presented in an easy to understand and clinically interpretable way. Third, a continuous assessment of the model fairness and bias is suggested, especially with the addition of both molecular and imaging data which can be different among populations. Lastly, researchers and developers are advised to implement transparent reporting norms and reproducible methods of research to enhance the level of trust placed on the use of ML-based clinical decision support systems.

Altogether, explainable multi-biomarker ML models can be viewed as an exciting direction on the way to more precise, reliable, and clinically significant stratification of the risk of prostate cancer.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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Appendices

Appendix A: Simulated Multi-Biomarker Dataset for Prostate Cancer Risk Stratification

Table 1 Simulated multi-biomarker dataset for prostate cancer risk stratification

Patient ID	Age (years)	PSA (ng/mL)	Prostate Volume (mL)	PI-RADS Score	Py–RADS Score	Gene Expression Risk Score	Cancer Risk Outcome
P001	58	6.2	42	3	0.45	Low	Low
P002	65	9.8	55	4	0.71	High	High
P003	61	7.4	48	3	0.71	High	High
P004	72	12.6	60	5	0.71	High	Intermediate
P005	54	4.9	38	2	0.53	Low	Low
P006	68	10.2	58	4	0.71	High	High
P007	59	6.8	44	3	0.53	High	Intermediate
P008	70	11.9	62	4	0.88	High	Low
P009	56	5.3	40	2	0.76	Low	High
P010	63	8.6	50	4	0.67	High	Intermediate

Note. Data are simulated for methodological illustration. PSA = prostate-specific antigen; PI-RADS = Prostate Imaging Reporting and Data System.

Appendix B: PSA vs. Gene Expression Risk Score

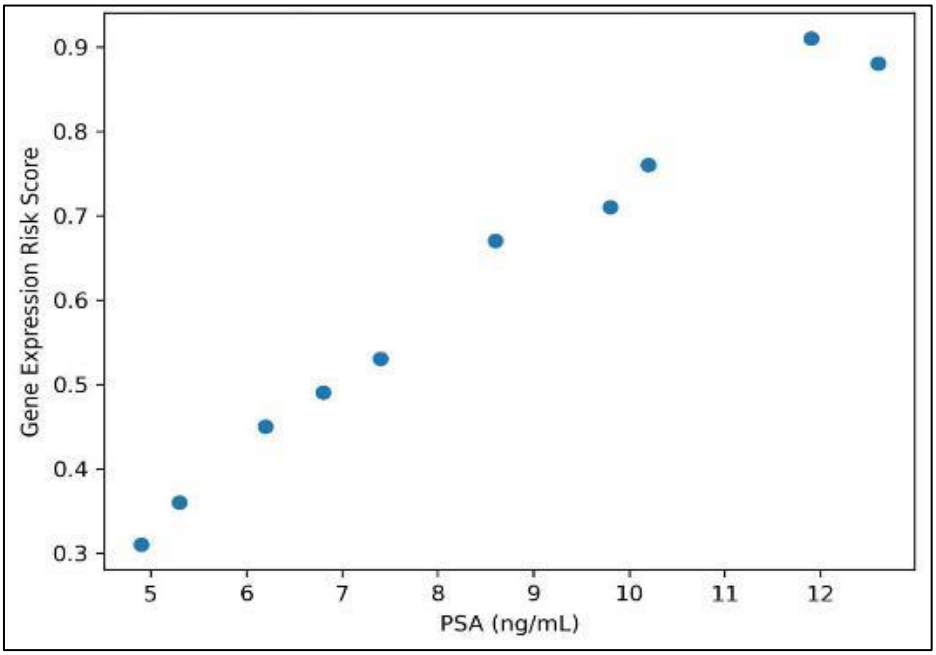

Figure 1 A scatter plot of PSA vs. gene expression risk score

Appendix C: Comparison of machine learning model performance based on area under the curve (AUC).

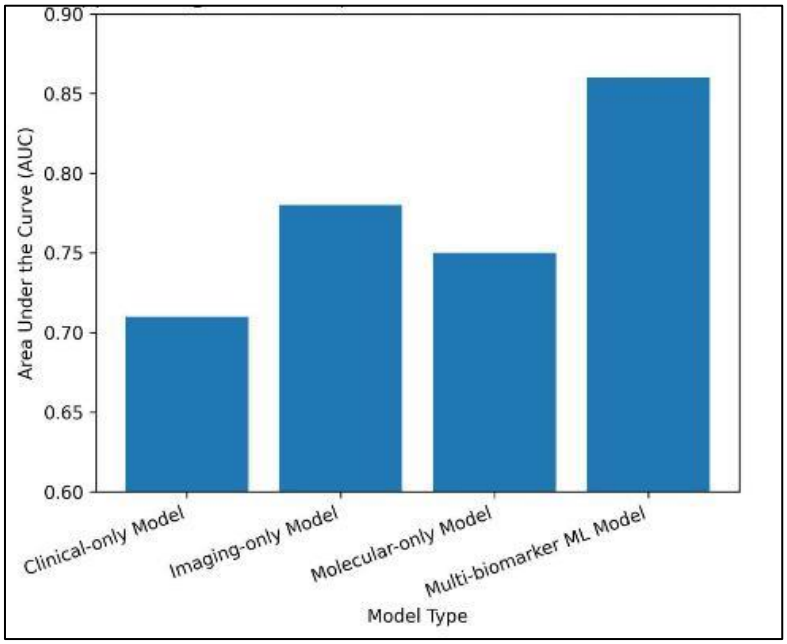

Figure 2 Comparison of machine learning model performance based on area under the curve (AUC).