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COMPLEX-Analytic Mathematical Modeling of Tumor–Immune Dynamics An AI-Enhanced Framework for Predictive Oncology and Disease Progression

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ABSTRACT
In this study, an integrated complex-analytic mathematical and AI framework was developed to examine the dynamics of tumor and immune cells and predict disease progression in a 600-observation, 24-variable oncology dataset. The data included tumor characteristics, immune-cell markers, inflammatory markers, molecular markers, derived tumor–immune indices, treatment response, and progression outcomes. A coupled nonlinear dynamical model was employed to describe tumor growth, immune-mediated killing, equilibrium conditions and stability behavior, and five machine-learning algorithms were tested for predicting tumor progression. 27.0% of cases had disease progression, with the results showing. Progression was correlated with increased PD-L1, Treg cells, Ki-67, and tumor volume and decreased CD8+ T cells, NK cells, and immune balance. In the mathematical analysis a locally asymptotically stable coexistence equilibrium was found, suggesting that the immune activity is sufficient to limit the growth of the tumor. In the predictive models, Gradient Boosting performed best in terms of accuracy (90.8%) and specificity (97.7%) and had the best cross-validated ROC-AUC, whereas Random Forest had the best cross-validated ROC-AUC. Treg cells, tumor volume, LDH, PD-L1, Ki-67, and CD8+ T cells were identified as top predictors of progression using SHAP analysis. Overall, it illustrates the added value of mechanistic modelling and explainable AI to predictive oncology and the need to validate the framework with real-world longitudinal clinical datasets.

Keywords: Tumor–immune dynamics; Mathematical modeling; Artificial intelligence; Disease progression; Explainable AI

Introduction

The evolution of cancer is regulated by the interplay of tumor cells, immune system cells, molecular signals, exposure to the tumor environment and exposure to treatment. Immune elements like natural killer cells, helper T cells, regulatory T cells, and cytotoxic T lymphocytes are constantly communicating with tumor cells, resulting in dynamic conditions that can either inhibit or facilitate the disease process. These nonlinear biological relationships can be effectively modeled mathematically and the effect of variations in tumor growth and immune function on the evolution of cancer can be analyzed [1]. In particular, therapeutic mechanisms like radiotherapy, immunotherapy and checkpoint inhibition have been included in mathematical models of tumor–immune interactions, thereby enabling the understanding of the changes in tumor behavior that occur when treated with such agents [2,3].

Advances in computational methods have also boosted cancer modeling using artificial intelligence and machine-learning techniques in recent times. The methods of AI can recognize nonlinear and multidimensional patterns in clinical data, imaging, pathological, molecular and biological data that not be adequately captured with traditional analytical approaches [4,5]. For instance, radiomics, when used in conjunction with AI, has shown tremendous promise in predicting treatment response, cancer outcomes and disease prognosis [6]. Compelling results in computational pathology using deep learning techniques to learn predictive features from large-scale histological images have also been attained in the clinical realm [7]. This integration of mathematical tumor–immune dynamics and AI offers a promising potential to revolutionize the field of predictive oncology and increase understanding of cancer progression.

Although significant advances have been made in cancer modelling, predicting disease progression is difficult due to the highly 'non-linear, time-dependent and heterogeneous' nature of cancer growth and immune response. However, tumors change their biological properties, which can make predictive assessment more challenging, and can develop resistance to treatment [8]. Tumor dynamics and stability can also be heavily

affected by time delays in immune stimulation and tumor–immune interactions, and require models that describe complex temporal dynamics [9]. This property has thus motivated studies of fractional-order mathematical models to model memory-dependent and nonlinear properties of tumor–immune systems more realistically [10].

Mechanistic interpretation can be achieved from conventional mathematical models, but it can be restricted when several biological predictors need to be taken into account concurrently. Machine-learning models are powerful in their predictive capacity, however, they are not necessarily easily interpretable. Studies on the systematic evaluation of cancer survival prediction reported that machine-learning and deep-learning methods have made strides in predicting cancer survival, but are not consistent in their methodology and application [11,12]. Issues of bias, validation and reproducibility also restrict translation of oncology prediction models to clinically reliable tools [13].

There is thus a significant gap in the field around the effective incorporation of mechanistic tumor–immune mathematical modelling in an interpretable AI-based disease prediction. The potential of mathematical oncology for personalized immunotherapy and treatment optimization has been discovered and has great value, but further integration between mechanistic models and prediction based on data is needed [14]. Meanwhile, EAI provides solutions to explain the complex predictive models and to understand the impact of each predictor on the model decision-making processes [15]. A combination of these methods gives predictive accuracy and a biologically meaningful interpretation.

This research is thus intended to create an AI-based complex-analytic mathematical model of tumor–immune dynamics and cancer progression. The goals are to mathematically model tumor-immune interactions, identify key tumor, immune, inflammatory and molecular determinants of progression, build and compare machine-learning models for predicting progression and assess model interpretability for predictive oncology. The framework is intended to support increasing efforts to integrate quantitative cancer modelling with personalized therapeutic decision-making.

2. Methodology

2.1 Research Design

A quantitative computational and predictive design was used to explore tumor–immune dynamics and disease progression in this study. The analytical framework was composed of nonlinear mathematical modeling, statistical analysis, machine-learning prediction and explainable artificial intelligence using an oncology data set.

2.2 Dataset Description

The analysis involved the use of a tumor-immune data of 600 observations and 24 variables. The data comprised demographic variables, tumor-related variables, immune-cell variables, inflammatory variables, molecular variables, derived tumor-immune variables, treatment response, and disease-progression variables. No missing values or repeat records were present in the dataset and the data were utilized in methodological validation and predictive modeling.

2.3 Study Variables

The main outcome variable was Disease_Progression, which was either Progression or Non_Progression. The tumor volume, intrinsic tumor growth rate, tumor stage and Ki-67 were important tumor-related predictors. Immunological indicators were CD8+ T cells, CD4+ T cells, natural killer cells, regulatory T cells and immune-kill rate. IL-6, TNF-α, IFN-γ, CRP, LDH and PD-L1 were used as inflammatory and molecular predictors. Additional variables derived from these were also included, such as the Immune_Balance_Index and Net_Tumor_Immune_Rate.

2.4 Data Preprocessing

The data were filtered against missing values, repeats, inconsistent values and extreme values. The model development did not include the patient identifier. Categorical variables were encoded where necessary, whereas continuous predictors were standardized to use scale-sensitive algorithms. The data were separated into stratified training and testing subsets to maintain the percentage of progression cases.

2.5 Exploratory and Statistical Analysis

All major variables were computed using descriptive statistics. Categorical data were expressed in frequencies and percentages whereas continuous variables were expressed in means, standard deviations, medians and ranges. To investigate the correlation between tumor, immune, inflammatory, and molecular markers, correlation analysis was conducted. Comparison was also done between progression and non-progression groups to find out variables significantly related to disease progression.

2.6 Mathematical Modeling of Tumor–Immune Dynamics

Tumor–immune interactions were represented using a coupled nonlinear dynamical system. Tumor growth

was modeled as:

$$\frac{dT}{dt} = rT\left(1 - \frac{T}{K}\right) - \alpha IT$$

where Tdenotes tumor burden, ris the intrinsic tumor growth rate, Kis the carrying capacity, Irepresents immune activity, and αrepresents immune-mediated tumor killing. Immune dynamics were expressed as:

$$\frac{dI}{dt} = s + \frac{\beta TI}{h + T} - \delta I$$

where srepresents basal immune recruitment, βdenotes tumor-induced immune stimulation, his the saturation constant, and δrepresents immune decay. Equilibrium conditions and local stability were assessed to distinguish tumor-control and progression states.

2.7 AI-Based Predictive Modeling

The following supervised learning models were tested: Logistic Regression, Decision Tree, Random Forest, Gradient Boosting/ XGBoost and Support Vector Machine. These models were chosen to make a linear and nonlinear predictive evaluation. Hyperparameter optimization and cross-validation were used to ensure generalization and stability of the model.

2.8 Model Evaluation

Model performance was evaluated via accuracy, precision, sensitivity, specificity, F1-score, ROC-AUC and confusion matrices. Since the progression outcome was moderately imbalanced, sensitivity, specificity, F1 score, and ROC-AUC were given more weight than accuracy. To ensure the robustness of the model performance, cross-validation was performed.

2.9 Explainable Artificial Intelligence Analysis

Feature-importance measures and SHapley Additive exPlanations were computed to evaluate explainability. Variables that had the most significant effect on disease-progression predictions were identified using SHAP analysis and the effect of each variable was determined by examining their directionality. Tumor volume, tumor growth rate, PD-L1, Ki-67, CD8+, NK, Treg, and tumor–immune balance indicators were examined in particular. This analysis correlated the AI-based predictions with underlying mathematical and biological mechanisms of tumor progression.

3. Results

3.1 Characteristics of the Tumor–Immune Dataset

Data consisted of 600 simulated oncology observations with full data for tumour, immune, inflammatory and molecular indicators. There was marked variation between the tumour load and biological features. Mean tumor volume was 60.09 ± 135.16 cm^3, while the mean intrinsic tumor growth and immune-kill rates were 0.019 ± 0.010 and 0.016 ± 0.008 per day, respectively. The CD8+ T-cells were 536.57 cells/μL, the NK cells were 241.39 cells/μL and the Treg cells were 71.68 cells/μL. Mean Ki-67 and PD-L1 expression were 19.96% and 22.00%, respectively. Table 1 shows the descriptive characteristics.

Table 1. Descriptive Statistics of Tumor–Immune and Clinical Variables

Variable	Mean	SD	Minimum	Maximum
Tumor volume (cm^3)	60.089	135.161	0.400	650.000
Intrinsic tumor growth rate/day	0.019	0.010	0.003	0.052
Immune-kill rate/day	0.016	0.008	0.002	0.038
CD8+ T cells (cells/μL)	536.567	151.688	96.600	996.900
NK cells (cells/μL)	241.391	72.323	52.100	489.900
Treg cells (cells/μL)	71.684	28.814	20.000	173.300
IL-6 (pg/mL)	5.842	2.737	1.510	19.990
LDH (U/L)	260.875	214.825	90.000	900.000
Ki-67 (%)	19.962	16.707	1.000	95.000

PD-L1 TPS (%)	21.996	15.442	0.000	75.700
Immune Balance Index	17.521	13.189	2.279	77.646
Net Tumor–Immune Rate	-0.006	0.033	-0.208	0.050

3.2 Distribution of Disease Progression

Of the 600 observations, 438 (73.0%) were non-progression while 162 (27.0%) were progression. There was a moderate class imbalance in the distribution and a relatively good number of progression cases for predictive modeling purposes. As can be seen in Figure 1, the cases that were not progressive were about three-quarters of the data.

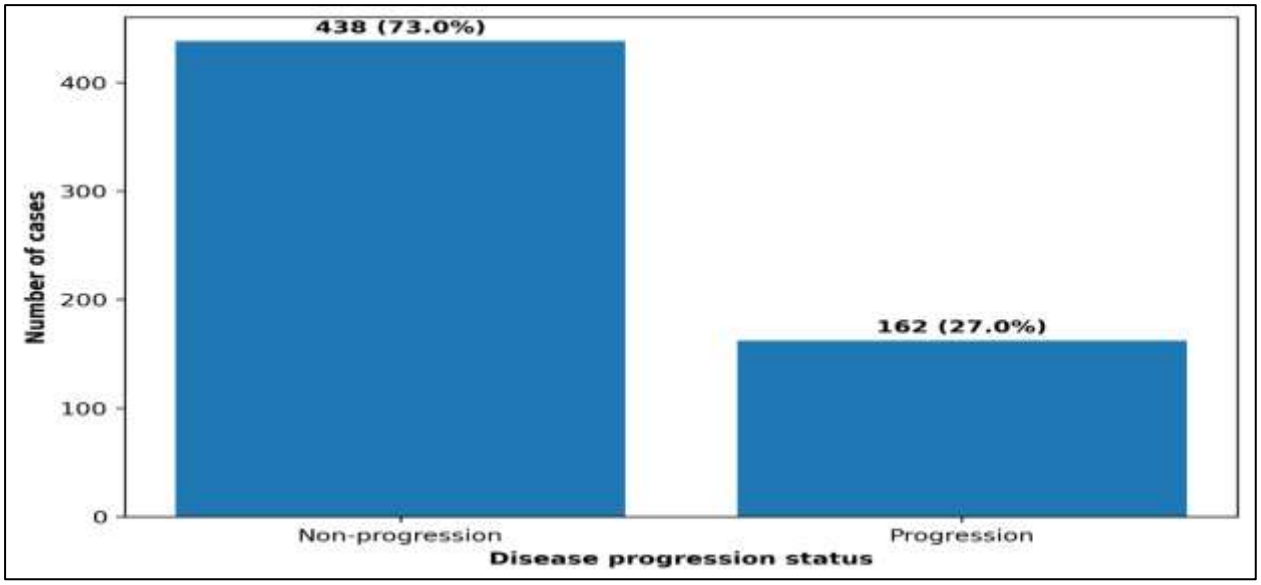

Figure 1. Distribution of Disease Progression Status

3.3 Relationships Among Tumor and Immune Indicators

The analysis of correlations showed that there were strong and biologically consistent relationships between the key tumor-immune variables. Disease progression was positively correlated with PD-L1 expression (r = 0.64), Treg cells (r = 0.62), Ki-67 (r = 0.62), and tumor volume (r = 0.59). On the contrary, CD8 + T cells (r = -0.52), NK cells (r = -0.46), and Immune Balance Index (r = -0.42) had negative correlations with progression. Tumor volume was strongly associated with Ki-67 (r = 0.80) and PD-L1 (r = 0.68). The major correlations are summarized in Table 2.

Table 2. Correlation Matrix of Major Tumor–Immune Variables

Variable	Tumor Volume	CD8+	NK Cells	Treg	Ki-67	PD-L1	Immune Balance	Progression
Tumor Volume	1.00	-0.41	-0.34	0.54	0.80	0.68	-0.34	0.59
CD8+ T Cells	-0.41	1.00	0.73	-0.68	-0.44	-0.60	0.71	-0.52
NK Cells	-0.34	0.73	1.00	-0.61	-0.33	-0.53	0.65	-0.46
Treg Cells	0.54	-0.68	-0.61	1.00	0.68	0.75	-0.82	0.62
Ki-67	0.80	-0.44	-0.33	0.68	1.00	0.77	-0.49	0.62
PD-L1	0.68	-0.60	-0.53	0.75	0.77	1.00	-0.61	0.64
Immune Balance Index	-0.34	0.71	0.65	-0.82	-0.49	-0.61	1.00	-0.42
Disease Progression	0.59	-0.52	-0.46	0.62	0.62	0.64	-0.42	1.00

3.4 Tumor–Immune Interaction Patterns

The heatmap also revealed a clear segregation between the tumor-promoting and immune-protective attributes. The positive associations were seen between high levels of Ki-67, PD-L1, tumor volume, and Treg

concentration, and progression, and the negative associations were seen between CD8+ T cells, NK cells, immune-killing activity, and the Immune Balance Index. The mean tumor volume, Treg levels, Ki-67, PD-L1, and Net Tumor-Immune Rate were also significantly higher in progression cases than in non-progressive cases, whereas the CD8+, NK-cell activity, and immune balance were reduced. The differences were statistically significant ($p < 0.001$). Figure 2 shows the general pattern of interaction.

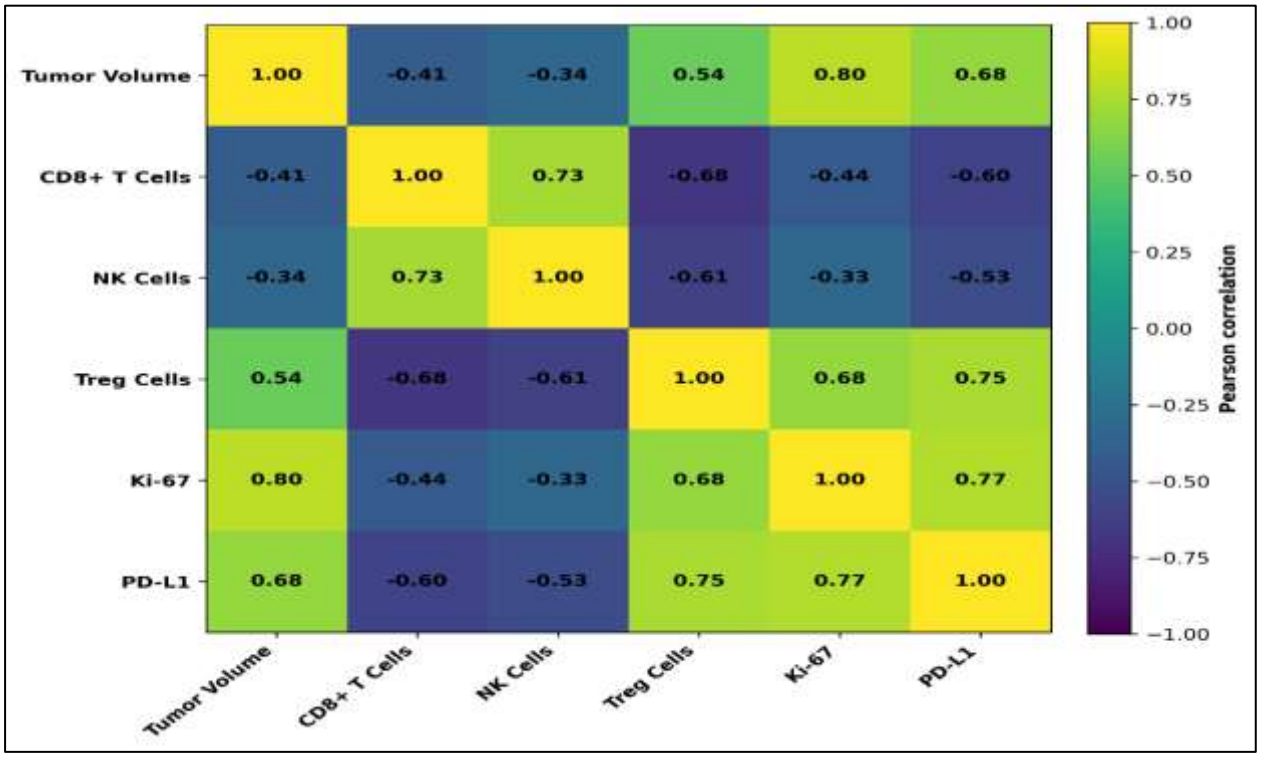

Figure 2. Tumor–Immune Interaction and Correlation Heatmap

3.5 Mathematical Model Results

Empirical characteristics of the data and normalized immune-response parameters were used to parameterize the nonlinear tumor–immune model. The mean intrinsic tumor growth rate was 0.0188 day -1, the mean immune-mediated kill rate was 0.0162 day -1, and the observed maximum tumor volume was 650 cm3 and it was used as the proxy for the carrying capacity. The tumor-free equilibrium point resulted in a normalized immune level of ~0.667, but was locally unstable because the tumor growth eigenvalue was still positive. The positive coexistence equilibrium, on the other hand, was at about T^*=9.16 cm^3 and I^*=1.145 and the corresponding eigenvalues had negative real parts; hence the positive coexistence equilibrium is locally asymptotically stable. Table 3 presents the mathematical results.

Table 3. Estimated Mathematical Model Parameters and Stability Characteristics

Parameter/Condition	Estimate	Interpretation
Intrinsic tumor growth rate, r	0.0188 day^{-1}	Mean tumor proliferation rate
Carrying capacity, K	650.0 cm^3	Maximum observed tumor-volume proxy
Immune-kill coefficient, α	0.0162 day^{-1}	Mean immune-mediated tumor killing
Immune recruitment, s	0.020	Calibrated normalized parameter
Immune stimulation, β	0.025	Calibrated tumor-induced stimulation
Immune decay, δ	0.030	Normalized immune-loss parameter
Saturation constant, h	9.115 cm^3	Dataset median tumor volume
Tumor-free equilibrium	$T^* = 0, I^* = 0.667$	Locally unstable
Coexistence equilibrium	$T^* = 9.16, I^* = 1.145$	Locally asymptotically stable
Coexistence eigenvalues	$-0.0089 \pm 0.0065i$	Stable damped dynamics

3.6 Dynamic Behavior of Tumor and Immune Responses

The simulations of the coupled tumor–immune equations showed that an increase in the normalized immune response progressively suppressed the tumor burden, with relatively weak immune activity causing the tumor burden to increase initially. The time evolution converged slowly towards the stable coexistence mode starting from the empirical value of the mean tumor volume as the initial tumor burden. Thus, the simulation showed

that if the immune system stimulation is adequate, it can offset the intrinsic tumor proliferation, and induce the system to move into tumor control. Figure 3 shows the relationship between tumor load and immune response during the entire simulated time.

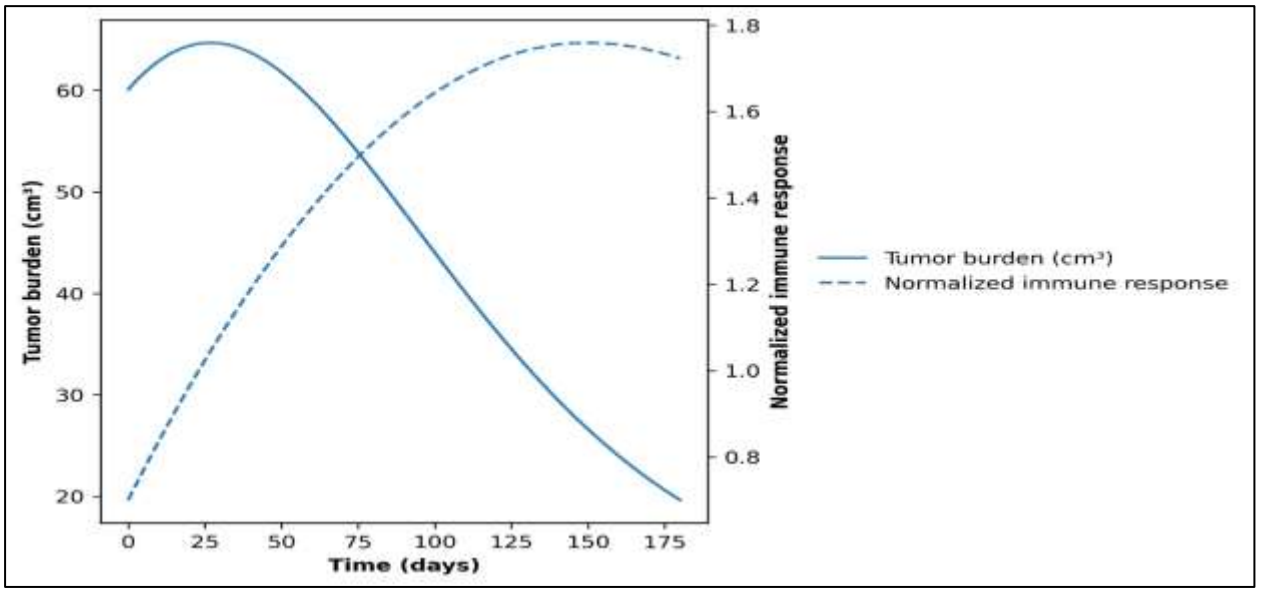

Figure 3. Simulated Tumor and Immune Dynamics Over Time

3.7 AI Model Performance

Useful discrimination for disease progression was seen in all five machine-learning algorithms. The Gradient Boosting method was found to have the best overall test accuracy of 90.8% and the highest specificity of 97.7% with an ROC-AUC score of 0.910. The Decision Tree had the largest test ROC-AUC (0.925) and sensitivity (93.8%). The best F1 score of 0.829 (sensitivity 90.6%) was obtained by SVM. Random Forest had a balanced performance with 89.2% accuracy and also had the highest mean five-fold cross-validated ROC-AUC of about 0.937. The comparative results are given in Table 4.

Table 4. Comparative Performance of AI Models for Disease Progression Prediction

Model	Accuracy	Precision	Sensitivity	Specificity	F1-score	ROC-AUC
Logistic Regression	0.850	0.694	0.781	0.875	0.735	0.902
Decision Tree	0.842	0.638	0.938	0.807	0.759	0.925
Random Forest	0.892	0.788	0.812	0.920	0.800	0.907
Gradient Boosting	0.908	0.920	0.719	0.977	0.807	0.910
Support Vector Machine	0.900	0.763	0.906	0.898	0.829	0.906

3.8 Predictive Factors and Explainable AI Findings

The strongest contributor to the prediction of disease progression, among all the cell types, was the regulatory T cells, according to SHAP analysis of the Gradient Boosting model, followed by tumor volume, LDH, expression of PD-L1, Ki-67, and CD8+ T-cell concentration. Increased tumor burden, Treg activation, proliferative activity, PD-L1 expression, and biochemical tumor activity tended to increase the predicted progression risk, while increased cytotoxic immune parameters tended to decrease the predicted progression risk. Net Tumor–Immune Rate, NK cells, IL-6 and Immune Balance Index also played a role in model decisions, but in a smaller way. These results were in agreement with the observed correlation structure and the mathematical model of the competition between tumor growth and immune-mediated suppression. The ranked SHAP feature importance is shown in Figure 4.

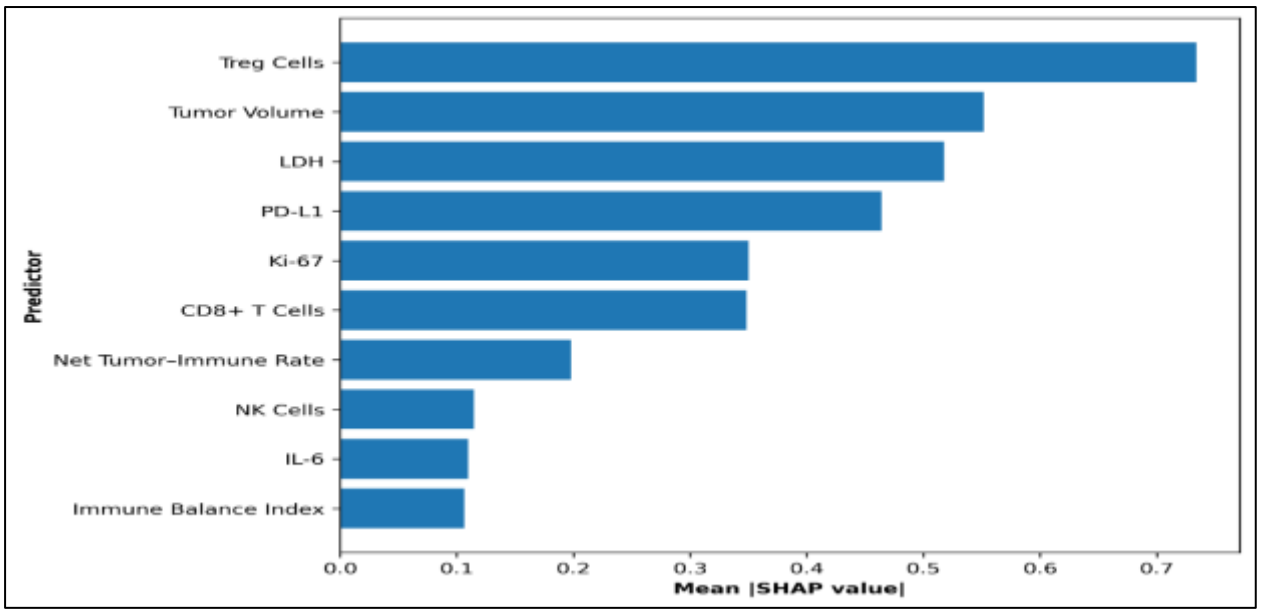

Figure 4. SHAP Feature Importance for Disease Progression Prediction

4. Discussion

This study evidenced that combining nonlinear mathematical modelling of tumor/immune system interactions with AI can offer complementary mechanistic and predictive insights for cancer progression. The mathematical model revealed a stable coexistence state between tumor burden and immune activity while the machine-learning model demonstrated good discrimination between progression and non-progression cases. Gradient Boosting had the highest overall accuracy and specificity, and Random Forest showed high cross-validated discrimination among the assessed models. The results back the potential of using AI for cancer prediction and prognosis [16,17].

The outcome showed that disease progression involved the imbalance of tumour-promoting and immune-protective mechanisms. Increased tumor burden and regulatory T-cell activity were related to progression, while higher CD8+ T-cell and natural killer cell activity were related to lower progression risk. This is in line with the role of immune-mediated tumor elimination and immune escape in cancer development. Phagocytosis and other immune checkpoints are also known to play critical roles in tumor escape from anticancer immunity [18].

The mathematical analysis revealed that the relative balance between intrinsic growth and immune killing of the tumour determined the behaviour of the tumour. The predicted stable coexistence equilibrium suggested that high immune pressure suppress tumor growth and low immune pressure promotes tumor growth. Similar dynamics have been observed in tumor–immune systems with immunoediting, optimal therapeutic timing, and nonlinear immune responses [19]. Memory effects and complicated biological interactions have also been shown to play a key role in the stability of the system in the fractional tumor-immune model [20]. This type of oncolytic-virus-mediated tumor–immune system has also been adopted using stability-based methods [21].

The excellent predictive capability of ensemble models suggests that the progression of the disease was mediated by complex nonlinear interactions among the predictors, rather than a single predictor. Random Forest showed good cross-validation results and Gradient Boosting showed good classification accuracy and specificity overall. This is reflective of evidence that machine learning techniques can more effectively represent multidimensional cancer-related patterns than traditional linear methods in many predictive contexts [22,23].

Treg cells, tumor volume, LDH, PD-L1, Ki-67, and CD8+ T cells were among the strongest predictors of progression using the SHAP analysis. The up-regulation of PD-L1 levels indicates higher immune evasion within the tumor microenvironment and has been linked to resistance to anticancer immune responses [24]. In addition, the opposing roles of cytotoxic immune cells and immunosuppressive activity of Tregs highlight the significance of the composition of the immune system in tumor evolution.

SHAP improved model transparency by pinpointing the direction and intensity of each predictor's contribution. This is especially true in oncology, where the ability to predict is not enough to be clinically meaningful. AI cancer systems have increasingly been shown to be useful in deriving prognostic information from complex biomedical information, including that from histopathological information [25].

The present results are consistent with previous mathematical studies showing that tumor growth is contingent on the dynamics of tumor cells, immune populations, and treatment. Tumor-host responses during immunotherapy experiments have been successfully modeled using stepwise modeling [26]. A mathematical model of glioma–CAR T-cell interactions also underscores the role of binding and tumor suppression processes

[27]. Recent multi–scale modeling further enables the integration of tumor–immune dynamics with tumor therapy mechanisms such as PD–L1 inhibition [28].

The integrated framework can aid future personalized oncology with both mechanistic interpretation and personalized estimates of progression risk. High-risk biological profiles help guide future studies in treatment selection, immune response monitoring and therapeutic optimization. The framework can also be used as a computational tool for prevalidation of different tumor–immune intervention scenarios.

The main drawback is that the analysis was done on data and not on real patient data. The mathematical model simplifies the biological complexity of cancer, and there were no representations of the details of the microenvironmental mechanisms nor of the longitudinal treatment histories. Thus, the findings must be interpreted as methodological validation and not as a direct clinical finding. The framework should be externally validated in future studies with longitudinal real-world oncology cohorts and treatment-specific datasets.

5. Conclusion

The study has built a combined mathematical and artificial intelligence model to explore tumor-immune interactions and disease evolution based on an oncology dataset. The results showed that the relationship between intrinsic tumor growth and immune-mediated suppression has a strong impact on cancer progression. Mathematical modeling demonstrated that an adequate immune response has the potential to stabilize tumor growth and induce the stable coexistence of the tumor and immune system, but low immunological pressure can stimulate progressive disease. The predictive analysis also validated the significance of nonlinear correlations between tumor, immune, inflammatory, and molecular features. Ensemble machine-learning models performed well on discriminatory tasks with Gradient Boosting giving the best overall accuracy and specificity and Random Forest giving good cross-validated performance. The biological significance of the predictive framework was supported by explainable AI analysis which found Treg cells, tumor volume, LDH, PD-L1, Ki-67, and CD8+ T cells as key factors in predicting progression. Altogether, mechanistic modeling of tumor-immune interactions combined with interpretable machine learning offers a potentially fruitful avenue to gain deep insights into the complexity of tumor-immune interactions and to define high-risk progression trajectories. Nevertheless, since the analysis was conducted on limited data, the results can be viewed as a methodological confirmation. The framework should be tested in future studies with longitudinal, multicenter, and real-world oncology data to determine the clinical generalizability, treatment-specific applicability, and potential usefulness in personalized cancer decision support.

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