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Machine learning for prediction of immunotherapy efficacy in nonsmall cell lung cancer from simple clinical and biological data

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BACKGROUND

- Immune checkpoint inhibitors (ICIs) are now a therapeutic standard in stage IV non-small cell lung cancer (NSCLC).
- However, 4 out of 5 patients don't respond to single agent ICI.
- Strong predictive markers for ICIs efficiency are still lacking.

OBJECTIVES

- Study the predictive power of **blood counts** before the start of immunotherapy
- Assess the utility of classical machine learning algorithms to **establish a predictive model of response**

MATERIAL AND METHODS

Data

- 298 2nd line or more stage IV NSCLC patients
- Pre-treatment blood count + clinical variables
- 12 variables :
 - hemoglobin
 - platelets
 - leukocytes
 - neutrophils
 - lymphocytes
 - eosinophils
 - monocytes
 - basophils
 - NLR (neutrophils to lymphocytes ratio)
 - PLR (platelets to lymphocytes ratio)
 - derived NLR (absolute neutrophils count / (white blood count – absolute neutrophils count))
 - BMI
 - patient status (dichotomized into < 2 or ≥ 2)
- Disease control (DCR) : patients with complete or partial response, or stable disease.

Machine Learning

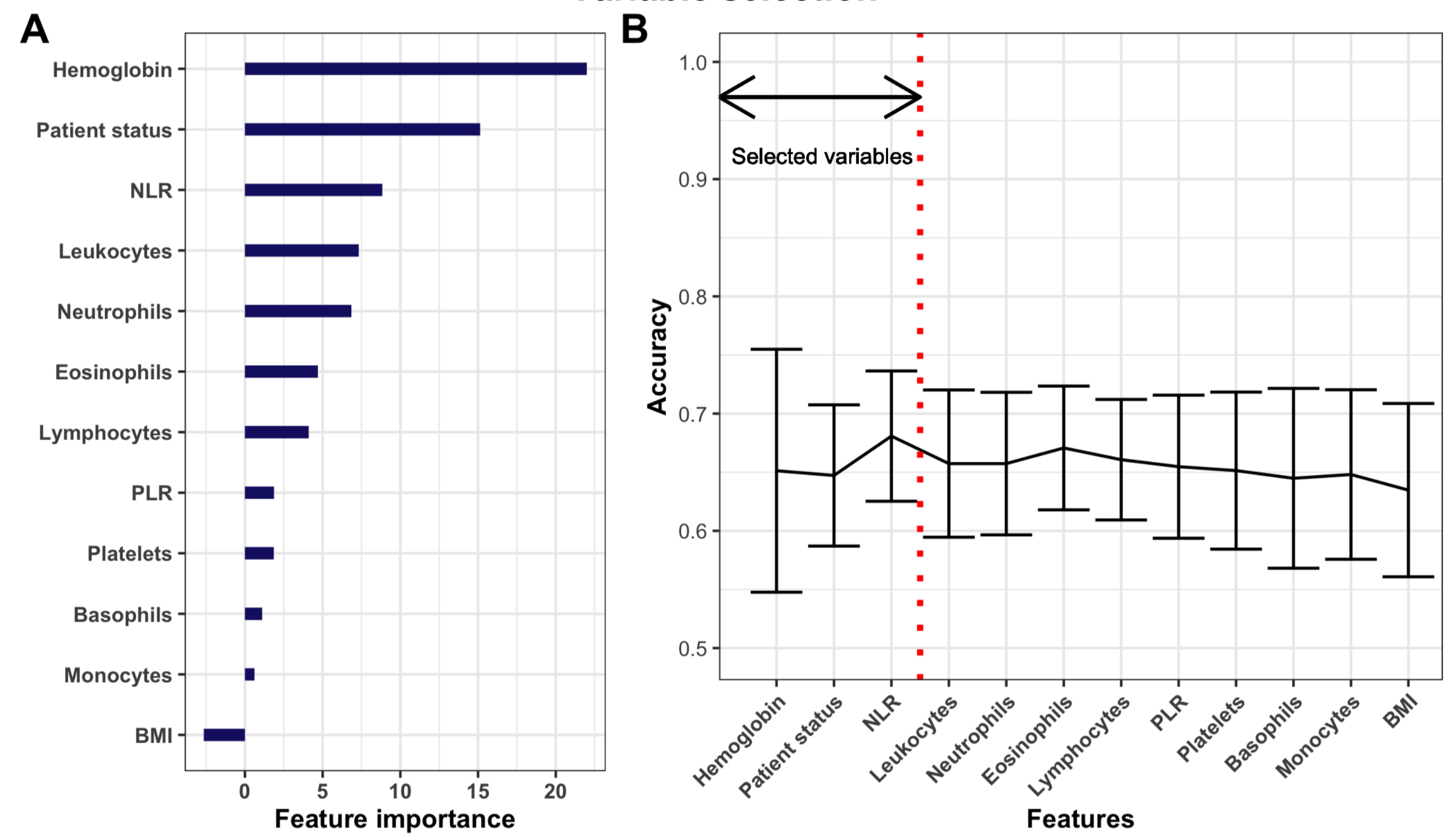
- Statistical analysis :**
 - univariable and multivariable logistic regression
- Feature selection :**
 - Feature importance from **random forest classification algorithm** (no tuning, 1,000 trees).
 - Sort by mean decrease accuracy
 - incremental logistic regression
 - Optimal set of features = maximal before observing a decrease in 10-fold cross-validated accuracy
- ML :**
 - Models :
 - logistic regression
 - random forest
 - single layer neural network
 - naïve Bayes
 - k-nearest neighbors
 - support vector models
 - tuned and trained on the train set (3-fold cross-validation, N=200)
 - predictions assessed on the test set (N=100)
 - **decision tree** for interpretability

RESULTS

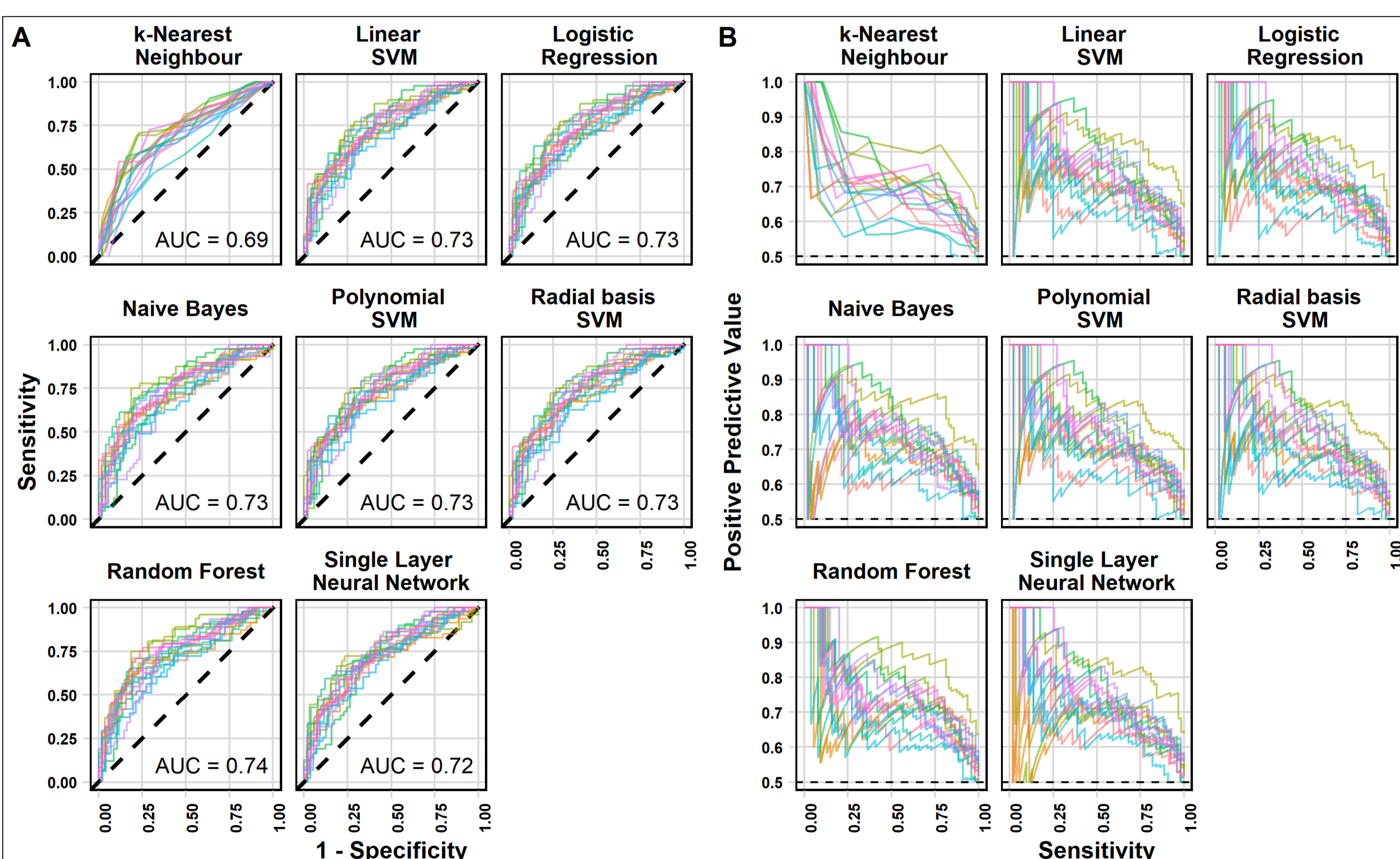
Logistic regression analysis for disease control

Variable	Univariable logistic regression		Multivariable logistic regression	
	Odds ratio [95% IC]	p signif	Odds ratio [95% IC]	p signif
Lymphocytes	1.1 [0.83, 1.4]	0.678	0.98 [0.15, 5.2]	0.984
NLR	0.49 [0.31, 0.73]	0.000879 ***	0.68 [0.098, 1.9]	0.651
Platelets	1 [0.82, 1.3]	0.762	1.3 [0.72, 2.4]	0.404
PLR	0.84 [0.64, 1.1]	0.156	1.1 [0.5, 2.4]	0.788
Leukocytes	0.68 [0.5, 0.89]	0.00791 **	0.6 [0.0022, 3e+02]	0.847
Hemoglobin	1.9 [1.5, 2.5]	9.26e-07 ***	1.8 [1.3, 2.4]	0.000122 ***
dNLR	0.63 [0.47, 0.83]	0.00155 **	0.8 [0.33, 2.7]	0.689
Neutrophils	0.62 [0.45, 0.83]	0.00232 **	1.5 [0.0047, 2.7e+02]	0.863
Monocytes	0.87 [0.69, 1.1]	0.226	0.86 [0.5, 1.4]	0.545
Eosinophils	1.3 [0.97, 1.9]	0.139	1.1 [0.75, 1.8]	0.582
Basophils	1.2 [0.95, 1.8]	0.177	1.2 [0.89, 1.8]	0.321
BMI	1.2 [0.95, 1.5]	0.123	1 [0.76, 1.3]	0.997
Performance status	0.5 [0.39, 0.64]	6.21e-08 ***	0.58 [0.44, 0.75]	7.79e-05 ***

Variable selection



Machine learning algorithms predictive performances



Summary of machine learning algorithms predictive performances

Model	Accuracy	ROC AUC	PPV	NPV	Sensitivity	Specificity
Random Forest	0.68 ± 0.04	0.74 ± 0.03	0.70 ± 0.08	0.68 ± 0.06	0.58 ± 0.08	0.78 ± 0.06
Logistic Regression	0.67 ± 0.04	0.73 ± 0.03	0.69 ± 0.08	0.67 ± 0.06	0.57 ± 0.09	0.77 ± 0.07
Naive Bayes	0.67 ± 0.04	0.73 ± 0.03	0.72 ± 0.07	0.65 ± 0.06	0.49 ± 0.07	0.83 ± 0.05
Single Layer Neural Network	0.66 ± 0.03	0.72 ± 0.03	0.69 ± 0.09	0.66 ± 0.06	0.54 ± 0.09	0.78 ± 0.07
k-Nearest Neighbour	0.66 ± 0.04	0.69 ± 0.04	0.65 ± 0.07	0.66 ± 0.06	0.58 ± 0.07	0.73 ± 0.07
Linear SVM	0.58 ± 0.09	0.73 ± 0.03	0.72 ± 0.09	0.58 ± 0.10	0.19 ± 0.25	0.94 ± 0.09
Polynomial SVM	0.55 ± 0.08	0.73 ± 0.03	0.61 ± 0.13	0.58 ± 0.13	0.19 ± 0.29	0.89 ± 0.23
Radial basis SVM	0.55 ± 0.08	0.73 ± 0.03	0.67 ± 0.17	0.56 ± 0.06	0.20 ± 0.28	0.88 ± 0.25

CONCLUSION AND PERSPECTIVES

Blood counts prior to ICIs (elevation of hemoglobin, decrease of NLR, leukocytes or neutrophils) and clinical status (good PS) were **significantly associated with better DCR** in multivariable analysis. The practical application of these associations using machine learning algorithms was able to **accurately predict individual response to treatment**. This could be improved further by increasing the number of variables in the model and should be further validated in an independent cohort.

References

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- Benzekry, S.; Grangeon, M.; Karlsen, M.; Alexa, M.; Bicalho-Frazeto, I.; Chaleat, S.; Tomasini, P.; Barbolosi, D.; Barlesi, F.; Greillier, L. Machine Learning for Prediction of Immunotherapy Efficacy in Non-Small Cell Lung Cancer from SimpleClinical and Biological Data. Cancers 2021, 13, x.

