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### ► To cite this version:

Sébastien Benzekry, Mathieu Grangeon, Mélanie Karlsen, Pauline Fleury, Maria Alexa, et al.. Machine learning for prediction of immunotherapy efficacy in nonsmall cell lung cancer from simple clinical and biological data. WCoP 2022 - World Conference on Pharmacometrics, Mar 2022, Cape Town, South Africa. hal-03935743

**HAL Id: hal-03935743**

**<https://inria.hal.science/hal-03935743>**

Submitted on 12 Jan 2023

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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

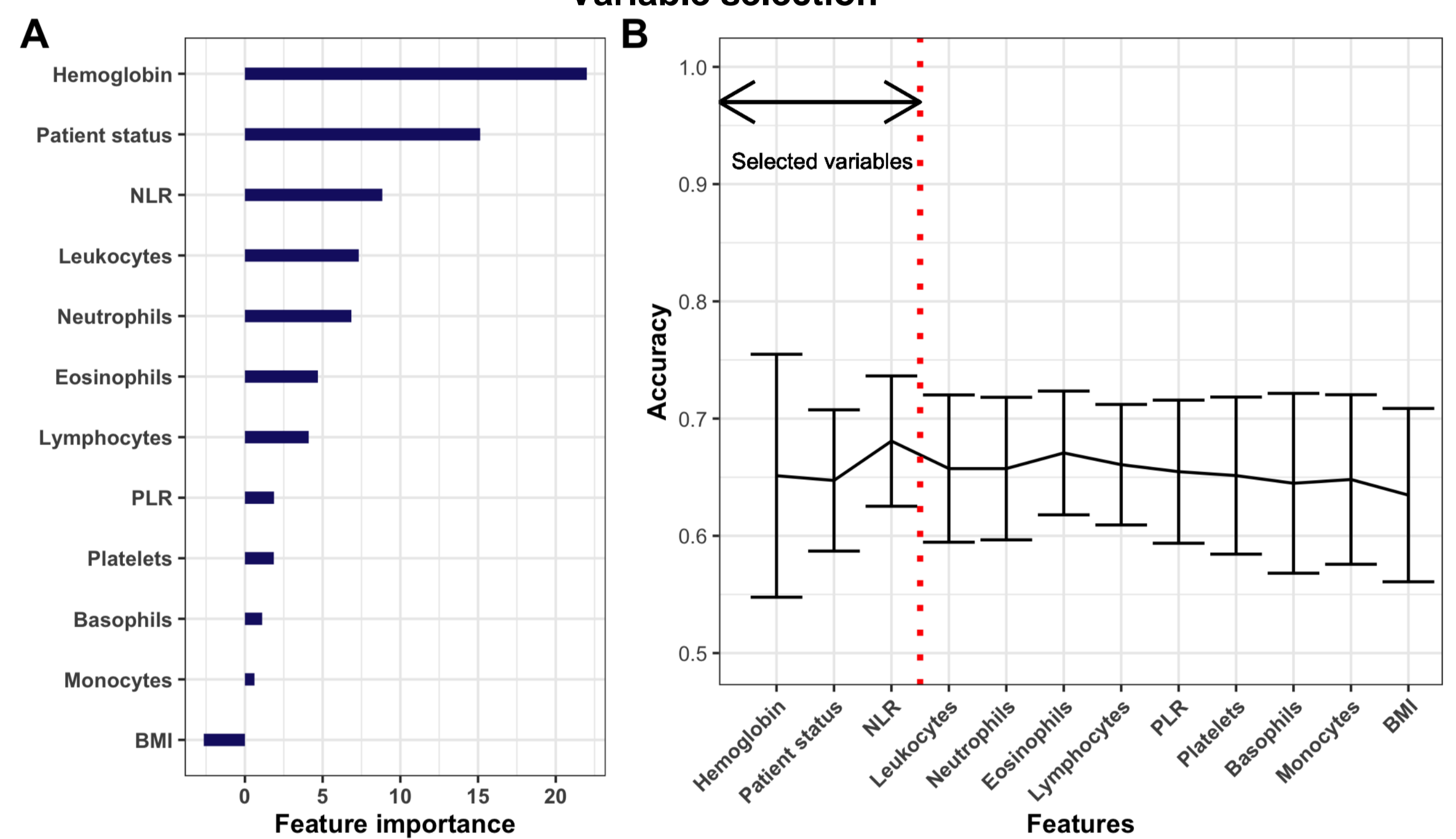
- Statistical analysis :**
  - univariable and multivariable logistic regression
- Feature selection :**
  - Feature importance from **random forest classification algorithm** (no tuning, 1,000 trees).
  - Sort by mean decrease accuracy
  - incremental logistic regression
  - Optimal set of features = 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

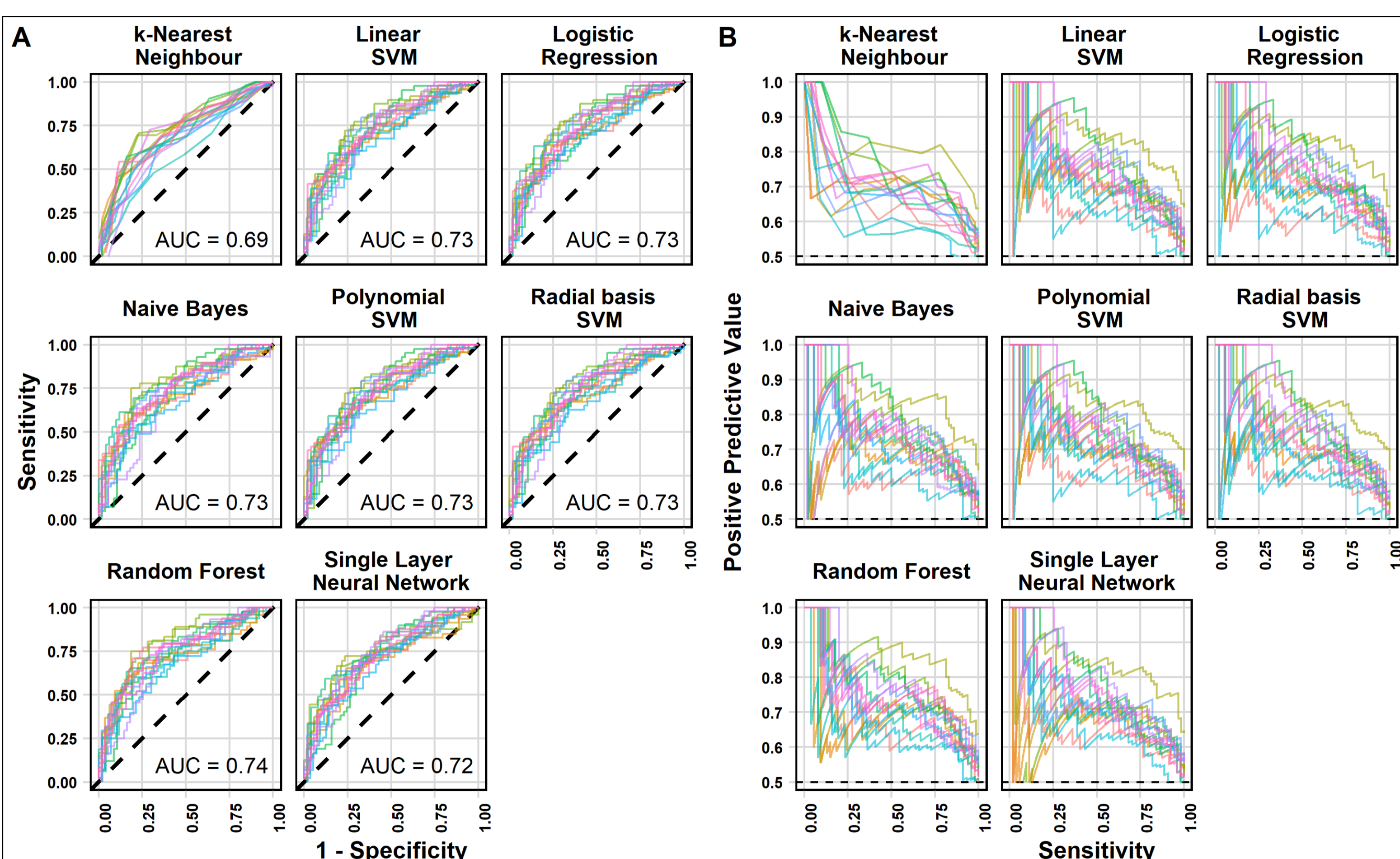
### Logistic regression analysis for disease control

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

- Benzekry, S.; Grangeon, M.; ... ; Barlesi, F.; Greillier, L.; et al. Machine learning for prediction of immunotherapy efficacy in non-small cell lung cancer from simple clinical and biological data.
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