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

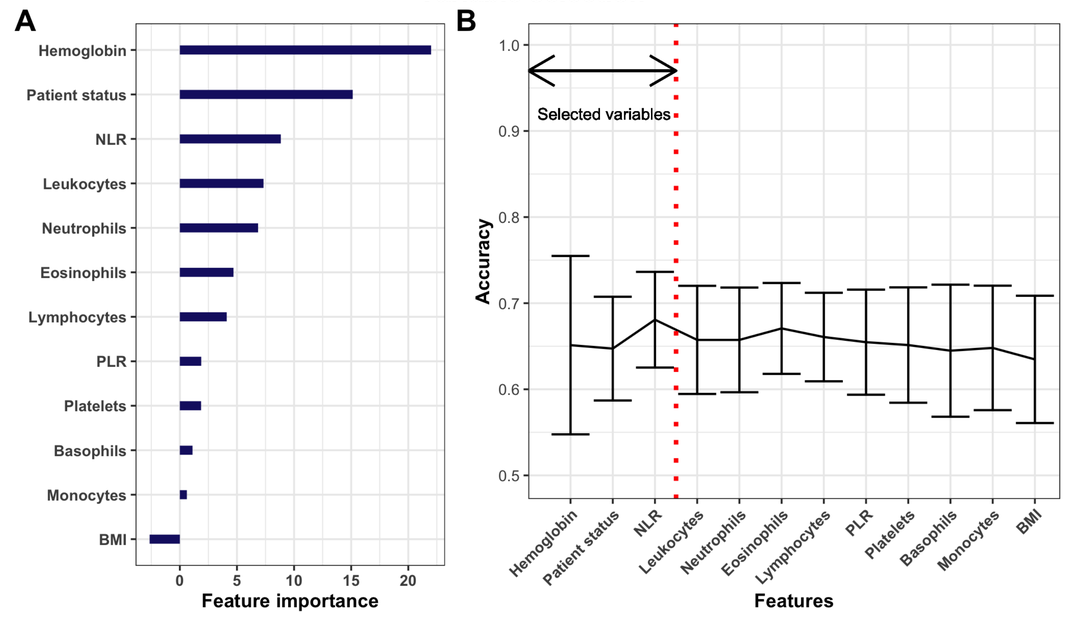
- **Statistical analysis :**
  - univariable and multivariable logistic regression
- **Feature selection :**
  - Feature importance from **random forest classification algorithm** (no tuning, 1,000 trees).
  - Sort by mean decrease accuracy
  - incremental logistic regression
  - Optimal set of features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

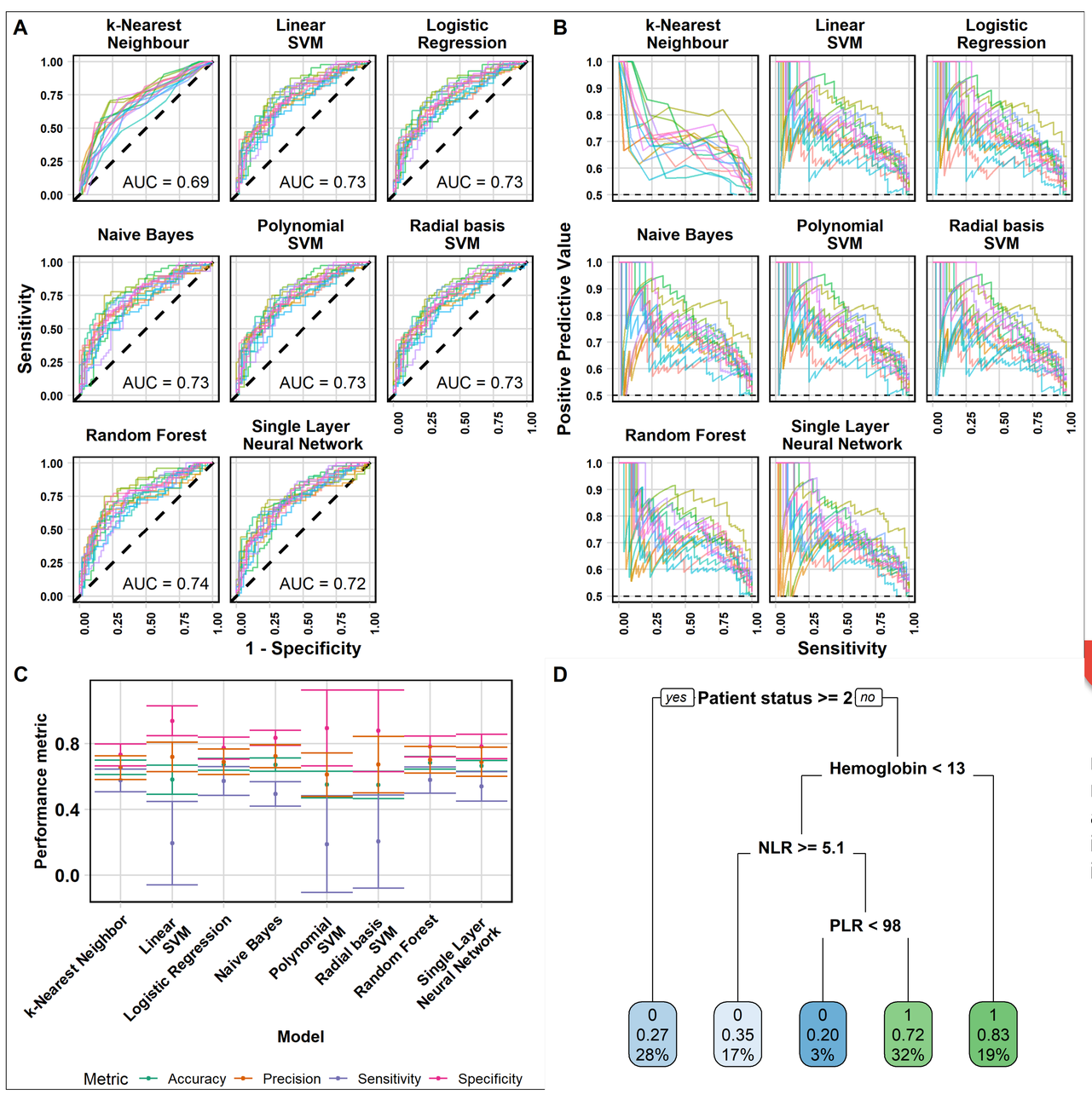
Logistic regression analysis for disease control

	Univariable logistic regression			Multivariable logistic regression		
Variable	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

1. 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.
2. 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.