#3071

Large retrospective validation study of metabolomic biomarkers for resectable lung cancer detection and risk assessment

Philippe Joubert [1], Lun Zhang [2], Clémence Boullier [1], Sophie Plante [1], Sabrina Biardel [1], Rupasri Mandal [2], David S. Wishart [2], Anatole Pelletier [3], Rashid Ahmed Bux [3], Jean-François Haince [3], Andrew Maksymiuk [4,5]

[1] Department of Pathology, Institut Universitaire de Cardiologie et de Pneumologie de Québec, Université Laval, Québec, QC, Canada, [2] Department of Biological Sciences, University of Alberta, Edmonton, AB, Canada, [3] BioMark Diagnostic Solutions Inc., Québec, QC, Canada, [4] Cancer Care Manitoba, Winnipeg, MB, Canada, [5] Department of Internal Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, MB, Canada

Background

Currently, the five-year survival rate of lung cancer patients is very low, largely attributed to newly diagnosed patients presenting with locally advanced or metastatic disease. Cancer can be regarded as a metabolic disease and many studies published aimed at identifying robust metabolites for lung cancer diagnosis using plasma samples. The purpose of this study is to validate whether a panel of metabolomic biomarkers would improve risk assessment for lung cancer detection in a large retrospective study using patients that underwent lung cancer resection, and to understand the potential role and intersection between lung cancer and other lung diseases.

Methods

Our study included plasma samples from 586 patients with surgery-confirmed lung cancer compared to 214 controls provided by the IUCPQ-UL Biobank. The control group consists of 90 healthy individuals and 124 with other non neoplastic lung conditions (Table 1). Plasma profiles of up to 138 different endogenous metabolites were generated using HPLC coupled with a targeted and quantitative mass spectrometry (MS/MS) approach. Metabolite concentrations, clinical data, and smoking history were used to develop logistic regression models to identify lung cancer at different stages using significant biomarkers.

Cases	Controls
N=586	**N=214**
275 NSCLC Adeno (Stage I & II)	91 healthy
141 NSCLC Squamous (Stage I & II)	31 asthma
50 NSCLC Advanced Stages	46 COPD
120 Pulmonary neuroendocrine tumors (NETs)	8 Bronchiectasis
	38 COVID

Table 1: Summary patient population and subgroups

Results

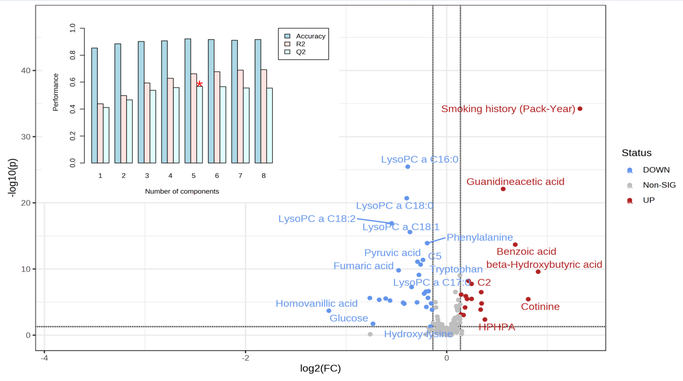
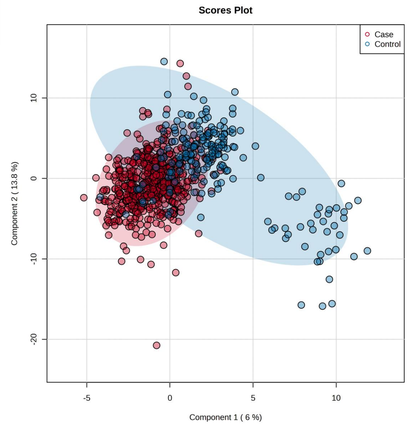


Figure 1: Differential metabolite concentration between lung cancer cases and control patients. The color dots indicate whether metabolite concentration is increased (red) or decreased (blue) in the controls vs. lung cancer patients. The upper left graph showed that combination of a least 5 metabolites is needed to yield accuracy > 90% and discriminate cancer cases from controls with strong diagnostic power.

Lung Cancer	Stage I	Stage II
AUC : 91% Se /Sp 91% / 78%	**AUC : 91%** Se /Sp 94% / 75%	**AUC : 93%** Se /Sp 92% / 81%
NSCLC	**Advanced Stage**	
AUC : 89% Se /Sp 87% / 74%	**AUC : 93%** Se /Sp 82% / 91%	

Figure 2: Summary of logistic regression prediction models in different subgroups. We constructed different model using the 9 most significant metabolites combined with smoking status to discriminate between controls vs all lung cancer cases, or controls vs NSCLC, as well as Stage I, Stage II and Advanced Stage NSCLC.



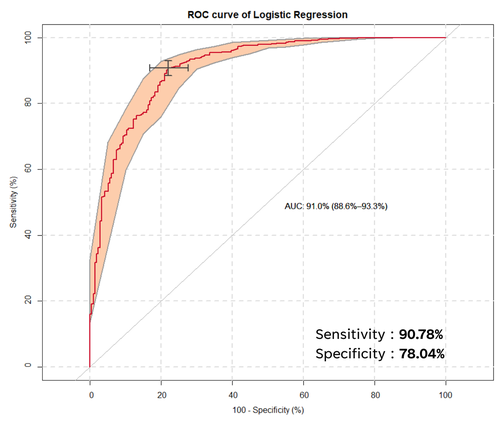


Figure 3: Contribution of metabolomic biomarker panel and smoking status for the detection and risk assessment of lung cancer. Partial least squares discriminant analysis (PLS-DA) scores plot shows the spatial separation of the cases from the controls using a set of 9 metabolites biomarkers. ROC curve were generated using the optimal logistic regression model for the lung cancer patients at all stages when smoking history is added. The area under the receiver-operator characteristic curves (AUC) and the 95% confidence intervals were calculated using the same biomarkers combination and smoking history. Sensitivities and Specificities were calculated at selected cut-off points determined by calculating the Youden Index (J = max {Sensitivity + Specificity – 1}).

Conclusion

- Separation of lung cancer patients from controls can be observed in the 2D scores plot using a panel of 9 metabolites.
- Linear regression model using metabolites and smoking status yielded an overall AUC of 0.91 with sensitivity of 91% and specificity over 78%.
- The blood-based metabolites panel validated on our current retrospective study exhibited robust performance for resectable lung cancer detection and risk assessment.
- A view and appreciation of cancer as a disease with a metabolic component should impact approaches to early diagnosis and overall cancer management and prevention.