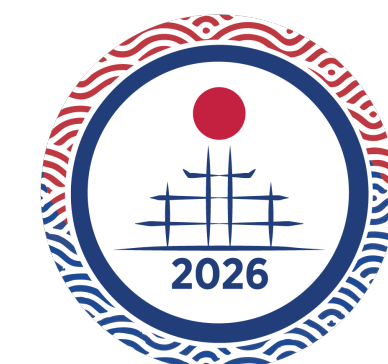


P2.171: Integrating Clinical Features and Single-Cell Immune Signatures for Risk Prediction of Checkpoint-Inhibitor Pneumonitis in Non-Small Cell Lung Cancer

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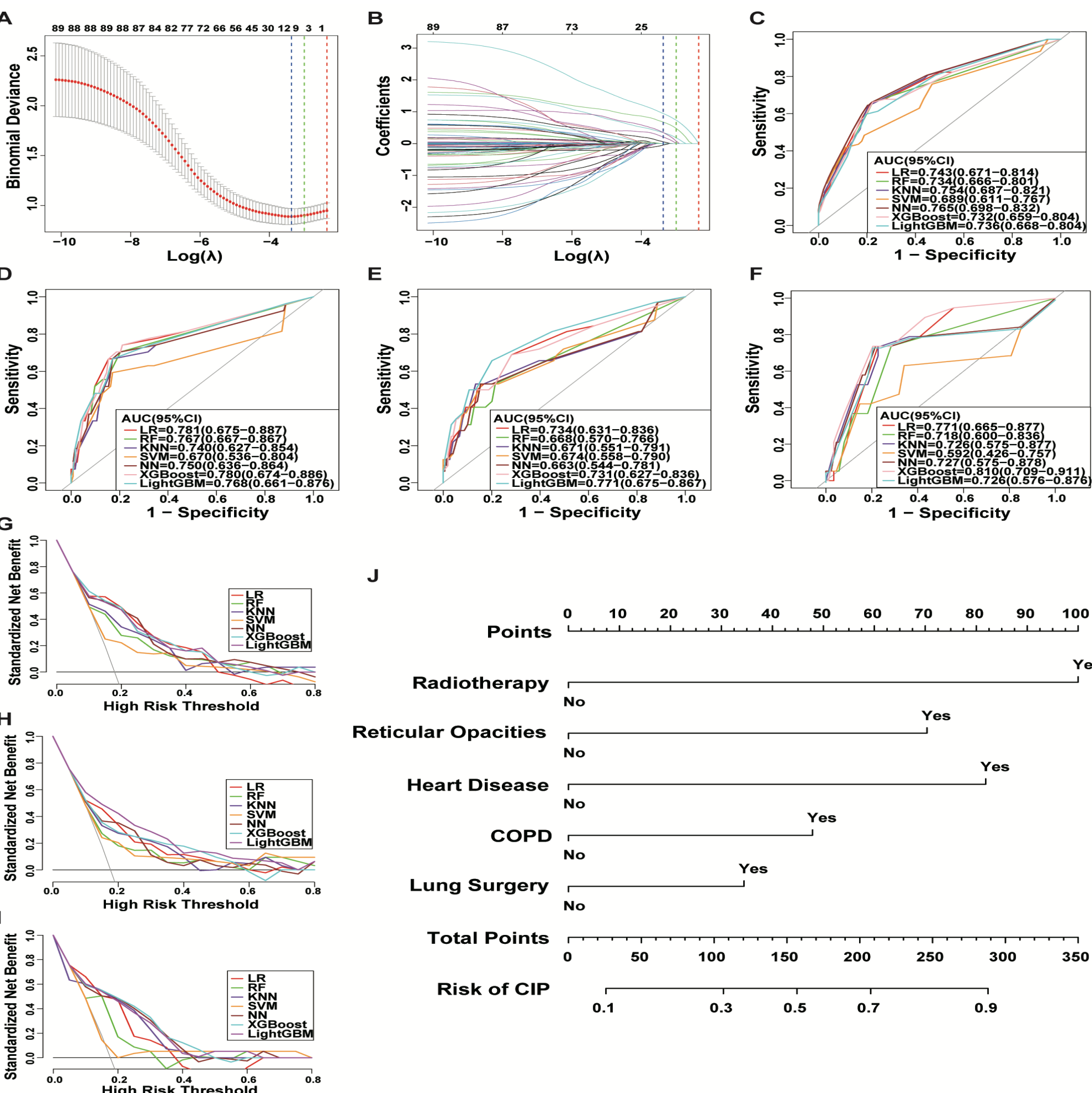
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INTRODUCTION

- ICIs have transformed NSCLC treatment, but CIP remains a serious toxicity.
- CIP risk factors are heterogeneous, limiting reliable pretreatment risk stratification
- Existing prediction models lack external validation and biological interpretability.
- Integrated clinical and immune biomarkers may improve individualized CIP prediction

Figure 1. Model development and validation for CIP risk-prediction.



METHODS

- Clinical cohorts:** 786 patients with advanced NSCLC were enrolled, including a modeling cohort and two independent external validation cohorts.
- Risk prediction:** LASSO regression was used for feature selection, followed by development and comparison of seven machine-learning models.
- Immune profiling:** High-dimensional CyTOF was performed on BALF samples to characterize CIP-associated lymphoid and myeloid immune remodeling.
- Translational validation:** Key immune subsets were validated in baseline tumor tissues and peripheral blood, then integrated with clinical variables to improve CIP prediction.

RESULTS

Clinical prediction model: Five key predictors of CIP were identified: prior chest radiotherapy, baseline reticular opacity, heart disease, COPD, and prior lung surgery. The LR model showed stable performance across internal and external validation cohorts (AUC 0.734–0.781).

BALF immune remodeling: CyTOF revealed marked immune dysregulation in CIP, characterized by enrichment of activated **ICOS⁺CD27⁺CD28⁺HLA-DR⁺CD4⁺ T cells (C02)** and reduction of an immunosuppressive **M2-like macrophage subset (C14)**.

Translational validation: The C02 subset was consistently increased, whereas C14 was reduced, in baseline tumor tissues and peripheral blood of patients who developed CIP, confirming the reproducibility of these immune signatures across different sample types.

Integrated prediction: Adding C02 and C14 immune features to the clinical model substantially improved CIP discrimination, with the best integrated model achieving an **AUC of 0.885**, supporting biologically informed individualized risk stratification.

Figure 2. BALF-CyTOF reveals activated CD4⁺ T-cell subset enrichment as a local immune signature of CIP.

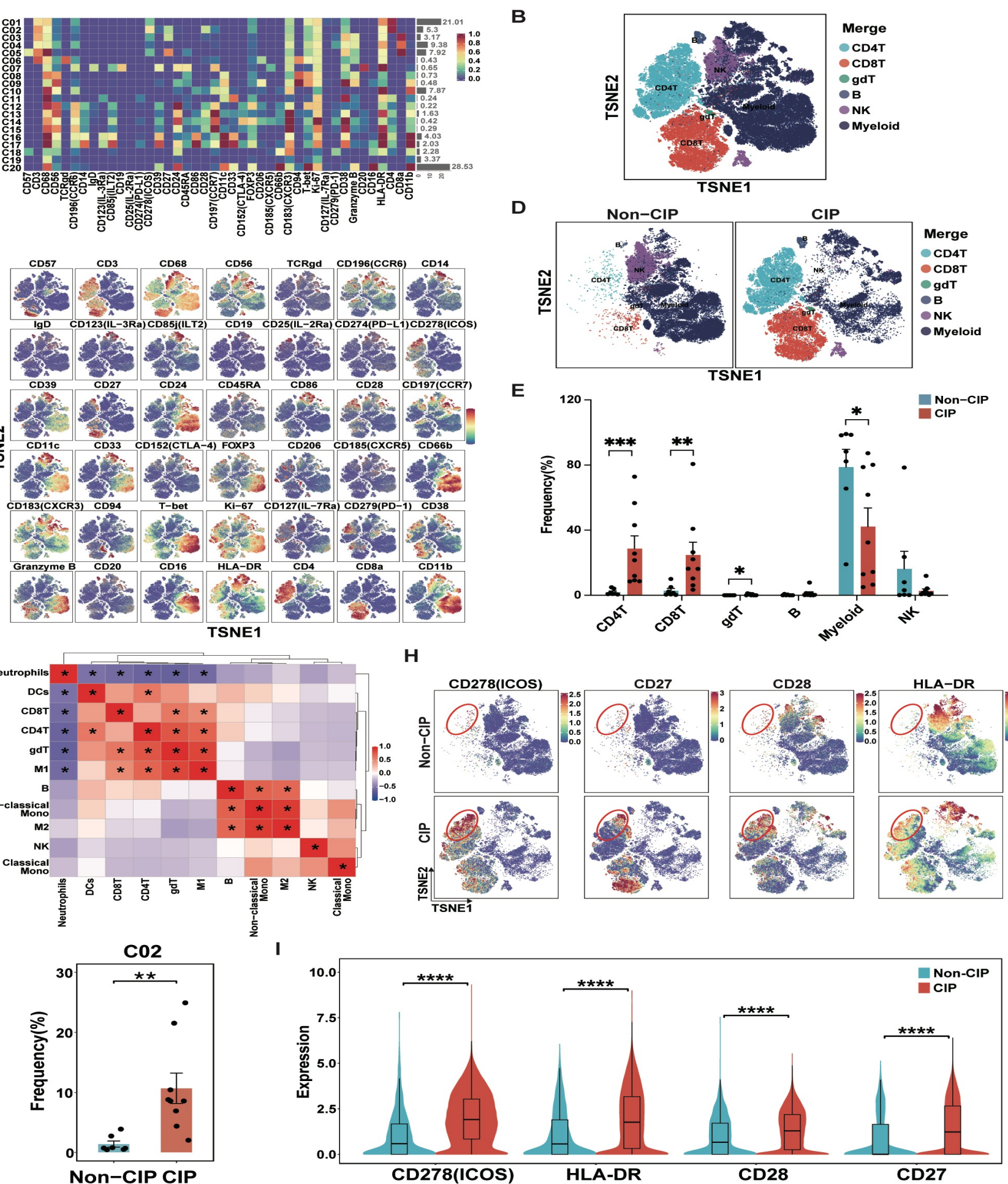


Figure 3. CIP is associated with monocyte-macrophage lineage remodeling and a reduction in the immunosuppressive phenotype of the M2-like macrophage cluster

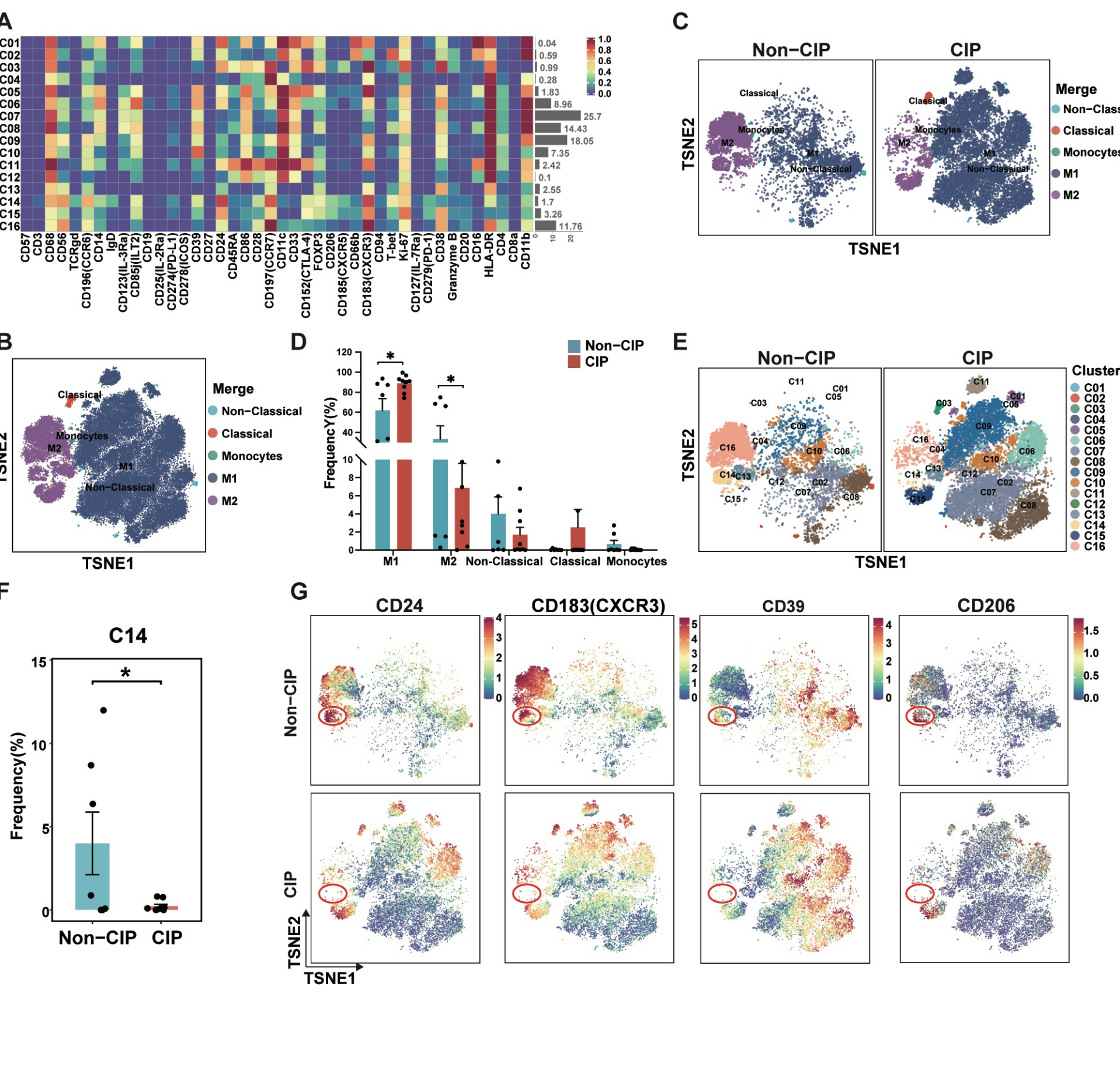
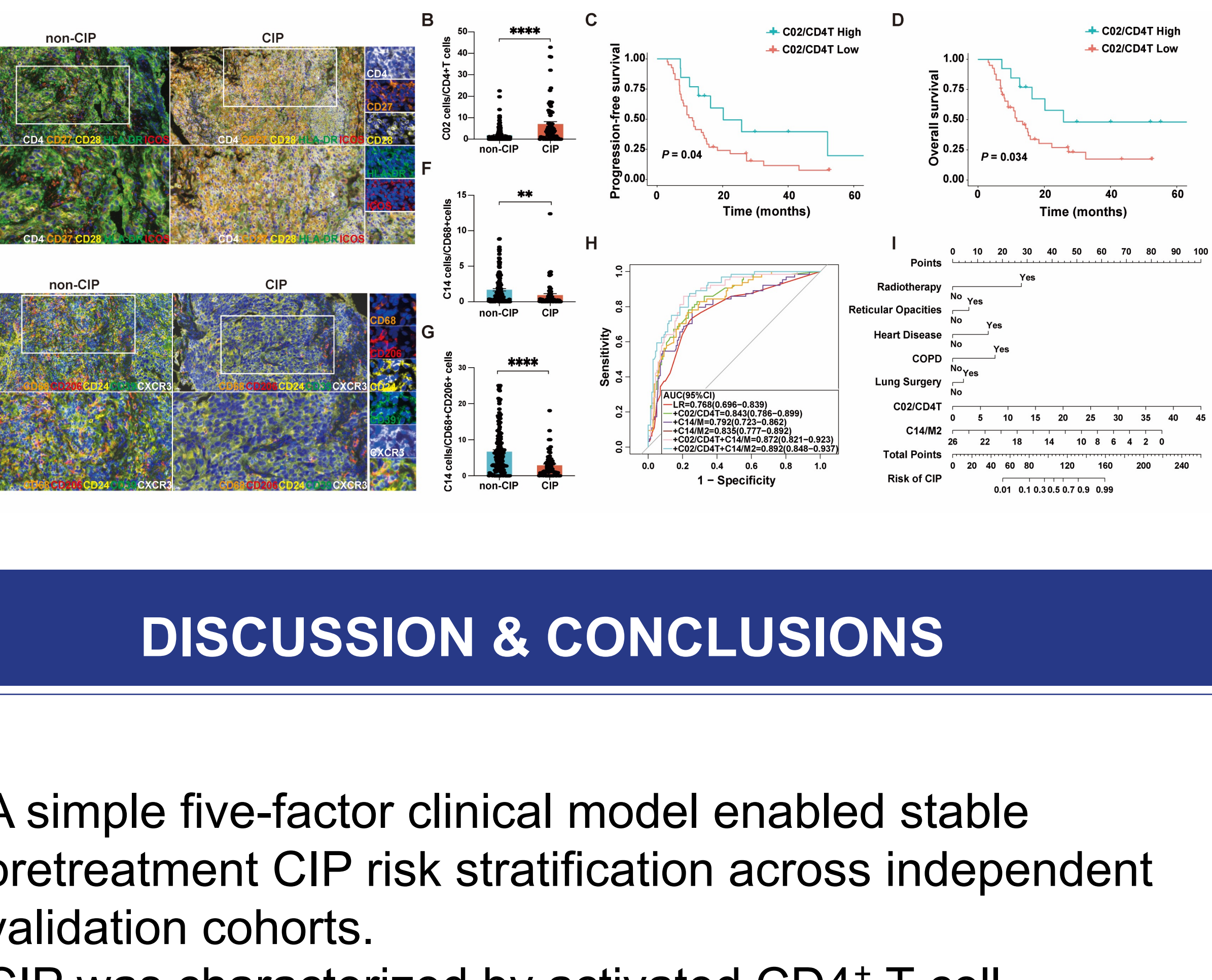


Figure 4. CyTOF-derived immune signatures are reproducible in baseline tumor tissues from the modeling cohort and improve CIP prediction.



DISCUSSION & CONCLUSIONS

- A simple five-factor clinical model enabled stable pretreatment CIP risk stratification across independent validation cohorts.
- CIP was characterized by activated CD4⁺ T-cell expansion and loss of immunosuppressive M2-like macrophage features.
- These immune signatures were reproducible across BALF, baseline tumor tissue, and peripheral blood, supporting translational robustness.
- Integrating C02 and C14 immune features with clinical variables substantially improved CIP prediction, with an AUC up to 0.885.
- Clinical-immune integration provides a biologically interpretable framework for individualized CIP risk assessment and early monitoring.

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