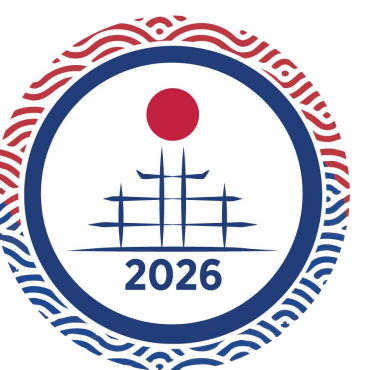




# EP04.05: Metabolic Characterization and Diagnosis of Checkpoint Inhibitor Pneumonitis Based on Exhaled Breath Metabolomics

**Y. Wu<sup>1</sup>**, M. Peng<sup>2</sup>, B. He<sup>1</sup>, S. Hong<sup>2</sup>, W. Lai<sup>1</sup>, C. Zhou<sup>1</sup>, H. Wang<sup>2</sup>, X. Qiu<sup>2</sup>, X. Su<sup>2</sup>, J. Wang<sup>2</sup>, H. Liang<sup>1</sup>, X. Lin<sup>1</sup>  
<sup>1</sup>State Key Laboratory of Respiratory Disease, National Clinical Research Center for Respiratory Disease, National Center for Respiratory Medicine, Guangzhou Institute of Respiratory Health, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China, <sup>2</sup>ChromX Health Co., Ltd., Guangzhou, China  
**Correspondence:** linxingqing81@163.com, 2506060319@qq.com



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## INTRODUCTION

Checkpoint inhibitor pneumonitis (CIP) is one of the most serious adverse events associated with immune checkpoint inhibitor (ICI) therapy, and its clinical diagnosis relies on an exclusion-based strategy with a risk of diagnostic delay. Exhaled breath volatile organic compound (VOC) analysis represents a non-invasive gas-phase metabolomics approach with emerging value in respiratory disease diagnosis. This study aimed to characterize exhaled breath VOC profiles of CIP patients using thermal desorption-gas chromatography/mass spectrometry (TD-GC/MS), identify CIP-specific differential VOCs, construct non-invasive diagnostic models, and evaluate their diagnostic performance, providing biomarkers and early diagnostic tools for CIP.

## METHODS

This prospective, single-center, non-interventional diagnostic clinical trial was conducted at The First Affiliated Hospital of Guangzhou Medical University (April 2025 to March 2026). NSCLC patients receiving ICI therapy, patients with infectious pneumonia, and healthy volunteers were enrolled. Exhaled breath samples were collected using thermal desorption (TD) tubes and analyzed by TD-GC/MS. A total of 61 valid samples were stratified into 7 groups: CIP onset (n=12), pre-ICI cycle 5 (Pre-ICI\_C5, n=12), pre-ICI treatment 1 (Pre-ICI\_T1, n=12), infectious pneumonia controls (n=6), pre-CIP (n=3), post-CIP corticosteroid treatment (n=4), and healthy controls (n=12). After peak detection and alignment (MS-DIAL), differential VOCs were identified via a dual-layer strategy combining univariate analysis (independent samples t-test) and multivariate analysis (OPLS-DA). Diagnostic models were constructed using five machine learning algorithms — logistic regression (LR), support vector machine (SVM), random forest (RF), K-nearest neighbor (KNN), and extreme gradient boosting (XGBoost) — and evaluated by Area Under the Curve (AUC). Longitudinal VOC dynamics and correlations with CIP severity (CTCAE 5.0), radiological subtypes, and clinical inflammatory markers were explored. The primary endpoint was the diagnostic performance (AUC) of machine learning-based exhaled breath VOC models for CIP identification.

## DISCUSSION AND CONCLUSION

### Key Message

- Exhaled-breath VOC profiles change characteristically at CIP onset and partially normalize after corticosteroid treatment.
- Hexanal and p-Cymene are the most robust candidate markers, consistently altered vs. Pre-ICI\_C5, Pre-ICI\_T1 and healthy controls.
- ML models built on these differential VOCs reached test-set AUC 0.91–1.00 for identifying CIP, including against infectious pneumonia.
- Pyruvic acid, dimethyl disulfide and pyridine correlate with CTCAE severity; ethylbenzene distinguishes mild (OP/HP) from severe (NSIP/DAD) subtypes.

### Future Directions

- Validate these VOC signatures in larger, multi-center cohorts with an independent test set.
- Translate TD-GC/MS findings into a portable e-nose / sensor platform for bedside, real-time CIP screening.
- Integrate breath metabolomics with radiological and other -omics data for a composite early-warning tool to safely guide immunotherapy continuation.

## REFERENCES & ACKNOWLEDGEMENTS

### Acknowledgements:

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### Artificial Intelligence (AI) Use Disclaimer:

No AI tools were used in the development of this poster's content.

## RESULTS

25 differential VOCs (16 after deduplication) were identified across four pairwise comparisons(Fig. 1). **Hexanal** and **p-cymene** were consistently detected across all three comparisons involving immunotherapy-phase groups and healthy controls. Machine-learning diagnostic models achieved test-set **AUC 0.91–1.00** across the four comparisons (Fig. 2). Most differential VOC abundances decreased at CIP onset and recovered following corticosteroid treatment(Fig. 3). Pyruvic acid, dimethyl disulfide, and pyridine were negatively correlated with CIP severity grade. Ethylbenzene was negatively correlated with radiological subtype severity, serving as the only differential VOC distinguishing mild (OP/HP) from severe (NSIP/DAD) patterns(Fig. 5).

Figure 1. Differential VOCs

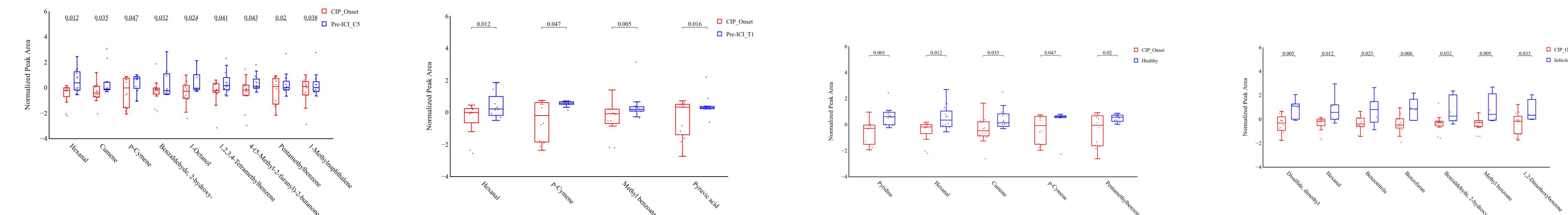
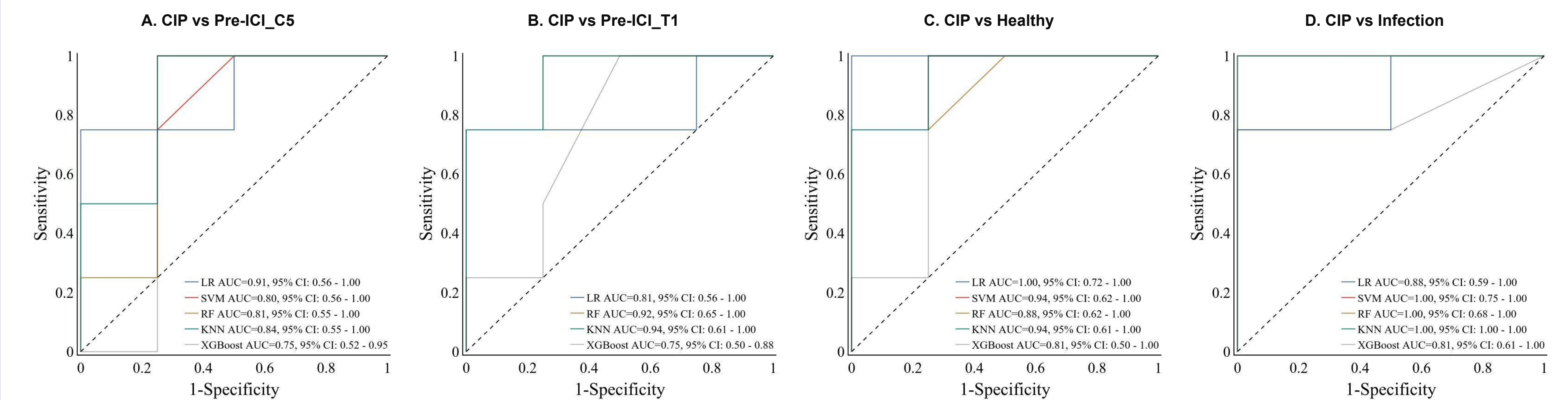
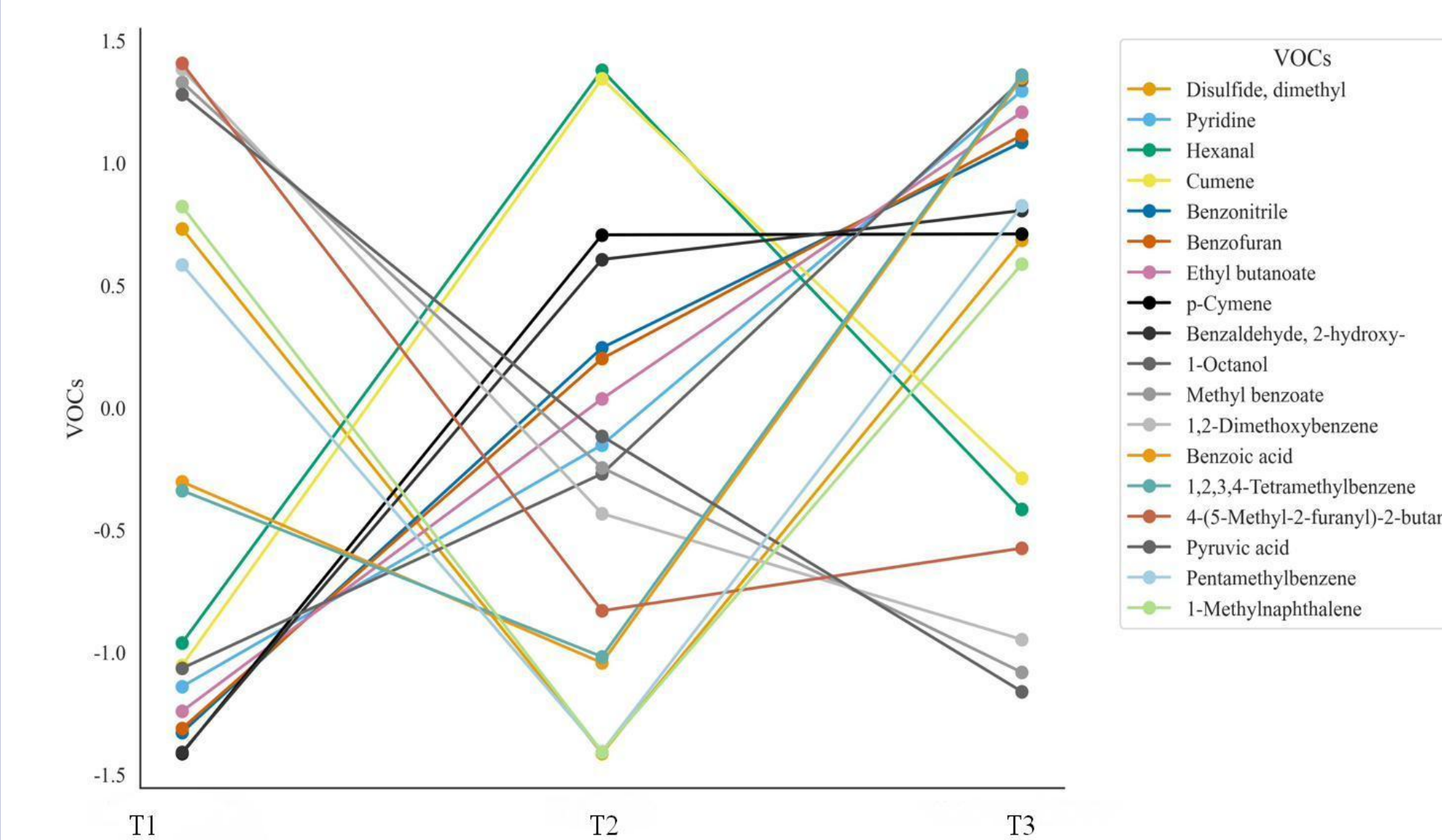


Figure 2. Diagnostic performance (test-set ROC curves, 5 ML models)



Best model per panel: LR AUC=0.91 (C5); KNN AUC=0.94 (T1); LR AUC=1.00 (Healthy); KNN AUC=1.00 (Infection).

Figure 3. CIP is reversible: individual-patient VOC trajectory

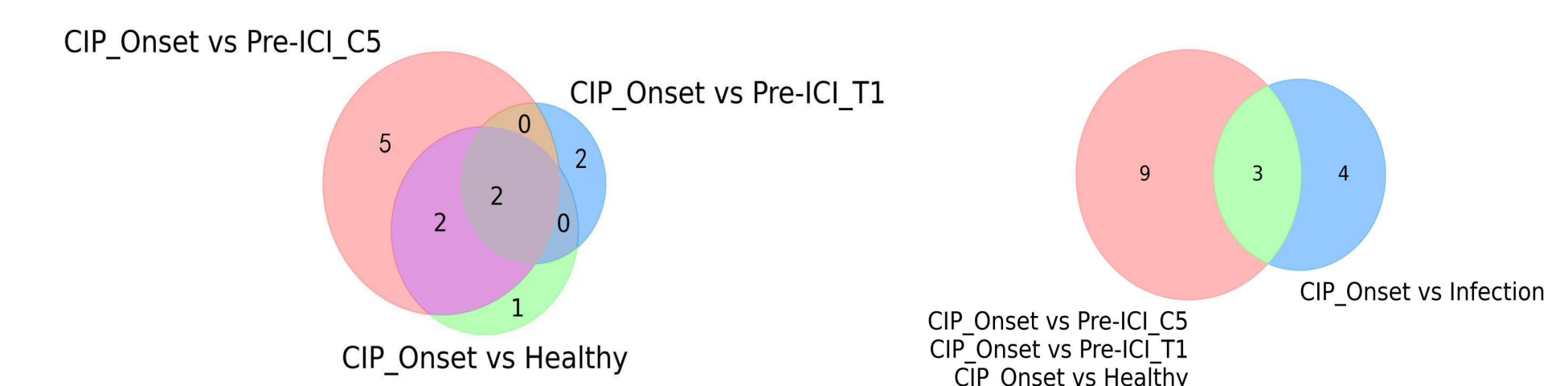


### 16 candidate VOCs tracked in one patient across:

- T1: mid-immunotherapy
- T2: CIP onset
- T3: post-corticosteroid recovery

Most VOCs dip at CIP onset and rebound after treatment — a reversible signature consistent with active, treatable inflammation.

Figure 4. Overlap of differential VOCs across comparisons



Left: Hexanal & p-Cymene overlap across CIP vs Pre-ICI\_C5 / Pre-ICI\_T1 / Healthy (n=2 shared).  
Right: 3 VOCs shared with CIP vs Infection (Hexanal, Benzaldehyde-2-hydroxy-, Methyl benzoate).

Figure 5. Association of Differential VOCs with Clinical Severity and Imaging Subtypes

