Preoperative CT Biomarkers Predict Chronic Lung Allograft Dysfunction After Transplantation

Lucy Pu [1], Emrah Duman [2], Ernest Chan [3], Norihisa Shigemura [4], Chadi Antonios Hage [5], Pablo Sanchez [6], Xin Meng [2]

[1] Department of Bioengineering, University of Pennsylvania, Philadelphia, Pennsylvania, USA

[2] Department of Radiology, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

[3] Department of Surgery, Section of Thoracic Surgery, University of Chicago, Chicago, Illinois, USA

[4] Division of Pulmonary Medicine and Critical Care, Department of Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA

[6] Division of Lung Transplant and Lung Failure, Department of Cardiothoracic Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA.

Rationale: Chronic lung allograft dysfunction (CLAD) remains the leading cause of late graft failure and mortality after lung transplantation, affecting over 50% of recipients within five years. Current diagnosis relies on spirometry, which detects decline only after irreversible injury. We hypothesized that quantitative imaging biomarkers derived from preoperative chest CT, particularly vascular morphology, body composition, and calcification metrics, could enable earlier, noninvasive prediction of CLAD risk and severity.

Methods: We retrospectively analyzed 999 lung transplant recipients (2007-2024) from the University of Pittsburgh Medical Center (UPMC). Fully automated deep learning pipelines quantified 61 CT features encompassing lung, vascular, body composition, and calcification compartments from preoperative scans. Demographic and clinical variables were also included. CLAD diagnosis and staging followed ISHLT criteria. Competing risk Fine-Gray (FG) and cause-specific Cox (CSC) regression models, along with random survival forests (RSF), were used to predict CLAD across multiple severity thresholds (any CLAD, Grade ≥2, ≥3, and =4). Model performance was evaluated with 5-fold cross-validation, time-dependent AUCs (2-10 years post-transplant), and Brier scores.

Results: The Fine-Gray (FG), Cox, and Random Survival Forests (RSF) models were evaluated for predicting CLAD development from 2 to 10 years post-transplant. The FG model consistently outperformed the others, with mean AUCs of 0.876 for any CLAD vs no CLAD, 0.871 for grade ≥2, 0.929 for grade ≥3, and 0.858 for grade=4, achieving the best calibration (lowest Brier score). The Cox model performed similarly but showed slightly lower calibration, while RSF exhibited stable performance over time but had lower AUCs and higher Brier scores. Key covariates contributing to CLAD risk included clinical features (longer ICU stay, ventilatory duration, and greater respiratory support), demographics (older age, lower BMI), and vascular features (increased vascular tortuosity and reduced vessel count). Body composition factors like intramuscular fat density and bone density were significant, with higher intramuscular fat increasing risk, while subcutaneous fat and higher bone density were protective.

Conclusion: Preoperative CT-derived vascular, body composition, and calcification biomarkers enable accurate, grade-specific prediction of CLAD years before spirometric decline. The Fine-Gray model provided the most discriminative and well-calibrated performance, highlighting

the prognostic value of vascular remodeling and systemic frailty markers such as intramuscular fat and bone density. Integrating these routinely available imaging features with clinical data offers a scalable, noninvasive framework for early CLAD risk stratification and personalized post-transplant management.

380 (max. 400) words

Funding sources: R01HL174570 and R01CA237277.