Original Investigation

Machine Learning Algorithms Utilizing Quantitative CT Features May Predict Eventual Onset of Bronchiolitis Obliterans Syndrome After Lung Transplantation

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Abbreviations and Acronyms

LTx lung transplantation

FRI functional respiratory imaging

qCT quantitative CT

BOS bronchiolitis obliterans syndrome

CLAD chronic lung allograft dysfunction

FEV_1 forced expiratory volume in the first second

TLC total lung capacity

FRC functional residual capacity

iVlobe imaging lobar volume

iVaw imaging airway volume

iRaw imaging airway resistance

iSaw imaging airway surface

Rationale and Objectives: Long-term survival after lung transplantation (LTx) is limited by bronchiolitis obliterans syndrome (BOS), defined as a sustained decline in forced expiratory volume in the first second (FEV_1) not explained by other causes. We assessed whether machine learning (ML) utilizing quantitative computed tomography (qCT) metrics can predict eventual development of BOS.

Materials and Methods: Paired inspiratory-expiratory CT scans of 71 patients who underwent LTx were analyzed retrospectively (BOS [$n = 41$] versus non-BOS [$n = 30$]), using at least two different time points. The BOS cohort experienced a reduction in FEV_1 of >10% compared to baseline FEV_1 post LTx. Multifactor analysis correlated declining FEV_1 with qCT features linked to acute inflammation or BOS onset. Student *t* test and ML were applied on baseline qCT features to identify lung transplant patients at baseline that eventually developed BOS.

Results: The FEV_1 decline in the BOS cohort correlated with an increase in the lung volume ($P = .027$) and in the central airway volume at functional residual capacity ($P = .018$), not observed in non-BOS patients, whereas the non-BOS cohort experienced a decrease in the central airway volume at total lung capacity with declining FEV_1 ($P = .039$). Twenty-three baseline qCT parameters could significantly distinguish between non-BOS patients and eventual BOS developers ($P < .05$), whereas no pulmonary function testing parameters could. Using ML methods (support vector machine), we could identify BOS developers at baseline with an accuracy of 85%, using only three qCT parameters.

Conclusions: ML utilizing qCT could discern distinct mechanisms driving FEV_1 decline in BOS and non-BOS LTx patients and predict eventual onset of BOS. This approach may become useful to optimize management of LTx patients.

Key Words: Lung transplantation; quantitative CT metrics; computer-assisted image processing; lung transplant rejection; bronchiolitis obliterans syndrome.

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INTRODUCTION

Lung transplantation (LTx) is an important treatment option for patients with advanced, irreversible lung disease (1). However, despite continued advancements in LTx techniques, long-term survival is limited by chronic lung allograft dysfunction (CLAD). The obstructive phenotype of CLAD is a form of chronic immune-mediated rejection that causes an obliterative bronchiolitis resulting in progressive airflow obstruction over time and eventual allograft failure and death (2,3). Because histopathologic confirmation of obliterative bronchiolitis is impractically obtained with surgical lung biopsy, given risks and cost, the clinically defined term bronchiolitis obliterans syndrome (BOS) was introduced (2). BOS is defined as a sustained decline in the forced expiratory volume in the first second (FEV_1) of the transplanted patient from the peak baseline post-transplant value not associated with other potential reversible causes such as pulmonary infections or pulmonary edema (2,3). Stage BOS 0-p is defined as a decline in FEV_1 of >10% from peak post-LTx FEV_1 (2,4).

The onset of BOS is associated with poor survival, with a median survival of 2.5 years after its onset (3,5). Its incidence is highest during the first 2 years after transplantation, but patients remain at risk indefinitely, and the cumulative incidence reaches more than 50% after 5 years (6). Although advances in LTx technique and postoperative care have resulted in improved short-term outcomes, there has been no substantial decrease in the incidence of BOS (5). Additionally, no effective treatments have been established yet, although there is evidence suggesting augmented immunosuppression may stabilize or cause regression of the disease if diagnosed in the early stages (7). Also, as BOS affects the small airways of the allograft, it may be that, by the time it is clinically diagnosed, a large proportion of the allograft airways have already been irreversibly affected. Therefore, earlier detection of BOS is of great interest because it might increase the probability of successful treatment with novel therapeutic agents in future clinical trials.

Currently, imaging is not consistently established as a diagnostic tool in lung transplant recipients to evaluate BOS (1). Nevertheless, previous studies have shown that standard high-resolution computed tomography (HRCT) scans may be useful in the management of post-transplant patients (1,3).

In the present study, quantitative computed tomography (qCT) metrics using functional respiratory imaging (FRI), a method based on HRCT quantitative computational image processing of lung parenchyma and airways, was used to assess post LTx changes in lung and airway structure and function. These changes were correlated with the onset of BOS as defined by sustained FEV_1 decline, and differentiated from other nonsustained mechanisms of FEV_1 decline in non-BOS subjects. FRI offers the possibility to extract regional lung parenchyma and airway information, allowing investigation of which regions in the transplanted lungs drive the decline in FEV_1. The second part of the present study evaluated the prospect of early-stage BOS detection by means of predictive modeling, assessing the ability of qCT FRI parameters to identify LTx patients at baseline (first visit after transplant) that will eventually develop BOS, on subsequent follow-up. Identifying key regions and changes in qCT FRI parameters in the lungs of patients affected by early, preclinical bronchiolitis obliterans and characterizing disease progression regionally can lead to an earlier diagnosis of BOS and potentially improved outcomes.

MATERIALS AND METHODS

Study Population

The present study was approved by the local institutional review board and was Health Insurance Portability and Accountability Act compliant. Patients were selected retrospectively by a board-certified cardiothoracic radiologist using the following inclusion criteria: status post unilateral or bilateral LTx, availability of at least two chest CTs performed at least 3 months apart, availability of pulmonary function testing (PFT) performed within 2 weeks of the date of each chest CT, and availability of volumetric paired inspiratory and expiratory CTs with thin-section (1 mm or less) contiguous reconstruction. Image quality was reviewed and poor quality CT scans were excluded. PFT data were collected and reviewed by a board-certified pulmonologist. All patient identifiers were removed, and the anonymized CT and clinical and PFT data were transferred to an outside facility for computational imaging analysis of the CT data. A total of 71 LTx patients with paired inspiratory and expiratory CTs were analyzed (Table 1).

Patients were divided into two groups: LTx with BOS (41 patients) and LTx without BOS (30 patients), based on clinical information in the electronic medical record, reviewed by a board-certified pulmonologist. BOS was defined using standard diagnostic criteria requiring a sustained decline of at least 10% of FEV_1 from the best baseline postoperative measure

TABLE 1. Patient Characteristics

Study Population	
Total subjects	71 (41 BOS and 30 non-BOS)
Gender	Male: 53, female: 18
Transplant type	14 right, 17 left, 40 bilateral
BOS onset	19 early onset (15 ± 9 mo after LTx), 13 late onset (56 ± 26 mo after LTx), 9 unknown
Pretransplant diagnosis	26 IPF, 23 COPD, 7 CF, 5 A1AD, 10 other
Number of scans per patient	3 ± 1 scans (mean ± SD), ranging from 2 to 8
Follow-up HRCT scans	4.1 ± 3.3 y (mean ± SD) after transplant, ranging from 15 d to 13 y

A1AD, alpha-1-antitrypsin deficiency; BOS, bronchiolitis obliterans syndrome; CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; HRCT, high-resolution computed tomography; LTx, lung transplantation; SD, standard deviation.