Long-term pulmonary function testing in pediatric bronchiolitis obliterans syndrome after hematopoietic stem cell transplantation

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Abstract
Rationale: Bronchiolitis obliterans syndrome (BOS) is a severe, chronic inflammation of the airways leading to an obstruction of the bronchioles. So far, there are only a few studies looking at the long-term development of pulmonary impairment in children with BOS.

Objective: The objective of this study was to investigate the incidence and long-term outcome of BOS in children who underwent allogeneic hematopoietic stem cell transplantation (HSCT).

Methods: Medical charts of 526 children undergoing HSCT in Frankfurt/Main, Germany between 2000 and 2017 were analyzed retrospectively and as a result, 14 patients with BOS were identified. A total of 271 lung functions (spirometry and body plethysmography), 26 lung clearance indices (LCI), and 46 chest high-resolution computed tomography (HRCT) of these 14 patients with BOS were evaluated.

Results: Fourteen patients suffered from BOS after HSCT (2.7%), whereby three distinctive patterns of lung function impairment were observed: three out of 14 patients showed a progressive lung function decline; two died and one received a lung transplant. In five out of 14 patients with BOS persisted with a severe obstructive and secondarily restrictive pattern in lung function (forced vital capacity [FVC] < 60%, forced expiratory volume in 1 second [FEV1] < 50%, and FEV1/FVC < 0.7) and increased LCI (11.67-20.9), six out of 14 patients recovered completely after moderate lung function impairment and signs of BOS on HRCT. Long-term FVC in absolute numbers was increased indicating that the children still have lung growth.
Since there is a global increase of aHSCTs, which is associated with significant morbidity and mortality, the importance of complications such as GvHD is growing. The pathophysiology is poorly understood but can be described as an exaggerated inflammatory response due to a mismatch between histocompatibility antigens between donor and recipient.

BOS has shown distinctive patterns of lung function decline which were associated with the survival outcome. Patients with a rapid lung function decline within 3 months after BOS was diagnosed, had a significantly poorer lung function and worse overall survival outcome compared with those with a gradual decline in lung function.

Current guidelines for BOS point out the need to find new sensitive lung function indices to detect early small airway impairment, as considerable peripheral lung damage can occur in airways less than 2 mm in diameter before this is sufficient to have an impact on airflow and to be detected by spirometry. Clinical studies have shown that the lung clearance index (LCI), a global measure of ventilation heterogeneity obtained by multiple breath washout (MBW) testing, is a feasible and sensitive tool to detect early small airway impairment in chronic lung diseases in children. Previous studies have used MBW measurements in pediatric patients with BOS and have revealed that LCI increased progressively according to the cGvHD score and was more sensitive compared with FEV1/forced vital capacity (FVC). Therefore, LCI can be considered as a potential early biomarker for the development of BOS.

The objective of this study is to assess the incidence of BOS in pediatric patients after aHSCT and to describe the long-term follow-up of PFTs and LCI in children with BOS after aHSCT.

## 2 MATERIALS AND METHODS

### 2.1 Patient setting

This is a retrospective cohort study of 526 children who underwent aHSCT between 2000 and 2017 at the Division for Stem Cell Transplantation, Immunology, and Intensive Care Medicine in Frankfurt/Main, Germany. The study was approved by the Ethics Committee of the Goethe University Frankfurt (number 116/19) and patient’s consent was waived.

BOS was defined as follows: clinical deterioration with respiratory symptoms such as tachypnea, cough, wheezing, exercise intolerance, and hypoxemia, impaired lung function pattern according to the NIH-CC, new onset of changes on CT including mosaic patterns, hyperinflation, bronchial wall thickening.

Medical data were collected from the patients’ charts and included routine clinical visits as well as additional consultations, for example, upon sudden deterioration. Patients that died within the first 4 weeks after aHSCT were excluded from the subsequent evaluation.
All patients with BOS were thoroughly investigated which included the analysis of 271 PFTs, 46 HRCT scans, and eight results of bronchoalveolar lavage (BAL).

### 2.2 Pulmonary function tests

PFTs were performed using a body plethysmograph (CareFusion, Germany) according to the recommendations of the American Thoracic Society (ATS) and the European Respiratory Society (ERS). The following measurements were obtained: FVC, FEV1, FEV1/FVC, RV, and RV/total lung capacity (TLC).

The LCI was measured using the MBW method by EasyOne Pro Lab (ndd Medical Technologies, Zurich, Switzerland) as described by Uhlving et al and Belachew et al. The LCI was defined according to the ERS/ATS consensus statement, as the number of lung volume turnovers (the cumulative expired volume divided by the functional residual capacity [FRC]) needed to lower the end-tidal tracer gas concentration to less than 1/40th (2.5%) of the starting concentration. The mean LCI result from three (minimum two) MBW measurements in each patient was used for the analysis.

PFT and LCI results and curves from each BOS patient were assessed by a pediatric pulmonologist. Suspicious PFTs and LCIs were reassessed and confirmed by a second pediatric pulmonologist.

### 2.3 High-resolution computed tomography

High-resolution computed tomography (HRCT) were acquired on a 128 slice CT scanner system (Somatom Definition AS+, Siemens). Results of 46 HRCT were reassessed by a pediatric radiologist, looking for high and low-density areas, bronchiectasis, mosaic patterns, and bronchial wall thickening in particular.

### TABLE 1 Characteristics of patients with aGvHD after aHSCT

| Number of patients | Sex          | Diagnosis | Donor | Organ manifestation |
|--------------------|--------------|-----------|-------|---------------------|
| n = 236 (45%)     | Female: 38.41% | ALL: 42.37% | MUD: 46.19% | Skin: 87%            |
|                   | Male: 61.86%  | AML: 15.25% | Haplo: 31.36% | GIT: 28%             |
|                   |              | MDS: 11.44% | MSD: 19.07% | Liver: 10%           |
|                   |              | MMUD: 2.54% |

Abbreviations: ALL, acute lymphoblastic leukemia; aGvHD, acute graft vs host disease; aHSCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukemia; GIT, gastrointestinal tract; MDS, myelodysplastic syndrome; MMUD, mis-matched unrelated donor; MSD, matched sibling donor; MUD, matched unrelated donor.

All patients with BOS were thoroughly investigated which included the analysis of 271 PFTs, 46 HRCT scans, and eight results of bronchoalveolar lavage (BAL).

### 2.4 BAL

General inhalation anesthesia was performed and BAL was carried out using the internal pediatric standardized protocol.

### 2.5 Statistical analysis

The data were analyzed using the statistical program GraphPad Prism and Microsoft Excel. Group differences between patients with BOS were analyzed using a Student two-tailed t test or two-tailed Wilcoxon-Mann-Whitney test depending on normality assumptions and homogeneity of variances. A probability of P < .05 was regarded as significant. Figures of PFT parameters were created with GraphPad Prism 5.

### 3 RESULTS

From a total of 526 patients aged 0.2 to 27.2 years (median 9.8 years) diagnosed with aHSCT, 236 (45%) developed an acute GvHD and are characterized in Table 1. Interestingly, the number of organ systems that were involved at the time of acute GvHD was directly related to mortality, as shown in Table 2.

The exact number of acute GvHD of the lung was difficult to determine, since systemic involvement and early death of patients hindered regular PFTs. Of 526 patients, 14 (2.7%) were identified with BOS. The diagnosis was based on a combination of respiratory symptoms (14/14), impaired lung function pattern (8/14), low FEV1 (8/14), and abnormalities on HRCT (13/14). In addition, BAL was obtained in seven (7/14) patients and investigated for noticeable differential cell counting. Table 3 shows the clinical characteristics and risk factor profile of these 14 patients with BOS.

In addition, acute pulmonary infections were excluded in patients by laboratory results (14/14) and by bronchoscopy and BAL (7/14).

### 3.1 Pulmonary function tests

PFTs of children with BOS that were able to perform spirometry and body plethysmography according to current ATS/ERS guidelines were analyzed over a period of median 4.67 (1.00-13.58) years. In total, 271 available lung function tests were evaluated and
TABLE 3 Profile of risk factors in BOS

| Patient number | Gender | Diagnosis | Donor | Age at HSCT | Busulfan conditioning | GvHD prophylaxis | Radiation | CMV (donor/patient) | Infections after HSCT | cGvHD | aGvHD |
|----------------|--------|-----------|-------|-------------|-----------------------|------------------|-----------|--------------------|----------------------|-------|-------|
| 1              | Male   | ALL       | Haplo | 6.50        | No                    | None             | None      | +/+                | CMV blood, adeno blood + stool |       | Skin  |
| 2              | Female | Fanconi anemia | MSD   | 6.33        | No                    | Unknown^1        | Unknown^1 | Unknown            | Unknown^1            |       | GIT   |
| 3              | Male   | ALL       | Haplo | 3.42        | No                    | None             | Full body (12.6 Gy) | +/+                | Skin                 |       |
| 4              | Female | MDS       | MSD   | 6.75        | Yes                   | CSA, sirolimus, and MMF | None | -/-               | Polyoma blood + urine | Gastrointestinal tract and skin |       |
| 5              | Male   | AML       | MUD   | 4.50        | Yes                   | CSA and MTX      | None      | -/-                | Gastrointestinal tract and skin |       |
| 6              | Male   | AML       | MUD   | 5.81        | No                    | CSA and ATG      | Full body (12 Gy) | +/-                | Gastrointestinal tract and skin |       |
| 7              | Female | ALL       | MUD   | 9.80        | Yes                   | CSA and MTX      | None      | +/-               | Sepsis                | Skin   |
| 8              | Male   | MDS       | MSD   | 0.84        | No                    | None             | None      | +/-               | Skin and eyes          | Gastrointestinal tract and skin |       |
| 9              | Female | ALL       | Haplo | 1.28        | No                    | CSA and MTX      | None      | +/-               | Adeno blood + stool     | Skin   |
| 10             | Female | MDS       | MSD   | 16.67       | No                    | CSA and MTX      | None      | +/-               | Skin and eyes          | Liver  |
| 11             | Male   | MDS       | MSD   | 5.17        | Yes                   | CSA             | None      | +/-               | Skin and eyes          | Skin   |
| 12             | Male   | ALL       | Haplo | 10.25       | No                    | MMF             | Craniospinal (18 Gy) | +/-               | BK                   | Gastrointestinal tract and skin |       |
| 13             | Male   | ALL       | MSD   | 12.25       | No                    | CSA             | Full body (12 Gy) | +/-               | CMV blood, BK urine     | Skin   |
| 14             | Male   | ALL       | MUD   | 5.17        | No                    | CSA and MTX     | Full body (12 Gy) | +/-               | CMV, adeno, and BK     |       |

Abbreviations: ALL, acute lymphoblastic leukemia; aGvHD, acute graft vs host disease; AML, acute myloid leukemia; ATG, antithymocyte globin; BK, human polyomavirus 1; BOS, bronchiolitis obliterans syndrome; cGvHD, chronic graft vs host disease; CSA, ciclosporin; CMV, cytomegalovirus; Gy, gray; HSCT, hematopoietic stem cell transplantation; MDS, myelodysplastic syndrome; MMF, mycophenolate mofetil; MSD, matched sibling donor; MTX, methotrexate; MUD, matched unrelated donor.

^1Patient was transplanted outside our department for Stem Cell Transplantation.
longitudinal changes in lung function parameters were analyzed (Figures 1–4). None of the patients showed abnormalities of PFT before aHSCT.

Three patterns of lung function decline were noted. Three out of 14 patients developed a significant progressive deterioration of their BOS despite intravenous steroid pulses (15-20 mg/kg high-dose systemic corticosteroid pulse on 3 consecutive days for 3 consecutive months) and maximal oral therapy with FAM (fluticasone, montelukast, and azithromycin). Two patients died, one patient received a lung transplant.

Five out of 14 patients developed persistent BOS with severe but almost compromised lung function, showing a combined restrictive and obstructive pattern with hyperinflation (FVC < 70%, FEV1 < 60%, FEV1/FVC < 70%, and RV/TLC > 150%). In addition, LCI revealed a significant inhomogeneity of lung ventilation with significantly elevated LCI measurements (median 14.90; range 12.59-20.90) (Table 4).

Interestingly, one of the persistent patients with BOS (patient 6; Table 5), who had high levels of lymphocytes (23%) in the BAL, responded well to oral corticosteroids (OS). However, when OS were stopped due to severe side effects including adrenocortical insufficiency, bone fractures, and Cushing’s syndrome, lung function rapidly deteriorated showing that GvHD was still active and only masked by OS (Figures 1, 2, and 4).

Lung function of patients with persistent BOS remained almost stable when expressed at the predicted level of normal during follow-up (Figures 1, 2, and 4). But there was a significant increase in lung volume growth (FVC: mean increase 13.08% per year and FEV1: mean increase of 9.40%, respectively) (Figure 3). Six out of 14 patients recovered completely after mild to moderate lung function impairment, clinical symptoms and signs of BOS on HRCT such as bronchial wall thickening and mosaic pattern of perfusion. Their PFT improved to normal values during the course of the disease (Table 4).

3.2 | HRCT and BAL findings

All 14 patients (14/14) diagnosed with BOS received a HRCT and seven patients (7/14) received a bronchoscopy with BAL: the results are listed in Table 5. Interestingly, BAL revealed a predominantly neutrophilic inflammation. These findings were in line with previous findings.22

4 | DISCUSSION

The diagnosis and treatment of BOS continues to be a challenge for the clinician. BOS is a severe, chronic inflammation of the airways, leading to obstruction of the bronchioles. However, at the beginning, BOS is often asymptomatic, and may be overlooked by clinicians, patients, and caregivers.16 As transplanted patients do not regularly exercise, it is difficult to assess their breathlessness early in the disease, as it was the case in our cohort, patients 4 and 8 were diagnosed with BOS in less than 2 years after the aHSCT. The true
The incidence of BOS is difficult to determine in view of several difficulties such as the inability to perform PFTs in very sick post-transplanted patients, the lack of regular PFTs, and CT scans, the focus on infections or the absence of potential early biomarkers such as LCI. The prevalence for BOS in our patient population was 2.7%, which was significantly lower than it has been described in adults, showing a prevalence of 4.8% to 6.5%, respectively.

Older age of both, recipient and donor, increases the probability of GVHD. This is most likely the main reason why the incidence of BOS is higher in adults compared with children.

Multiple factors are known to increase the risk of BOS after aHSCT. The presence of GvHD at another organ site is closely associated with the development of BOS and also decreases survival in patients with BOS. In our cohort, all patients with BOS suffered from an acute or chronic GvHD of at least one organ site. Furthermore, we revealed that the mortality was significantly higher when three organ sites were affected by GvHD (Table 2). Known important risk factors, which may contribute to BOS such as myeloablative

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**FIGURE 2** A. Long-term RV in BOS patients with respiratory failure. B. Long-term RV in patients with chronic BOS. C. Long-term RV in patients with transient BOS. BOS, bronchiolitis obliterans syndrome; RV, residual volume [Color figure can be viewed at wileyonlinelibrary.com]

**FIGURE 3** A. Long-term FVC in absolute values (l) in chronic BOS. B. Long-term FEV1 in absolute values (l) in chronic BOS. BOS, bronchiolitis obliterans syndrome; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity [Color figure can be viewed at wileyonlinelibrary.com]
busulfan-based conditioning regimen, unrelated donor, gastro-esophageal reflux disease, acute or chronic viral, and bacterial infections, \textsuperscript{13,34,36} were investigated and displayed in Table 3. Seven patients suffered from infections after aHSCT, four patients received a busulfan-based conditioning regime, and four patients had an unrelated donor. The pulmonary toxicity of busulfan has been described in the past and interestingly, 30% of our patients diagnosed with BOS post aHSCT received busulfan-based conditioning while there were only 11% of our patient aHSCT cohort who received busulfan-based conditioning and were not diagnosed with BOS. Although all patients received regular antibiotic prophylaxis (co-trimoxazol 5 mg/kg 3 d/wk until day +200, aciclovir 15 mg/kg per day until day +200, penicillin 25,000 IE/kg until 2 years post aHSCT, voriconazol or AmBisome/Mykamine until T-cells stable >200/µL, IgG if IgG levels < 600, and immunization with Infanrix Hexa and Prevenar 13 from day 200 onwards), 50% of our patient group had underlying infections which may have influenced the influx of neutrophils and triggered the chronic inflammatory response. \textsuperscript{32}

The decline of FEV1 in BOS has been shown to be variable, from rapid progression to chronic BOS and from transient decline to full recovery. \textsuperscript{37} Lung function testing of our patients with BOS revealed three distinctive patterns: In patients with persisting BOS, the spirometry showed a restrictive and obstructive flow volume curve (FVC < 60%, FEV1 < 50%, and FEV1/FVC < 70). The body plethysmography showed a significantly increased residual volume (RV) and functional residual capacity (RV/TLC).

During follow-up, four out of five patients with a persistent disease presented with constantly low FEV1 < 50%, and showed no or little response to treatment with FAM or OS whereas one patient responded to OS. It is well known that steroid resistance is often associated with a very poor prognosis. \textsuperscript{38} Importantly, although predicted levels of lung function in patients with persistently stable BOS were constantly below the 50%, total lung function volume increased during their regular follow-ups. These findings indicate that lung growth is present in children with BOS. This positive effect on lung growth was also described in patients with postinfectious bronchiolitis. \textsuperscript{32} The steady growth of lung volume went along with a better performance during exercise and less symptoms during viral infection.

Taking the strict criteria of the NIH-CC into account, most patients fulfilled these criteria. However, several investigators already discussed that the NIH-CC criteria for BOS have some limitations in children. \textsuperscript{39} Previous longitudinal studies in lung transplanted adults revealed, that a concurrent FEV1 and FVC decline from the baseline is associated with a poor prognosis, \textsuperscript{40} which accords with our study cohort where patients with mild BOS presented with a mild decline in FEV1 and FVC and had a much better clinical prognosis, despite similar clinical symptoms. In addition, in a recent study of 1461 adults undergoing HSCT 95 (6.5%) patients were diagnosed with BOS. \textsuperscript{11} Interestingly, a 25% decline in FEV1 within the first 3 months after BOS separated the patients’ group into a subgroup with an initially rapid decline and another subgroup with an initially gradual decline in lung function. \textsuperscript{11} The overall survival was significantly worse in the group with the rapid decline. Although our pediatric group was small,
we showed that patients with an early rapid decline had a very poor outcome.

It is well known that current guidelines recommend the need to find new sensitive lung function indices to detect early small airway impairment in BOS.\textsuperscript{11} With regard to the literature, data are scant of studies using MBW methods for patients post aHSCT.\textsuperscript{25,26} In a longitudinal study of 33 adults post aHSCT, Lahzami et al\textsuperscript{25} showed elevated LCI and Sacin values. These findings are in line with a study which included 225 patients post aHSCT, describing highly pathological LCI values in 96% of cases whereas FEV1/FVC was decreased only in 57% of cases.\textsuperscript{26} This is in accordance with our study, which showed that all patients with chronic BOS had significantly elevated LCI values. In view of this, LCI is not only a valuable tool to improve early diagnosis of BOS, but would be specifically useful to diagnose early BOS in younger patients as it is independent from active breathing maneuvers compared with spirometry. In addition, in patients without reproducible pulmonary lung function testing, HRCT can reveal changes of BOS such as vascular attenuation, mosaic perfusion, central bronchiectasis, and air trapping in time.\textsuperscript{42}

At present, there is no accepted treatment protocol for BOS and there are only few randomized placebo-controlled trials in children with BOS. Most published reports on treatment options suffer from a small number of patients, absence of controls, and a diversity of patients at the start of therapy. The overall consensus is, that in addition to optimal supportive therapy, anti-inflammatory drugs like corticosteroids pulses, which impair lymphocyte proliferation, should be used as a first line treatment. Although steroids are effective during an acute deterioration and by improving lung function and exercise capacity, the long-term benefit is largely unknown.

There are several limitations of our retrospective cohort study. There was a lack of standardized follow-up protocol for lung function to detect BOS. We suggest that this may have resulted in an underestimation of the true prevalence of BOS in our population. However, the diagnosis of BOS is specifically difficult to establish in those children, who recover completely after a transient loss of lung function post aHSCT.

\section*{5 \ \ | \ \ \ \ \ \ \ \ \ Conclusion}

Our results indicate that BOS presents with three distinctive patterns of pulmonary function: a rapid decline, a transient decline with full recovery, and a chronic but stable course. Long-term follow-up of patients with chronic BOS showed severely impaired PFTs, displaying an obstructive and secondarily restrictive pattern with air trapping. Risk factors such as busulfan induction, nonrelated donors, and especially silent infections have to be looked at carefully. In addition to PFTs, LCI can be a helpful tool to assess ventilation inhomogeneity.

### TABLE 4 Lung function parameters correlated with lung clearance index in BOS

| Patient number | Follow-up time | LCI  | FVC (%) | FEV1 (%) | FEV1/FVC | RV (%) | RV/TLC (%) | Outcome                      |
|----------------|----------------|------|---------|----------|----------|--------|------------|-------------------------------|
| 1              | 1.98           | 33.7 | 36.5    | 95.87    | 329.7    | 288.1  | Death due to respiratory failure |
| 2              | 1.23           | 27.6 | 23.9    | 78.70    | 272.2    | 285.2  | Death due to respiratory failure |
| 3              | 13.58          | 54.8 | 53.4    | 81.13    | 133.60   | 171.0  | Successful LTX                  |
| 4              | 4.50           | 58.7 | 46.5    | 67.96    | 327.3    | 262.0  | Chronic BO                        |
| 5              | 6.33           | 59.0 | 43.1    | 61.47    | 312.8    | 236.8  | Chronic BO                        |
| 6              | 4.83           | 73.4 | 69.2    | 79.43    | 223.3    | 185.8  | Chronic BO                        |
| 7              | 9.75           | 67.6 | 55.2    | 69.10    | 154.9    | 180.1  | Chronic BO                        |
| 8              | 6.37           | 54.1 | 56.1    | 77.41    | 323.8    | 244.5  | Chronic BO                        |
| 9\textsuperscript{a} | 3.18           |      |         |          |          |        | Recovered                          |
| 10             | 11.08          | 83.3 | 89.5    | 93.49    | 148.9    | 140.3  | Recovered                          |
| 11             | 6.92           | 70.7 | 68.0    | 82.12    | 175.1    | 179.6  | Recovered                          |
| 12             | 3.33           | 70.4 | 74.8    | 88.57    | 123.4    | 143.1  | Recovered                          |
| 13             | 1.92           | 71.5 | 71.9    | 86.92    | 197.0    | 175.4  | Recovered                          |
| 14             | 1.92           | 79.1 | 62.4    | 66.76    | 163.1    | 167.0  | Recovered                          |

Abbreviations: BOS, bronchiolitis obliterans syndrome; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LCI, lung clearance index; LTX, lung transplant; RV, residual volume; TLC, total lung capacity.

\textsuperscript{a}Patient was too young to perform spirometry.
### Table 5  HRCT, BAL, treatment, and outcome in BOS

| Patient number | CT findings                                                                 | BAL     | FAM | IV Steroids | Outcome                                 |
|----------------|------------------------------------------------------------------------------|---------|-----|-------------|-----------------------------------------|
| 1              | Mosaic pattern with low density areas                                        | Yes     | Yes | Death due to respiratory failure         |
| 2              | Mosaic pattern with high density areas                                       | Yes     | Yes | Death due to respiratory failure         |
| 3              | Bronchial wall thickening, bronchiectasis, and mosaic pattern high density areas | No      | No  | Successful LTX                           |
| 4              | Bronchiectasis and mosaic pattern with high density areas                    | 88%     | Yes | Chronic BO                               |
| 5              | Mosaic pattern with high density areas and bronchial wall thickening         | 4%      | Yes | Chronic BO                               |
| 6              | Bronchiectasis                                                               | 66%     | Yes | Chronic BO                               |
| 7              | Mosaic pattern with high density areas, bronchial wall thickening, bronchiectasis, and lymphadenopathy | 15%     | Yes | Chronic BO                               |
| 8              | Mosaic pattern with low density areas                                        | Yes     | Yes | Chronic BO                               |
| 9              | Mosaic pattern with high density areas                                       | No      | No  | Recovered                                |
| 10             | Mosaic pattern with low density areas, bronchial wall thickening, and bronchiectasis | No      | Yes | Recovered                                |
| 11             | Mosaic pattern with high density areas                                        | 9%      | No  | Recovered                                |
| 12             | Bronchial wall thickening, bronchiectasis, and mosaic pattern with low density areas | No      | No  | Recovered                                |
| 13             | Normal                                                                       | 95%     | No  | Recovered                                |
| 14             | Mosaic pattern with low density areas and lymphadenopathy                    | 4%      | Yes | Recovered                                |

Abbreviations: BAL, bronchoalveolar lavage; BOS, bronchiolitis obliterans syndrome; CT, computed tomography; FAM, fluticasone, montelukast, and azithromycin; HRCT, high-resolution computed tomography; IV, intravenous; LTX, lung transplant.
and to detect BOS early and accurately. Although BOS is a severe, chronic disease, pediatric patients with BOS still have lung growth.

CONFLICT OF INTERESTS
All the authors declared that there are no conflict of interests.

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