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Early View

Original article

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Noninfectious lung complications after allogeneic haematopoietic stem cell transplantation

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Summary of the "take home" message: Chest irradiation, pneumonia and low FEF 25-75 predict lung complications after allogenic bone marrow transplantation.

Abstract

Epidemiological data on late noninfectious pulmonary complications (LONIPCs) following allogeneic haematopoietic stem cell transplantation (HSCT) are derived exclusively from retrospective studies and conflicting. We aimed to evaluate prospectively their incidence, risk factors and outcomes.

All consecutive patients scheduled to receive allogeneic HSCT between 2006 and 2008, at the university-teaching Saint Louis Hospital (Paris, France) were screened for inclusion. Eligible patients were those surviving at day 100. Among 243 screened patients, 198 patients were included in the analysis. The median follow-up was 72.3 months [IQR: 15.2-88.5]. Fifty-five LONIPCs were diagnosed in 43 patients. Bronchiolitis obliterans syndrome (n=22) andinterstitial lung disease (n=12) were the most common LONIPC. At 36 months after inclusion, the estimated cumulative incidence of LONIPCs was 19.8% (95% CI: 14.2-25.3%). The estimated median survival after the diagnosis of LONIPCs was 78.5 months (95% CI: 20.0-not reached). Based on a multivariable Cox model, a history of chest irradiation anytime prior to HSCT, a history of pneumonia within the 100 days post-HSCT and a low mean forced expiratory flow between 25% and 75% of forced vital capacityat day 100 were associated with the development of LONIPCs.

Our data provide clues to identify patients at high risk of LONIPCs. These patients should be targeted for close monitoring to provide earlier LONIPC treatment or prophylactic treatment.

Keywords: Late-onset noninfectious pulmonary complications, bronchiolitis obliterans, incidence, pulmonary function testing, risk factors

Introduction

Late-onset noninfectious pulmonary complications (LONIPCs) that occur beyond the third month following allogeneic haematopoietic stem cell transplantation (HSCT) have a significant effect on patient outcomes, with high associated mortality and morbidity rates (1-3). Most of these lung complications that have been associated with chronic graft-versus-host disease (GVHD) mainly occur during the first year after HSCT, and rarely occur beyond two years (3-6). Although lung biopsy is the gold standard to classify most LONIPCs, fewer patients undergo lung biopsy, and the diagnosis mostly now relies on pulmonary function testing (PFT) and lung computed tomography (CT) scanning (7).

Findings from the available studies regarding both the incidence and risk factors for LONIPCs show many discrepancies. In fact, the reported incidence of LONIPCs ranges from 10% to 26% (1, 2, 7-11), while contradictory findings have been reported regarding the predictive role of the conditioning regimen, GVHD or stem cell sources (1-3, 7-11). The main reason for these discrepancies is that all previous studies were retrospective, leading to significant biases, including incomplete data, an absence of detailed lung function and a lack of clinical correlation with most of the studies focused on PFT. Furthermore, most studies reviewed long periods characterized by variations in PFT screening strategies and diagnostic criteria for LONIPCs and HSCT procedures. Furthermore, although recommended, adherence to lung function testing guidelines in HSCT recipients is poor in routine practice and leads to missing data (12).

Specific limitations can be addressed for studies focused on bronchiolitis obliterans syndrome (BOS), which is the most frequent LONIPCs. One of the main limitations is based on the difficulty in determining an accurate PFT definition for BOS to compare studies. Indeed, prior to the 2005 National Institutes of Health (NIH) consensus diagnostic criteria for BOS (13), various PFT criteria were used. Even after 2005, authors have used modified

criteria to improve their sensitivity (4, 14, 15). In addition, recent studies have shown that regardless of the diagnostic criteria of BOS , a significant proportion of patients experience a significant decline in forced expiratory volume in one second (FEV1) after HSCT (12). Data suggest that this decline could be a good predictor for the development of subsequent BOS.

Besides PFT, lung CT scan is an essential diagnostic tool for pulmonary complications. The evidence of air trapping by expiratory CT scan, small airway thickening or bronchiectasis are part of the BOS diagnostic criteria (15). Whether any CT scan sign can predict the occurrence of post HSCT BOS or other LONIPC remains unknown.

Improved specification by LONIPC and identification of early risk factors in a prospective study are mandatory to focus on high-risk allogeneic HSCT recipients to achieve an earlier diagnosis, initiate earlier treatment and evaluate prophylactic strategies to improve prognoses.

Methods

Study design and participants

In this observational prospective cohort study, all consecutive patients who were scheduled to receive an allogeneic HSCT between January 31, 2006 and December 31, 2008 at the university-teaching Saint Louis Hospital (Paris, France) were screened for inclusion within the two weeks before transplantation. Those allogeneic HSCT recipients surviving at day 100 in the absence of early relapse of hematological disease or refusal were included in the cohort. This study was approved by a central institutional review board (CCPPRB Saint-Louis, Paris, France). All of the patients or legal guardians of the patients under 18 years of age provided written informed consent before transplant, though definite inclusion occurred at day 100 after checking all inclusion and exclusion criteria. The trial was registered with ClinicalTrials.gov, number NCT 01219972.

Procedures

At inclusion (day 100), the history of the underlying haematological disease, the characteristics of the transplant and the occurrence of GVHD in the first 100 days after HSCT were recorded.

Pulmonary function testing (PFT), lung high resolution computed tomography (HRCT) scans and a clinical assessment with a pulmonologist were performed sequentially before transplant; at inclusion; and then at 6, 12, 18, 24 and 36 months after HSCT. Thereafter, PFT was performed annually. Additional explorations were performed in the case of new onset respiratory symptoms. PFT was performed using a body plethysmograph (Jaeger Masterscreen Body; CareFusion Germany 234 GmbH; Hoechberg, Germany). Predictive values were determined as previously described (16). As a pretransplant lung function score (LFS) was previously associated with allogeneic HSCT recipient outcomes, LFS was determined (17).

HRCT scans were performed on every patient using a multi slice CT scanner (GE Healthcare Optima 660CT with low dose device, Milwaukee, USA). Helicoidal acquisitions were acquired during both deep inspiration and expiration. The images were reconstructed using a high-spatial frequency algorithm. One radiologist (CDMM) and two experienced pulmonary physicians (AB, KC) who were unaware of both the clinical and PFT results reviewed the CT scans and reached a conclusion by consensus. On the expiratory scans, the extent of air trapping was estimated at three levels on axial images: upper, middle and lower for each lung as follows: 1, 0-25% of the affected lung; 2, 25–50% affected; 3, 50-75% affected; 4, 75-100% affected. For each lung, the score ranged from 6 to 24 (18, 19). An air trapping score of more than 6 was considered clinically significant.

End points and definitions

Although previous studies suggested that LONIPCs mainly occur during the first year after HSCT, and rarely occur beyond two years, in our clinical experience, LONIPCs could occur beyond 2 years, particularly interstitial pneumonias. Therefore, in this prospective study, we decided to choose a follow-up of 36 months to get a further insight in such late occurrences, by allowing providing an estimate of occurrence over time within the first 3 years of HSCT. The main end point was thus the occurrence of LONIPCs during the first 36 months following study inclusion. LONIPCs were classified as BOS, interstitial lung disease (ILD) and "others" which included thromboembolism disease, air leak syndrome (i.e. pneumothorax or pneumomediastinum), exudative pleural effusion and restrictive lung disease. Any LONIPC were considered during all the follow-up, i.e. both at the time of planned CT scan or if diagnosed between two study visits. BOS was defined previously as: (i) an absence of respiratory infection at the time of PFT; (ii) either an FEV1<75% of predicted or a decline >10% of FEV1 from the pretransplant value; (iii) either FEV1/vital capacity (VC)<0.7 or a concomitant decrease in both FEV1 and VC<80% of predicted, with a total lung capacity (TLC)>80% of predicted (4, 20). Concordance with the NIH definition was investigated for each case (13, 15). These abnormalities persisted for two subsequent PFT measurements at four-week intervals. A restrictive lung defect was defined as a TLC<80% of the predicted value. ILD was diagnosed when diffuse opacities were present on HRCT, and an infectious cause for these opacities was ruled out as we previously reported (5). Thromboembolism disease included pulmonary embolism diagnosed by computed tomography pulmonary angiography or deep venous thrombosis diagnosed by ultrasound. Lower respiratory tract infection (LRTI) was defined as an association of fever, respiratory symptoms and a new lung infiltrate on chest x-ray or lung CT scan. All these events were investigated with a bronchoalveolar lavage as described previously (5). LRTI was defined as

if a pathogen was documented. LRTI was defined as probable if clinical and radiological abnormalities improved with antimicrobial treatment but no pathogens were identified. Diagnostic criteria and severity of acute and extra-thoracic chronic GVHD were assessed according to the NIH criteria, with a grading scale from 1 to 4 for acute GVHD (21) and the global score of mild, moderate, and severe reflects the degree of organ impact and functional impairment due to chronic GVHD (15).

Secondary end points were survival after LONIPCs and long-term time course of PFTs (FEV1, forced vital capacity (FVC), TLC, mean forced expiratory flow between 25% and 75% of FVC -FEF25-75), instantaneous forced expiratory flow when 50% of the FVC has been expired (FEF50)). For descriptive purposes, overall survival was also computed.

Statistical analysis

Summary statistics were reported, namely the median [interquartile range, IQR], unless otherwise specified. All analyses of survival data were performed using data obtained up to June 2016.

Survival after inclusion (day 100 after HSCT) and survival after LONIPCs were both estimated using the Kaplan-Meier method; a Cox model with a time-dependent variable was used to assess the impact of LONIPCs on survival. Competing-risk end points (LONIPC, BOS, chronic GVHD and relapse) were computed from study inclusion in which patients who died free from the event of interest were considered competing-risk events. Early risk factors were defined as those present before transplantation or at inclusion (day 100). Predictive analyses of the hazard of LONIPCs or BOS occurrence within the first 36 months were based on cause-specific Cox models. First, univariate models were fitted whereby all the covariates previously reported as risk factors for LONIPCs were considered fixed covariates; chronic GVHD after inclusion was tested as a time-dependent covariate. Then, multivariable models

were fitted on those predictors selected from univariable analyses at the 10% level, segregating pretransplant, transplant and post-transplant (at day 100) characteristics. Finally, multivariable models were fitted based on all potential predictors selected whatever the time of measurement at the 10% level, with model selection based on a stepwise procedure using variables associated with the outcome at the 5% level and after multiple imputations with chained equations (MICE) of missing data, averaging the estimates over 50 data sets. Sensitivity analyses based on a complete case analysis (CCA) were also performed.

To describe the course of PFTs over time, we used a nonparametric K-means algorithm for clustering longitudinal data, providing several techniques for dealing with missing values in trajectories; the number of trajectories was defined as those maximizing the Calinski & Harabatz criterion as given by the kml package (22). All estimates of cumulative incidence, survival rates and cause-specific hazard ratios were reported with 95% confidence intervals (95% CI).

Statistical analyses were performed using SAS 9.3 (SAS Inc., Cary, NC) and R 3.2.2 (http://www.R-project.org/) software packages. Two-sided P-values of 0.05 or less indicated statistical significance.

Results

From May 2006 to April 2009, 198 of 243 screened patients were included in the analysis (Figure 1). Pretransplantation data are summarized in table 1.

Table 1: Patient characteristics measured before or at the time of allogeneic HSCT and at the time of inclusion (day 100 after allogeneic HSCT)

Number of patients	198
Base line characteristics (before transplant)	
Male	
Age at transplant (years): median [IQR]	120 (61)

History of smoking	38.2 [24.9;53.4]
Underlying disease	65 (33)
Acute leukaemia	
Myelodysplastic syndrome	98 (49)
Myeloproliferative syndrome	13 (7)
Lymphoma	19 (10)
Myeloma	25 (13)
Others	13 (6)
Status of disease at transplant	30 (15)
CR1/chronic phase	
Prior autologous HSCT	103 (52)
History of chest irradiation	37 (19)
Donor	15 (8)
Related	
Unrelated*	108 (55)
Stem cell source	90 (45)
Peripheral stem cells	
Bone marrow	126 (64)
Cord blood	60 (30)
Conditioning regimen	12 (6)
Nonmyeloablative	
TBI	87 (44)
BU-based	95 (48)
Cy-based	60 (30)
ATG	98 (50)
GVHD prophylaxis	43 (22)
Cyclosporine-MMF	
Cyclosporine-MTX	99 (50)
Other‡	90 (46)
CMV status donor – recipient	9 (4)
Positive-positive	
Positive-negative	61 (31)
Negative-negative	46 (23)
Negative-positive	62 (31)
Lung CT scan findings before transplant (n)	29 (15)
Abnormal†	151 (76)
Air trapping score >6	52 (34)
Parenchymal opacities§	35 (23)
Nodules	13 (9)
Micronodules‖	14 (9)
Bronchial thickening	5 (3)
Pulmonary function testing before transplant	
FEV1 %pred	157 (79)
TLC	102 [92;112]
FVC	100 [92;110]
SVC	100 [91;109]
FEV1/FVC	101 [92;111]
FEV1/SVC	86 [80;90]
FEF25	84 [78;88]
FEF50	90 [69;117]
FEF25-75	99 [79;116]
TLCO	106 [85;122]
LFS	73 [64;81]
Normal	
Mildly decreased	39 (25)
Moderately decreased	68 (43)

Severely decreased	47 (30)
	3 (2)
Day 100 characteristics (after transplant)	
Time from HSCT to inclusion (days)	
Karnofsky index	101 [99;106]
Current smoking	80 [70;90]
Medical history between HSCT and inclusion	14 (7)
Acute GVHD grade ≥2 **	
Acute GVHD grade ≥3	80 (40)
Chronic GVH **	33 (17)
Mild	46 (23)
Moderate/severe	35 (18)
LRTI	11 (6)
Viral URTI	18 (9)
CMV reactivation	13 (7)
EBV reactivation	83 (42)
Lung CT scan findings at inclusion	40 (20)
Abnormal†	171 (86)
Air trapping score >6	80 (47)
Parenchymal opacities§	58 (34)
Nodules	21 (12)
Bronchial abnormalities‖	21 (12)
Pulmonary function testing	25 (15)
FEV1 %pred	183 (92)
TLC	95 [85;106]
FVC	95 [86;104]
FEV1/FVC	93 [84;106]
FEV1/SVC	84 [79;88]
FEF25	82 [77;87]
FEF50	80 [57;102]
FEF25-75	93 [74;113]
TLCO	97 [75;118]
LFS	67 [60;76]
Normal	
Mildly decreased	32 (17)
Moderately decreased	82 (45)
Severely decreased	57 (31)
Change in FEV1 (mL)	12 (7)
Change in FEV1 (%pred)	-50 [-360;112]
10% FEV1 decline (%pred)	-1.9 [-10;3.5]
	40 (28)

The data are shown as n (%) unless specified.
CR1: 1st complete response; HSCT: haematopoietic stem cell transplantation; TBI: total body irradiation; BU-based: busulfan based; Cy-based: cyclophosphamide-based; ATG: antithymocyte globulin; GVHD: graft-versus-host disease; MMF: mycophenolate mofetil; MTX: methotrexate; CMV: cytomegalovirus; CT: computed tomography; IQR: interquartile range.
FEV1: forced expiratory volume in one second; TLC: total lung capacity; FVC: forced vital capacity; SVC: slow vital capacity; FEF: forced expiratory flow; TLCO: transfer factor of the lung for carbon monoxide; LFS: lung function score; a score separate from FEV1 and TLCO was provided (>80%=1, 70–80%=2, 60–70%=3, <60%=4). These scores were summed to the LFS and then divided into four categories (normal, LFS=2; mildly decreased, LFS=3-4; moderately decreased, LFS=5-6; severely decreased, LFS=7-8); pred: predicted; LRTI: lower respiratory tract infection; URTI: upper respiratory tract infection; EBV: Epstein-Barr virus
*10/10 and 9/10 allelic unrelated donors and cord blood transplants. ** Acute GVHD usually includes erythema, maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea, ileus, or cholestatic liver disease. Acute GVHD was graded from 1 to 4, according to the severity, using the National Institutes of Health consensus criteria (21). Chronic GVHD is a syndrome of variable clinical features resembling autoimmune and other immunologic disorders such as scleroderma, Sjögren's syndrome, primary biliary cirrhosis, wasting syndrome, bronchiolitis obliterans, immune cytopenias, and chronic immunodeficiency; manifestations of chronic GVHD may be restricted to a single organ or site or may be widespread. The global score of mild, moderate, and severe reflects the degree of organ impact and functional impairment due to chronic GVHD. It has been established according National Institutes of Health consensus criteria (15); † Any lung opacities excluding air trapping; ‡Tacrolimus/sirolimus or MTX/tacrolimus; §including ground glass opacities and consolidations; ‖ including centrilobular micronodules and tree in bud.

Two (1%) patients had an FEV1/VC ratio <0.7, and nine (5%) had a restrictive lung defect (RLD). LFS was impaired in 118 (75%) patients. Thirty-five (23%) patients had a significant air trapping score, > 6, on chest CT scan.

Inclusion data (day 100) are summarized in Table 1.

Within the 100 days following HSCT, 33 (17%) patients developed grade ≥3 acute GVHD (skin, n=31; liver, n=7; gut, n=19), and 11 (6%) had extensive chronic GVHD. Nine of the 18 LRTI were documented (bacteria n=3, fungus n=2, virus n=4). There were no notable differences between the patients included and not included in the study (see the online supplement table S1, p 4).

The median duration of follow-up was 72.3 [IQR: 15.2-88.5] months. Three patients were lost to follow-up at 5, 14 and 28 months, respectively; 40 patients relapsed; and 81 patients died (48 free of relapse and 33 after relapse), 68 within 36 months, with a 3-year

survival of 65.4% (95% CI: 59.1-72.4%) (Figure 2a). Besides relapse, patients died mostly from pulmonary causes (n=18, including 14 due to infectious pneumonia and 4 from respiratory failure), 16 from GVHD, 7 from other causes, while 11 causes of death were unknown.

Fifty-five episodes of LONIPCs were diagnosed in 43 patients (Figure 1). Diagnoses included BOS (n=22 in 22 patients), ILD (n=12 in 12 patients) and others (n=21 in 19 patients). LONIPCs other than BOS and ILD included various diagnoses (Table 2). Ten patients developed more than one LONIPC (BOS and ILD n=2; RLD and ILD n=1; BOS and VTED n= 1; pleural effusion and VTED, n=1; VTED and ILD, n=1; BOS and RLD, n=2; BOS and ILD and pneumothorax, n=1; BOS, pneumothorax and VTED, n=1).

Table 2: Diagnoses of LONIPCs observed in the sample

Diagnosis	Number of episodes
LONIPCs	55
BOS	22
ILD	12
Others	21
Venous thromboembolic disease	9
Pneumomediastinum	2
Exudative pleural effusion	2
RLD with no ILD or pleural disease*	8

LONIPCs: late-onset noninfectious pulmonary complications; BOS: bronchiolitis obliterans syndrome; ILD: interstitial lung disease; RLD: restrictive lung disease *including 3 with skin sclerosis GVHD

Most of the patients (39/43, 91%) developed the first episode of LONIPC within 36 months (Figure 3). At that time, the estimated cumulative incidence of LONIPCs was 19.8% (95% CI: 14.2-25.3%). All 22 episodes of BOS occurred within 36 months, with an observed median time of 8.8 [IQR: 2.9-19.7] months after inclusion. The cumulative incidence of BOS at 36 months was 10.7% (95% CI: 6.3-15.1%) (Figure 3). Of the 22 BOS, 20 (91%) fulfilled the NIH criteria, either at the same time (n=8) or subsequently within a median time of 106 [IQR: 17-128] days (n=12).

We evaluated early predictive factors for LONIPCs diagnosed in the first 36 months after HSCT, and factors selected by univariate analyses are presented in Table 3. Multivariable models were fitted based on pre-transplant, transplant, and post-transplant characteristics, separately (Table 3). They exhibit the summarized predictive value of sex and history of chest irradiation before transplant, of HLA-related donor at transplant, and of the occurrence of a lower respiratory tract infection within the 100 days post-transplant.

Table 3: Predictive factors for the development of BOS and LONIPC during the first three months after transplantation - results of univariate and multivariate analyses

	LONIPC				BOS			
	HR	**95%CI**	**p-value**	**Adjusted HR* (95CI)**	**HR**	**95%CI**	**p-value**	**Adjusted HR *(95CI)**
Pretransplant data								
Age at transplant (yr)	1.01	(0.99; 1. 03)	0.27		1.01	(0.99; 1. 04)	0.32	
Age >60 yr	2.33	(0.83; 6. 56)	0.11		3.27	(0.97; 11. 06)	0.06	2.33 (0.68; 8.06)
Female	**0.41**	**(0.19; 0. 86)**	0.02	**0.41 (0.19; 0.87)**	**0.32**	**(0.11; 1. 04)**	0.04	0.40 (0.13; 1.23)
History of smoking	1.66	(0.88; 3. 11)	0.12		**2.30**	**(0.99; 5. 31)**	0.05	1.72 (0.72; 4.13)
Malignant haematological disease	1.61	(0.67; 3. 84)	0.29		1.79	(0.53; 6. 03)	0.35	
History of autologous HSCT	1.47	(0.72; 3. 03)	0.29		1.28	(0.47; 3. 47)	0.63	
History of chest irradiation	**3.63**	**(1.59; 8. 29)**	0.00	**3.63 (1.58; 8.31)**	2.51	(0.74; 8. 52)	0.14	
PFT								
FEV1 %pred/10% variation	0.91	(0.72; 1. 15)	0.42		0.92	(0.67; 1. 25)	0.58	
TLC %pred/10% variation	0.86	(0.66; 1. 13)	0.29		0.99	(0.69; 1. 41)	0.94	
DLCO %pred/10% variation	0.99	(0.70; 1. 40)	0.95		0.93	(0.59; 1. 46)	0.74	
FEF 25-75 %pred/10% variation	0.93	(0.81; 1. 07)	0.31		0.95	(0.80; 1. 14)	0.61	
Decreased LFS	0.98	(0.43; 2. 22)	0.96		0.94	(0.32; 2. 79)	0.91	
Lung CT scan								
Normal	0.94	(0.45; 1. 97)	0.87		0.50	(0.20; 1. 26)	0.14	
Air trapping score >6	0.89	(0.38; 2. 07)	0.79		1.61	(0.60; 4. 29)	0.34	
Transplant data (day 0)								
Disease Status, CR1	1.23	(0.65; 2. 31)	0.53		1.09	(0.47; 2. 52)	0.84	
CMV status	0.71	(0.38; 1. 34)	0.29		0.71	(0.31; 1. 64)	0.42	

Source of cells								
HLA related	**0.53**	**(0.28; 1. 00)**	0.05	**0.44 (0.23; 0.85)**	0.81	(0.35; 1. 86)	0.62	
PBSC	**2.36**	**(1.08; 5. 13)**	0.03	1.58 (0.64; 3.94)	**6.11**	**(1.43; 26. 1)**	0.01	6.11 (1.43; 26.1)
Cord blood	1.24	(0.38; 4. 04)	0.72		0.72	(0.10; 5. 32)	0.74	
Conditioning								
Nonmyeloablative	1.72	(0.91; 3. 23)	0.09	1.61 (0.68; 3.83)	1.32	(0.57; 3. 05)	0.51	
Cyclophosphamide-based	**1.97**	**(1.02; 3. 79)**	0.04	1.24 (0.46; 3.35)	1.91	(0.80; 4. 56)	0.14	
ATG	0.45	(0.18; 1. 15)	0.09	0.38 (0.14; 1.01)	0			
Busulfan-based	1.27	(0.66; 2. 45)	0.47		1.23	(0.51; 2. 93)	0.64	
TBI	1.57	(0.83; 2. 95)	0.16		1.46	(0.63; 3. 38)	0.38	
GVHD prophylaxis								
cyclo-MTX	0.65	(0.34; 1. 26)	0.20		0.66	(0.28; 1. 57)	0.35	
cyclo-MMF	1.46	(0.77; 2. 76)	0.25		1.22	(0.53; 2. 83)	0.64	
Inclusion data (day 100)								
Time from HSCT to inclusion (days)	1.01	(0.99; 1. 03)	0.27		1.02	(1.00; 1. 05)	0.10	
CMV reactivation	0.64	(0.32; 1. 26)	0.19		1.04	(0.45; 2. 44)	0.54	
Acute GVHD (all grades)**	1.29	(0.68; 2. 42)	0.44		1.07	(0.46; 2. 51)	0.87	
Acute GVHD grade ≥3	1.73	(0.82; 3. 65)	0.15		0.81	(0.24; 2. 74)	0.74	
Chronic GVHD**	0.72	(0.32; 1. 63)	0.43		0.33	(0.08; 1. 41)	0.14	
Moderate/severe chronic GVHD	0.63	(0.09; 4. 56)	0.64		0			
LRTI within the 100 days post-transplant	**3.87**	**(1.77; 8. 45)**	0.00	**2.94 (1.04; 7.90)**	**3.81**	**(1.40; 10. 4)**	0.01	2.34 (0.72; 7.58)
PFT								
FEV1 (%pred)/10%	**0.74**	**(0.62; 0. 88)**	0.00	0.95 (0.71; 1.27)	**0.75**	**(0.61; 0. 94)**	0.01	0.94 (0.67; 1.32)
TLC (%pred)/10%	0.83	(0.67; 1. 04)	0.09		0.95	(0.71; 1. 26)	0.71	
TLCO (%pred)/10%	1.02	(0.80; 1. 31)	0.85		1.10	(0.81; 1. 49)	0.54	
FEF 25-75 (%)/10%	**0.81**	**(0.72; 0. 91)**	0.00	0.82 (0.61; 1.09)	**0.83**	**(0.71; 0. 97)**	0.02	0.85 (0.61; 1.18)
FEF 50 (%)/10%	**0.83**	**(0.74; 0. 94)**	0.00	1.07 (0.79; 1.46)	**0.83**	**(0.71; 0. 98)**	0.02	1.04 (0.74; 1.47)
Decreased LFS	0.77	(0.35; 1. 67)	0.51		0.52	(0.20; 1. 34)	0.18	
Severely decreased	**2.21**	**(1.01; 4. 81)**	0.05	1.00 (0.30; 3.28)	0.73	(0.17; 3. 14)	0.68	
5% FEV1 decline from baseline***	**3.20**	**(1.46; 6. 99)**	0.00	1.19 (0.32; 4.42)	2.25	(0.84; 6. 04)	0.11	0.42 (0.05; 3.14)

10% FEV1 decline from baseline*	**4.21**	**(1.97; 9. 01)**	0.00	1.41 (0.36; 5.49)	**3.89**	**(1.45; 10. 45)**	0.01	2.64 (0.37; 18.75)
Lung CT scan								
Normal	**0.53**	**(0.28; 1. 01)**	0.05	1.04 (0.46; 2.37)	0.49	(0.21; 1. 14)	0.10	
Air trapping score >6	1.28	(0.66; 2. 46)	0.47		1.53	(0.66; 3. 54)	0.32	
Bronchial abnormalities****	**2.58**	**(1.13; 5. 94)**	0.02	1.22 (0.46; 3.22)	**6.03**	**(2.40; 15. 10)**	**0.00**	**3.00 (1.06; 8.48)**

* after multiple imputation; ** Acute GVHD usually includes erythema, maculopapular rash, nausea, vomiting, anorexia, profuse diarrhea, ileus, or cholestatic liver disease. Acute GVHD was graded from 1 to 4, according to the severity, using the National Institutes of Health consensus criteria (21). Chronic GVHD is a syndrome of variable clinical features resembling autoimmune and other immunologic disorders such as scleroderma, Sjögren's syndrome, primary biliary cirrhosis, wasting syndrome, bronchiolitis obliterans, immune cytopenias, and chronic immunodeficiency; manifestations of chronic GVHD may be restricted to a single organ or site or may be widespread. The global score of mild, moderate, and severe reflects the degree of organ impact and functional impairment due to chronic GVHD. It has been established according National Institutes of Health consensus criteria (15) ***As measured by absolute differences in %predicted; **** including centrilobular micronodules, tree in bud and bronchial thickening.

CI: confidence interval

Yr: year; BOS: bronchiolitis obliterans syndrome; LONIPC: late-onset noninfectious pulmonary complication; PFT: pulmonary function testing; pred: predicted; FEV1: forced expiratory volume in one second; TLC: total lung capacity; FEF: forced expiratory flow; TLCO: transfer factor of the lung for carbon monoxide; LFS: lung function score; CT: computed tomography; CR1: 1st complete remission; CMV: cytomegalovirus; PBSC: peripheral blood stem cell; GVHD: graft-versus-host disease; cyclo: cyclosporine; MTX: methotrexate; MMF: mycophenolate mofetil

Based on multivariable Cox models that included all previously selected predictors, pretransplant chest irradiation, LRTI before inclusion and low FEF 25-75 at inclusion were jointly associated with the occurrence of LONIPC (Table 4). Similar results were obtained for CCA.

Table 4: Predictive factors for developing BOS and LONIPC during the first three months after transplantation - results of the multivariate analyses

LONIPC	**HR**	**95% CI**	**p-value**
Multivariate analysis after multiple imputation (198 patients, 39 LONIPC)			
Chest irradiation prior to HSCT	3.60	(1.57; 8. 28)	0.0025
History of LRTI within the 100 days after HSCT	3.12	(1.38; 7. 07)	0.0065
Low FEF 25-75 at day 100	0.84	(0.75; 0. 94)	0.0034
Multivariate analysis on complete cases (182 patients, 36 LONIPC)			
Chest irradiation prior to HSCT	3.12	(1.29; 7. 57)	0.0118
History of LRTI within the 100 days after HSCT	2.57	(1.04; 6. 33)	0.0407
Low FEF 25-75 at day 100	1.21	(0.73; 0. 94)	0.0025
BOS	**HR**	**95%CI**	**p-value**
Multivariate analysis after multiple imputation (198 patients, 22 BOS)			
PBSC	6.07	(1.40; 26. 2)	0.0158
History of LRTI within the 100 days after HSCT	3.28	(1.20; 8. 88)	0.0198
Bronchial abnormalities on CT scan at day 100	2.96	(1.02; 8. 57)	0.0449
Multivariate analysis on complete cases (144 patients, 16 BOS)			
PBSC	7.69	(1.00; 58. 9)	0.0495
10% FEV1 decline between baseline and day 100	3.07	(1.14; 8. 29)	0.0271

BOS: bronchiolitis obliterans syndrome; LONIPC: late-onset noninfectious pulmonary complication; LRTI: lower respiratory tract infection; HSCT: haematopoietic stem cell transplantation; FEV1: forced expiratory volume in one second; FEF: forced expiratory flow; PBSC: peripheral blood stem cell; CT: computed tomography.

We re-evaluated these predictors to predict BOS (Table 3). Multivariable models selected the use of PBSC and bronchial abnormalities on the CT scan (including centrilobular micronodules, tree in bud, and bronchial thickening) at inclusion as associated with the occurrence of BOS. Based on CCA, LRTI and a 10% FEV1 decline from baseline to day 100 were selected instead of bronchial abnormalities (Table 4).

We further investigated whether the occurrence of chronic GVHD after inclusion (i.e. any time during the whole follow-up from day 100 and before the LONIPC) was predictive of LONIPC/BOS. The cause-specific hazard of LONIPCs was increased by 2.25 (95% CI, 1.07-4.75; p=0.03) after the occurrence of a chronic GVHD; that of BOS increased by 2.90 (95% CI, 0.98-8.60; p=0.05).

Among the 43 patients with LONIPCs, 18 died (nine after BOS; three after ILD; two after VTED; two after RLD; one after both BOS and RLD; and one after pneumomediastinum, BOS and ILD), with a median survival after diagnosis of 78.5 months (95% CI: 20.0 not reached). At three years after BOS, survival was 63.6% (95% CI: 46.4-87.3) (Figure 4). The occurrence of LONIPCs was associated with an increased hazard of death (HR=2.18, 95% CI=1.14-4.15; p=0.02).

At the end of follow-up (i.e., 100 months), almost 80% of the patients presented a significant PFT decrease at least once, particularly a 10% decline in FEV1 (see the online supplement figure S1). As depicted in Figure S2 (see the online supplement), all patients who were free from LONIPCs had roughly stable FEV1 values over time, regardless of their baseline value. By contrast, the FEV1 trajectories differed among patients with BOS with two different clusters (see the online supplement, figure S3).

Discussion

We confirmed prospectively that LONIPC is a frequent complication that largely occurred within two years after allogeneic HSCT with a poor outcome. Although BOS accounted for more than half of LONIPCs, these complications included heterogeneous entities, demonstrating that the risk factors for LONIPC and BOS are distinct.

Most of the variables that we tested as risk factors have previously been associated with LONIPCs or BOS in one or more previous retrospective studies, with contradictory

conclusions. Because the procedures applied for allogeneic HSCT change over time, including conditioning regimens and stem cell sources, the evaluated risk factors for LONIPCs have evolved over time. Some studies have proposed that chronic GVHD is a risk factor for BOS (6, 23). Due to the retrospective design of these studies, we wondered whether chronic GVHD was contemporaneous to LONIPC/BOS rather than a predictive risk factor. As expected, few patients developed chronic GVHD within 100 days following transplantation. However, prolonged follow-up of our patients led us to conclude that chronic GVH was actually associated with the occurrence of LONIPCs. The physiopathological hypotheses of LONIPC/BOS is that lung injury caused by various insults could be the trigger of an uncontrolled inflammatory reaction, leading to an aberrant tissue repair (24). We found that a history of chest irradiation and the occurrence of early pneumonia after HSCT were strongly predictive of LONIPC/BOS, reinforcing this hypothesis.

The diagnosis of post-transplant BOS using noninvasive methods is challenging (24). In the early 2000s, lung CT scan emerged as a promising tool to diagnose BOS (25, 26). Some authors have even suggested that the presence of air trapping on expiratory cuts could precede PFT impairment (27, 28). These data led to the inclusion of air trapping as a diagnostic criterion for post-allogeneic HSCT BOS in the NIH consensus (13, 15). We were surprised to find that nearly a quarter of patients had significant air trapping before transplantation. This phenomenon could be attributed to the observation that allogeneic HSCT recipients are older and have a history of respiratory events explaining the air trapping, including respiratory infection during a prior course of chemo-radiotherapy. Furthermore, although the proportion of patients with significant air trapping increased at day 100 after transplant, air trapping was not predictive of BOS. Conversely to air trapping, bronchial abnormalities at day 100, including centrilobular micronodules, tree in bud and bronchial thickening, were predictive of BOS. This finding is of particular interest because these CT

scan abnormalities could reflect the early phase of inflammatory BO when treatment could be effective.

To date, PFT is the cornerstone of BOS diagnosis (15). However, the current criteria do not allow for consideration of all BOS (4, 29, 30). Recently, Thompson et al. showed that the median ΔFEV1 from pretransplant to day 100 in patients who subsequently developed LONIPCs was significantly greater than that in unaffected patients (3). We found that a decrease in airflow at day 100, both in proximal and small airways (i.e., FEV1 and FEF), was predictive of LONIPC/BOS. In particular, a 10% decline in FEV1 from pretransplant to day 100 was predictive of BOS in the multivariate analysis. These findings strongly encourage monitoring spirometry early after an allogeneic HSCT and suggest consideration of the trajectory of FEV1 rather than the absolute value at a given time. This finding is consistent with the findings of Cheng et al, who observed a rapid FEV1 decline during the 6 months prior to BOS diagnosis (31).

Our prospective cohort provides a unique opportunity to assess allogeneic HSCT recipient lung function over a long follow-up period. Thus, we have shown that lung function fluctuated and that a very significant proportion of patients experienced a significant decline in airflow at least once during their follow-up. However, FEV1 or FEF mostly returned to baseline values in the follow-up PFT. The many events that occur after transplant can explain this issue, especially respiratory infections and a transient deterioration in general condition that jeopardizes the quality of spirometric performance.

Finally, we provide important data regarding BOS. We used a definition that differs from that of the NIH consensus, which allowed an earlier diagnosis of BOS. Of note, we used this definition in previous studies (4, 20). In addition, we identified two phenotypes of BOS according to the trajectory of FEV1 with different outcomes. This result raises the question of a different pathophysiologic mechanism, and different approaches for management should be

investigated.

Our study has several limitations. First, due to the small number of patients who experienced LONIPCs other than BOS, we could not reliably evaluate the risk factors for each specific LONIPC. Second, our study was a single-center study; however, given all the PFTs were performed at the same place using the same plethysmograph, this reinforces the value of our PFT variations findings reducing inaccuracy and avoiding potential bias incurred by PFT performed using different machines. Nevertheless, the single-center recruitment limits the external validity required to support widespread changes in practice; results should thus apply at the bedside only after comparing the context of the study with the context of clinical experience. Third, some data were missing, especially some PFT and some CT scans during forced expiration, which were difficult to obtain in patients with poor general health. However, missing data were imputed with no main modifications of the results. Indeed, the various predictive factors for BOS that were identified either after multiple imputation or multivariate analysis of the complete cases were actually correlated (data not shown). Finally, we did not collect data to allow calculating scores that was shown to be independently predictive of increased mortality after allogeneic HSCT, such as the Comorbidity Index or the Disease Risk Index (32, 33). So, this issue avoided their assessment in our predictive models for LONIPC. This could be explored in further studies.

In conclusion, our data provide clues to identify patients with a high risk of developing LONIPCs. These patients should be targeted for close monitoring, especially PFT, and thus offered earlier treatment of LONIPCs or prophylactic treatment to improve outcomes.

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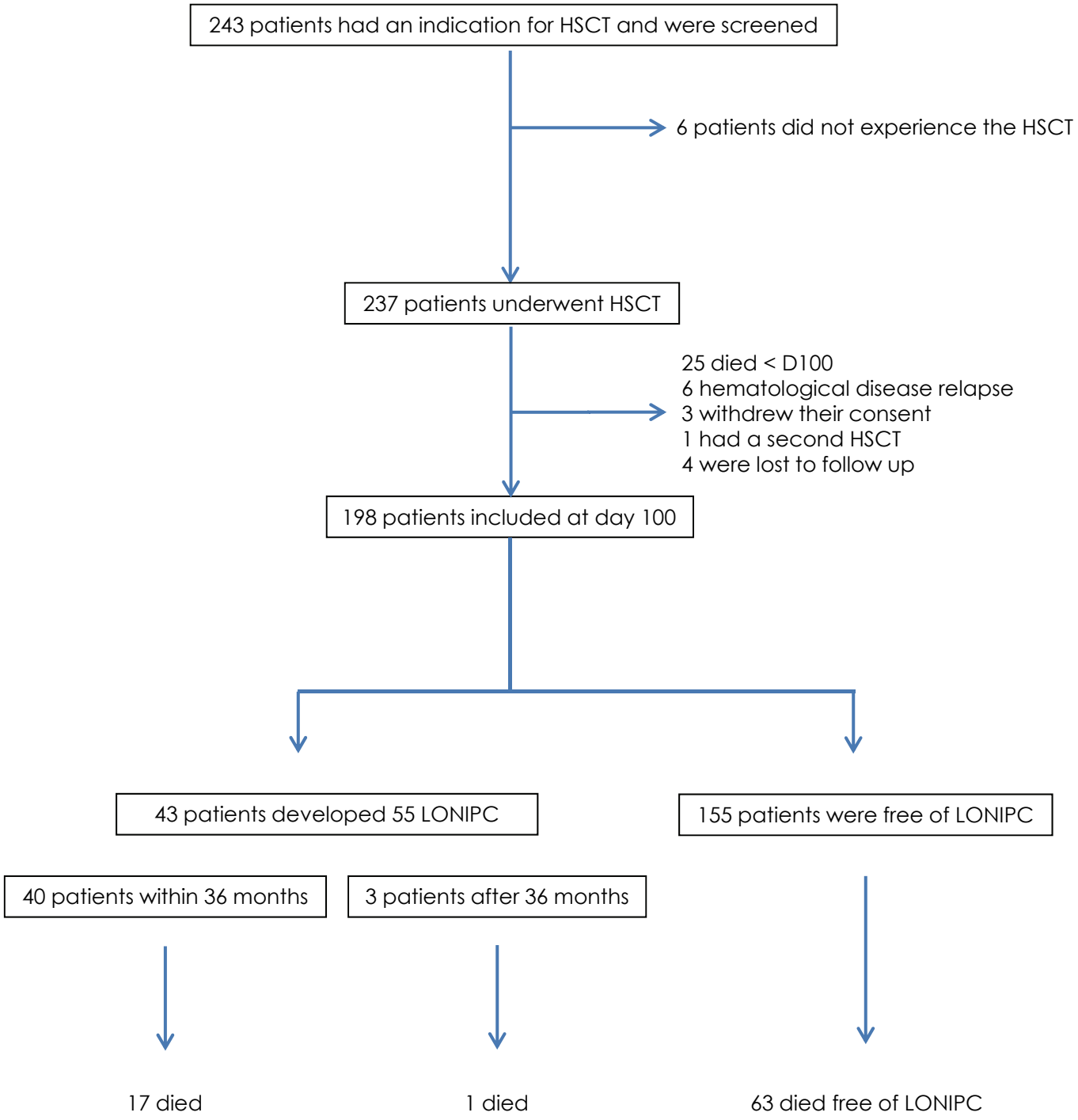
Figure legends

Figure 1: Study flow chart.

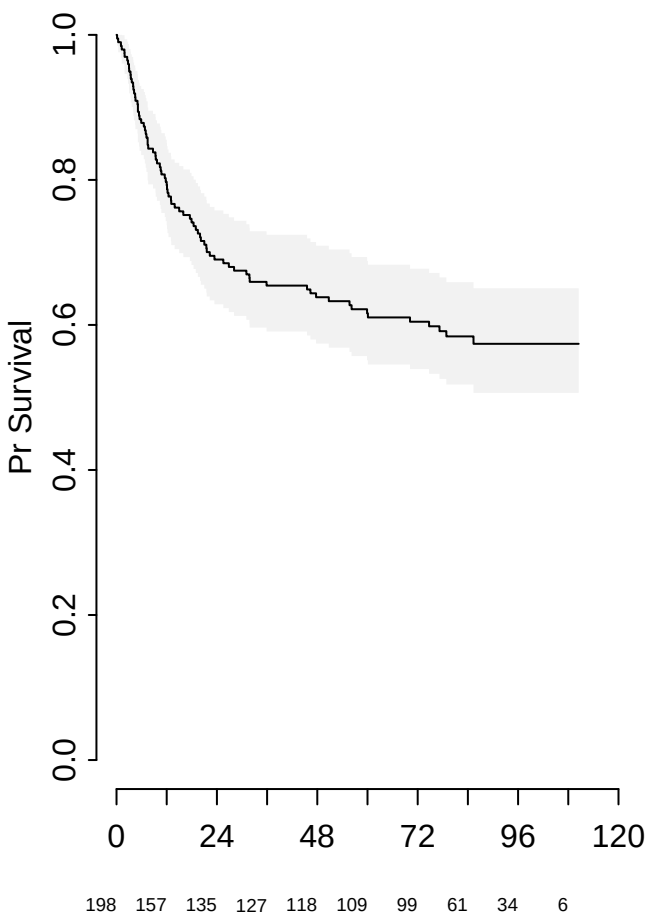
Figure 2: Estimated survival of allogeneic HSCT recipients included in the cohort (100 days after transplantation), either overall whatever the cause of death (Fig 2a) or cumulative incidence of death according to cause (Fig 2b)

Figure 3: Cumulative incidence of LONIPCs, overall and segregated into BOS, PID and others.

Figure 4: Overall survival after LONIPCs according to each LONIPC.



HSCT: hematopoietic stem cell transplantation; LONIPC: late-onset noninfectious pulmonary complications.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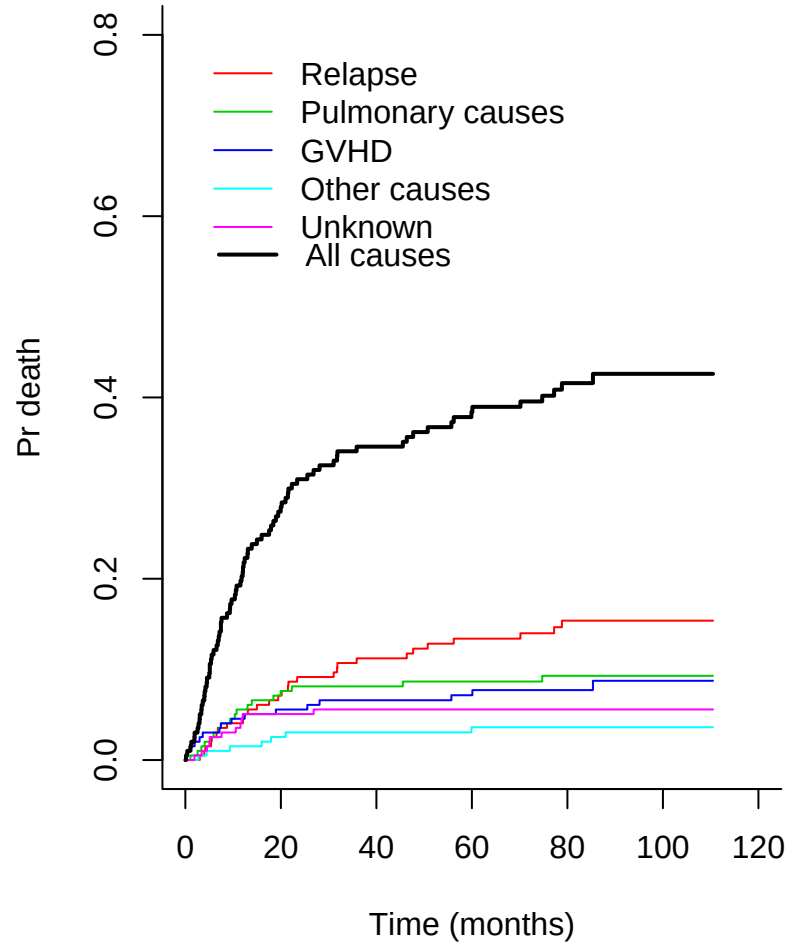
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All causes
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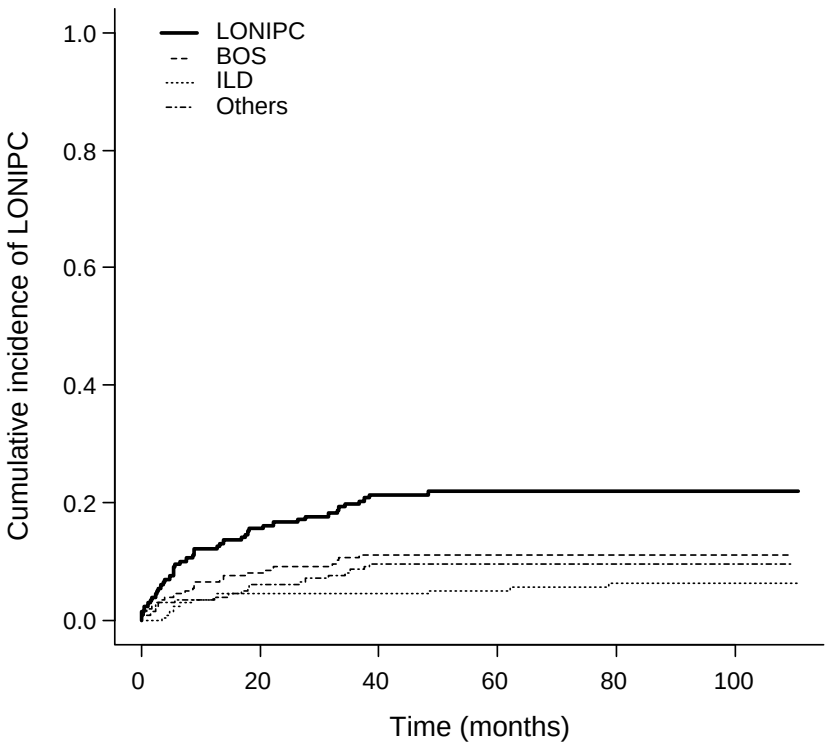
100
120
Time (months)


LONIPC
BOS
ILD
Others
Cumulative incidence of LONIPC
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20
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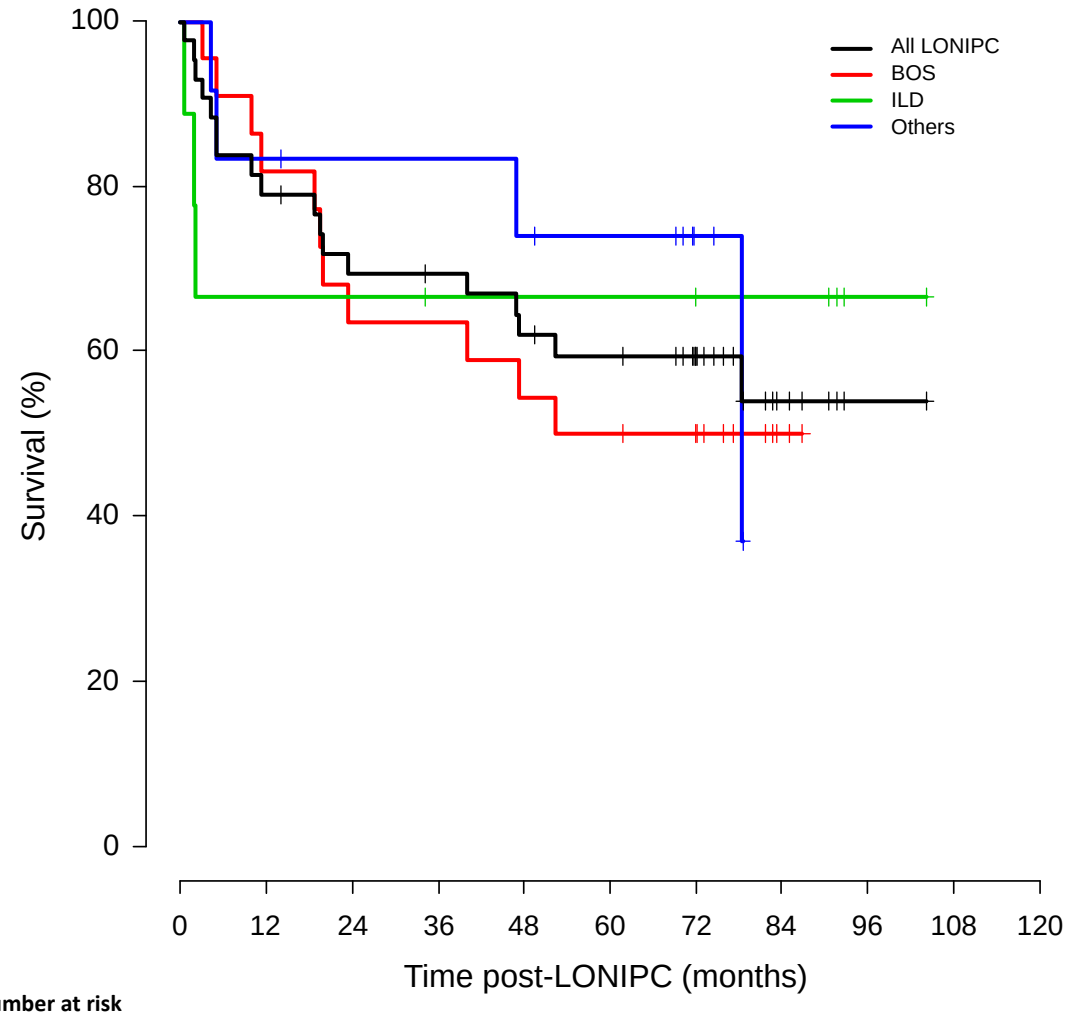
100
Time (months)



Number at risk

BOS	22	18	14	14	12	11	10	2	
ILD	9	6	6	5	5	5	5	4	1
Others	12	10	9	9	8	7	3		

SUPPLEMENTARY MATERIAL

Supplementary Table

Table S1: Characteristics of the screened population at the time of HSCT with a comparison between included and excluded patients

Variables **Median [IQR]; n (%)**	**N=45 excluded**	**N=198 included**
Patients and Disease characteristics		
Age at screening (year)	42.4 [18.4;54.3]	38.2 [24.9;53.4]
Male	30 (67%)	120 (61%)
History of smoking	11 (30%)	65 (33%)
Hematologic disease		
AML	10 (27%)	59 (30%)
ALL	9 (24%)	39 (20%)
CML and other MPS	3 (8%)	19 (10%)
Lymphoma	5 (13%)	25 (13%)
Myeloma	3 (8%)	13 (6%)
MDS	3 (8%)	13 (6%)
Aplastic anemia	2 (5%)	19 (10%)
Others	2 (5%)	11 (5%)
History of autologous HSCT	6 (13%)	37 (19%)
Disease status: first complete remission	16 (35%)	113 (57%)
Allogeneic HSCT characteristics	**n=39**	**n=198**
Stem cell source		
PBSC	22 (60%)	126 (64%)
BM	6 (16%)	60 (30%)
Cord blood	9 (24%)	12 (6%)
Sex mismatch: Donor-Recipient Sex		
MM/MF/FM/FF	11/5/8/3	63/38/53/34
Donor HLA status		
Related	9 (24%)	108 (55%)
Unrelated*	28 (76%)	90 (45%)
CMV serologic status donor-recipient		
Pos-Pos/Neg-Pos/Pos-Neg/Neg-Neg	8/12/1/12	60/45/27/59

Conditioning regimen		
Nonmyeloablative conditioning	18 (49%)	87 (44%)
Cyclophosphamide-based	22 (49%)	98 (49%)
BU-based	11 (24%)	60 (30%)
ATG-based	6 (13%)	43 (22%)
TBI	23 (51%)	95 (48%)
GVHD prophylaxis		
Cyclo-MTX	17 (38%)	90 (45%)
Cyclo-MMF	16 (35%)	99 (50%)
Pretransplant PFT	**n=11**	**n=154**
FEV1 (% of predicted)	103 [90-111]	101.5 [91.0-111.0]
TLC (% of predicted)	110 [93-119]	99.5 [91.0-110.0]
FEV1/VC	86.3 [75.8-88.8]	85.6 [80.4-89.3]
FEV1/FVC <0.7	1 (9%)	5 (3%)
TLC <80% of predicted	2 (18%)	
TLCO (% of predicted)	69 [63.5-73.5]	72 [64-81]
LFS score†		
Normal	0	38 (19%)
Mildly decreased	7 (64%)	66 (33%)
Moderately decreased	3 (27%)	46 (23%)
Severely decreased	1 (9%)	48 (24%)
Pretransplant chest CT scan	**n=14**	**n=157**
Air trapping score >6	1 (7%)	34 (22%)‡
Opacities		52 (33%)
Ground-glass opacities	2 (14%)	5 (3%)
Nodules	2 (14%)	13 (8%)
Centrilobular micronodules	1 (7%)	4 (3%)
Consolidation	1 (7%)	6 (4%)
Linear opacities	0	19 (12%)

AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; CML: chronic myeloid leukemia; MPS: myeloproliferative syndrome; MDS: myelodysplastic syndrome; HSCT: hematopoietic stem cell transplantation; PBSC: peripheral blood stem cell; BM: bone marrow; M: male; F: female; CMV: cytomegalovirus; BU-based: busulfan based; ATG: antithymocyte globulin; TBI: total body irradiation; Cyclo: cyclosporine; FEV1: forced expiratory volume in one second; TLC: total lung capacity; FVC: forced vital capacity; FEF: forced expiratory flow; TLCO: transfer factor of the lung for carbon monoxide; LFS: lung function score; a separate score to the FEV1 and TLCO was provided (>80%=1, 70–80%=2, 60–70%=3, <60%=4). These scores were summed to the LFS and then distinguished into four categories (normal, LFS=2; mildly decreased, LFS=3-4; moderately decreased, LFS=5-6; severely decreased, LFS=7-8); CT: computed tomography.

*10/10 and 9/10 allelic unrelated donors and cord blood transplants. †Lung function score (LFS): a separate score from the FEV1 and TLCO was provided (>80%=1, 70–80%=2, 60–70%=3, <60%=4). These scores were summed to the LFS and then distinguished into four categories (normal, LFS=2; mildly decreased, LFS=3-4; moderately decreased, LFS=5-6; severely decreased, LFS=7-8). ‡The quality of only 118 chest CT scans performed at expiration allowed the evaluation of air trapping.

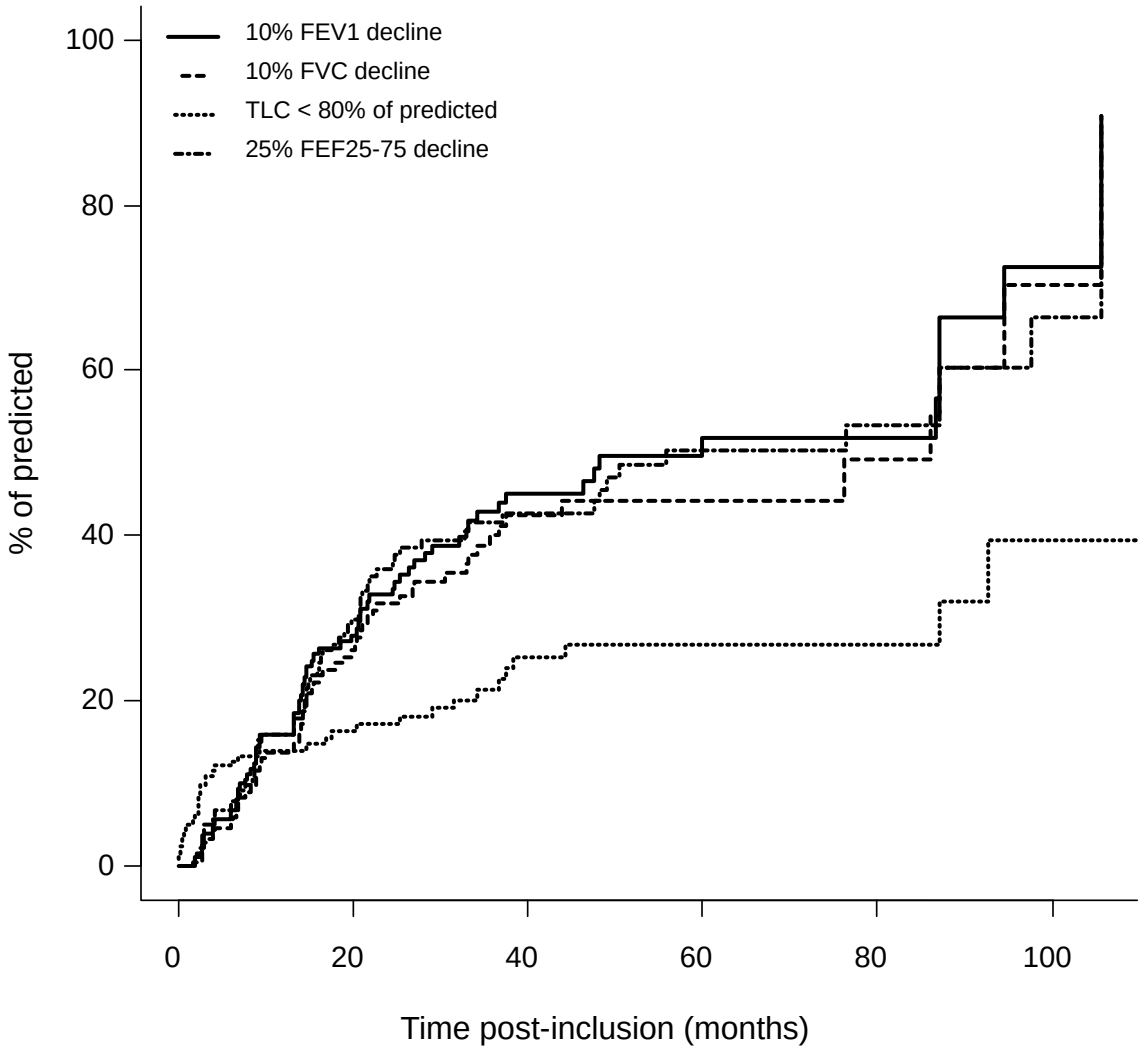
Supplementary Figure Legends

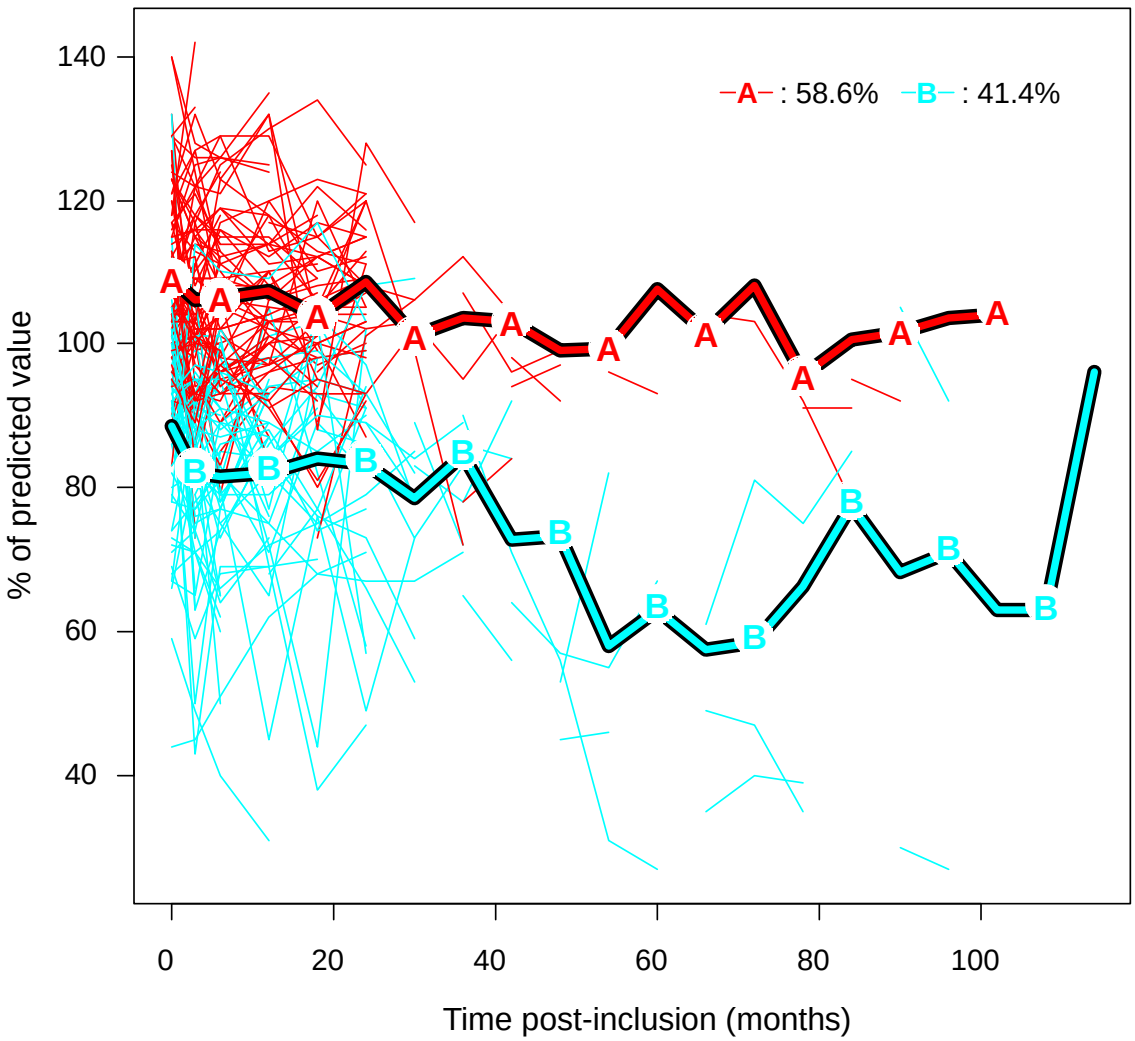
Figure S1: Cumulative incidence of a 10% decrease in FEV1 or FVC or a TLC<80% of predicted, or a 25% decrease in FEF 25-75.

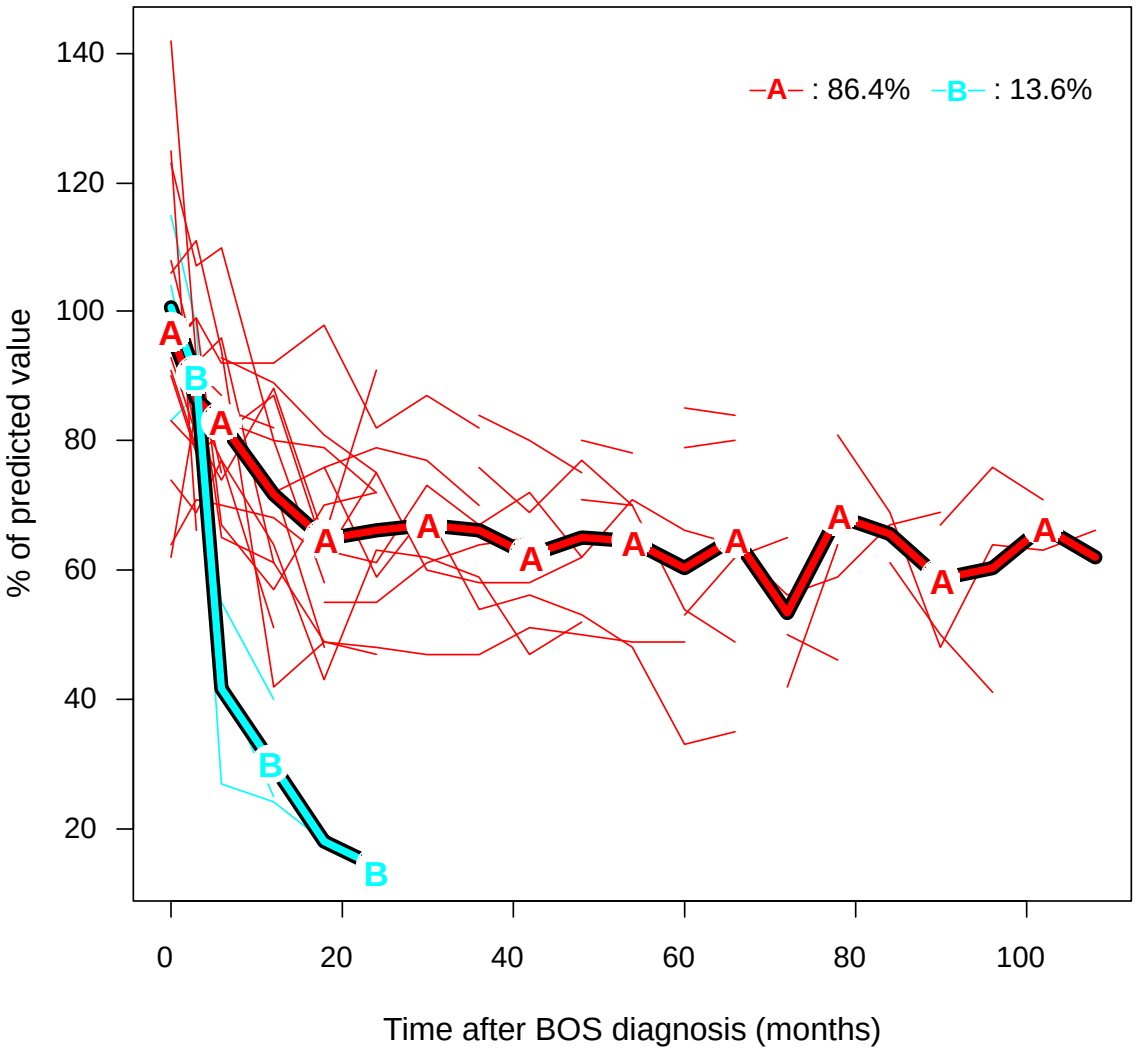
Figure S2: Long-term follow-up of FEV1 trajectories (% predicted) in patients who did not develop LONIPC.

Figure S3: Trajectories of FEV1 (% predicted) in patients who developed BOS: Cluster A (n=19, median time to BOS: 9 months after day 100 post-transplantation [IQR: 4.4; 19.0]; Cluster B (n=3, median time to BOS: 2.8 months after day 100 post-transplantation [IQR: 2.2; 3.3].

Cluster B was characterized by a sudden and deep FEV1 decline that occurred early after transplantation and was of poor prognosis; all died free from hematological relapse. Cluster A was characterized by a less severe FEV1 decline followed by a global stabilization of lung function with 8 deaths; 3 died free from relapse, and 5 died from relapse.


10% FEV1 decline
10% FVC decline
TLC < 80% of predicted
25% FEF25-75 decline
% of predicted
0
20
40
60
80
100
Time post-inclusion (months)


A : 58.6%
B : 41.4%
% of predicted value
Time post-inclusion (months)
140
120
100
80
60
40
0
20
40
60
80
100


–A– : 86.4%
–B– : 13.6%
% of predicted value
140
120
100
80
60
40
20
0
20
40
60
80
100
Time after BOS diagnosis (months)
A
B