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1 **Stable Long-Term Pulmonary Function after Fludarabine, antithymocyte globulin, and**
2 **intravenous Busulfan for reduced-intensity conditioning allogeneic stem cell**
3 **transplantation**

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16

17 **Running head:** Stable pulmonary function after Flu Bu ATG based RIC

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23

1 ABSTRACT

2 Lung function decline is a well-recognized complication following allogeneic stem cell
3 transplantation (allo-SCT). Reduced-intensity conditioning (RIC) and in vivo T-cell depletion
4 by administration of antithymocyte globulin (ATG) may play a protective role in the
5 occurrence of late pulmonary complications. This retrospective study reported the evolution
6 of lung function parameters within the first 2 years after allo-SCT, in a population receiving
7 the same RIC regimen including fludarabine and i.v. busulfan in combination with low dose
8 ATG. The median follow-up was 35.2 months. With a median age of 59 years at time of
9 transplant, at 2 years, the cumulative incidences of non-relapse mortality was as low as 9.7%.
10 The cumulative incidence of relapse was 33%. At 2 years, the cumulative incidences of
11 extensive chronic graft-versus-host disease (cGVHD) and of pulmonary cGVHD were 23.1%
12 and 1.9%, respectively. The cumulative incidences of airflow obstruction and restrictive
13 pattern were 3.8% and 9.6%, respectively. Moreover, FEV1, FVC and FEV1/FVC ratio
14 remained stable from baseline up to 2 years post transplantation ($p=0.26$, $p=0.27$ and $p=0.07$,
15 respectively). These results compare favorably with results obtained with other RIC regimens
16 not incorporating ATG, and suggest that ATG may play a protective pulmonary role after
17 allo-SCT.

18 **Key Words:** pulmonary function, reduced intensity conditioning, ATG

19

1 INTRODUCTION

2 Allogeneic hematopoietic stem cell transplantation (allo-SCT) is a well-established therapy
3 for several hematological diseases. Unfortunately, allo-SCT is limited by the high incidence
4 of non-relapse mortality (NRM), mainly due to acute and chronic graft versus host disease
5 (aGVHD, cGVHD) ¹. Importantly, pulmonary complications, which occur in 30 to 60% of
6 patients after allo-SCT ², account for meaningful mortality and morbidity, and up to 50% of
7 transplant-related deaths.³ Multiple factors can contribute to pulmonary complications,
8 notably the type of conditioning regimen used. Reduced-intensity conditioning (RIC)
9 regimens are being used with the aim of decreasing NRM in elderly patients, in heavily
10 pretreated patients or in patients with medical comorbidities precluding the use of standard
11 myeloablative conditioning (MAC). One study already showed that the use of RIC regimen
12 can reduce the risk of developing late pulmonary complications, with protection against
13 declining lung function and a reduced incidence of bronchiolitis obliterans syndrome (BOS) ⁴.
14 Beyond the degree of myeloablation of the preparative regimen itself (RIC or standard
15 myeloablative conditioning), it is well admitted that the use of total body irradiation (TBI) in
16 the conditioning is also associated with pulmonary toxicity ⁵. In contrast, *in vivo* T cell
17 depletion seems to reduce the risk of developing pulmonary complications after allo-SCT ⁶.
18 Also, cGVHD has been identified as a risk factor for late onset non-infectious pulmonary
19 complications and in particular BOS ⁷⁻¹⁰. On the other hand, cGVHD is usually significantly
20 reduced in patients receiving *in vivo* T cell depletion by administration of antithymocyte
21 globulins (ATG) ¹¹. However, the onset of long term pulmonary complication in patients
22 receiving an ATG-based RIC regimen, without TBI, has not yet been investigated. This study
23 evaluated the evolution of lung function parameters within the first 2 years following allo-
24 SCT, in a population undergoing the same RIC regimen including fludarabine, i.v. busulfan in
25 combination with low dose ATG.

1 PATIENTS AND METHODS

2 Patients' characteristics

3 This retrospective single-center study included 52 consecutive patients who received allo-
4 SCT between January 2007 and September 2010 at the University Hospital of Nantes (CHU
5 de Nantes, Nantes, France). Per study inclusion criteria, all patients with available pre- and
6 post-transplant pulmonary function tests (PFT) and who received RIC regimen including 30
7 mg/m² fludarabine for 5 or 4 consecutive days, 6.4 mg/kg total dose IV busulfan and 5 mg/kg
8 total dose ATG (Thymoglobulin; Genzyme/Sanofi, Lyon, France), were included. In our
9 transplant program, eligibility criteria for RIC allo-SCT that preclude the use of standard
10 myeloablative conditioning (MAC) allo-SCT include: (i) patient age older than 50 years; (ii)
11 heavily pretreated patients who received auto-SCT or with more than 2 lines of chemotherapy
12 before allo-SCT; and (iii) patients with poor performance status because of significant
13 medical comorbidities as described by Sorror et al ¹². Patients were treated as part of different
14 prospective clinical trials, and written informed consent was obtained from each patient and
15 donor. All clinical data were prospectively collected.

16 All patients received the preparative regimen as inpatients in private rooms, and remained
17 hospitalized until hematopoietic and clinical recovery. 29 donors (56%) were HLA-identical
18 sibling donors, while 20 (38%) were HLA-unrelated donors (MUD) and 3 (6%) were HLA
19 unrelated donors with one locus mismatch. The stem cell source was bone marrow in 2 cases
20 (4%) and G-CSF-mobilized peripheral blood stem cells in 50 cases (96%). In this series, the
21 median age was 59 (range, 23-70) years. Twenty-two patients were treated for acute myeloid
22 leukemia (42%), 10 patients had a myelodysplastic syndrome (19%), 13 patients had non
23 Hodgkin lymphoma (25%), 3 patients had Hodgkin disease (6%), 3 patients had multiple
24 myeloma (6%) and 1 patient had acute lymphoblastic leukemia (2%).

25 Supportive care and antimicrobial prophylaxis were given as reported previously ¹³. For

1 GVHD prophylaxis, patients received either CSA alone in case of an HLA-sibling donor or
2 CSA and mycophenolate mofetil (MMF) in case of an HLA-matched unrelated donor¹⁴. In
3 this series, CSA was administered at a dose of 3 mg/kg/day by continuous intravenous
4 infusion starting from day -3 or -2, and changed to twice daily oral dosing as soon as tolerated
5¹⁵. MMF was given at a fixed oral dose of 2 g/day. No treatment adjustment was performed
6 for MMF. MMF was decreased progressively over 4 weeks starting from day 60 and CSA
7 from day 90 if no GVHD appeared. Of note, during the whole study period supportive care
8 was the same. CMV infection management was also homogeneous. All blood products were
9 filtered irradiated and CMV screened. In the first 100 days post allo-SCT, patients were
10 assessed at least once per week for CMV reactivation by PCR assay in order to initiate
11 preemptive ganciclovir therapy. Acute GVHD was evaluated according to the Seattle standard
12 criteria¹⁶.

13

14 **Pulmonary Function Testing**

15 PFT were performed before allo-SCT and then repeated 100 days, one and two years after
16 transplant. All PFT were performed in the same laboratory in accordance with the American
17 Thoracic Society and European Respiratory Society criteria¹⁷. Lung volumes and spirometry
18 were measured with a Jaeger constant volume body plethysmograph with a
19 pneumotachograph connected to an Epson PC-AT (Epson, Suwa, Japan). All PFT values,
20 except FEV₁/FVC ratio were expressed as a percentage of predicted values in healthy controls
21 with corresponding age and gender. Published equations were used to calculate predicted
22 values of forced expiratory volume in 1 second (FEV₁), forced vital capacity (FVC), total
23 lung capacity (TLC) and lung carbon monoxide diffusing capacity (DLCO)¹⁸. DLCO was
24 measured using the single breath technique of Ogilvie et al. and corrected for the most recent
25 hemoglobin concentration but not corrected for the alveolar volume¹⁹. In those patients who

1 received a bronchodilator challenge, the prebronchodilator values were used. A lung function
2 score (LuFS) was calculated before transplantation, and at day 100, 1 year and 2 years after
3 transplant in order to grade the extent of lung function impairment (if any). A separate score
4 was assigned to relative values of FEV₁ and DLCO (>80% = 1, 70-79% = 2, 60-69% = 3, 50-
5 59% = 4, 40-49%=5, <40%=6), these scores were then summed and divided into four
6 categories as LuFS (LuFS score 2 = category 0 [normal]; LuFS score 3-5 = category 1 [mildly
7 decreased]; LuFS score 6-9 = category 2 [moderately decreased]; LuFS score 10-12 =
8 category 3 [severely abnormal]), according to NIH recommendations ²⁰. Restrictive lung
9 disease (RLD) was defined as TLC <80% of the predicted value, and was graded as mild at
10 70–79%, moderate at 60–69%, moderately severe at 50–59%, and severe at <50%. Diffusion
11 impairment was defined as DLCO <80% of the predicted value and was graded as mild at 60–
12 79%, moderate at 40–59%, and severe at <40% ²¹. Airflow obstruction (AFO) was defined by
13 a FEV₁/FVC < 70. Criteria from the NIH consensus guidelines were used for diagnosis of
14 BOS: 1) FEV₁/ FVC < 70% and FEV₁ < 75% of predicted value, 2) radiological, histological
15 or lung volume evidence of air trapping and 3) absence of respiratory tract infection ²⁰.

16 The occurrence of infectious respiratory complications during the follow-up period of interest
17 was collected in medical records. Expiration scans to evaluate air trapping, chest high
18 resolution computed tomography and bronchoalveolar lavage with bacterial, fungal and
19 virological searches were left to the discretion of the attending physician, according to
20 symptoms presented by the patient.

21

22 **Statistical Methods**

23 Continuous variables were presented as mean ± standard deviation (SD) or median
24 (range), categorical variables as count and percent. Mixed models were used to analyze
25 PFT data during time (before transplantation until 2 years post transplantation). Comparison

1 between LuFS scores before transplantation and at 100 days, 1 year and 2 years post
2 transplantation was performed with the *McNemar's test*. Overall survival (OS) and
3 progression-free survival (PFS) were calculated by the Kaplan-Meier method. Probabilities of
4 relapse, NRM and GVHD were calculated using the cumulative incidence procedure. The risk
5 of respiratory failure, RP and AFO were also calculated using the cumulative incidence
6 procedure with death considered as the competing event. Data were computed using SAS
7 software version 9. 3, the R package (R Development Core Team, 2006. R: A language and
8 environment for statistical computing. R Foundation for Statistical Computing, Vienna,
9 Austria. ISBN 3-900051-07-0, URL <http://www.R-project.org>) and GraphPad Prism 5.0
10 (GraphPad Software, San Diego, CA).

11

1 RESULTS

2 Patients' characteristics

3 In this series, the overall median follow-up was 35.2 months (range, 20.0-59.8) among
4 surviving patients. Patients, donors and transplant characteristics are summarized in **Table 1**.
5 The median age was 59 (range 23-70) years. Patients engrafted at a median of 17 (range, 0-
6 48) days after allo-SCT. The cumulative incidence of severe grade III-IV aGVHD at day 100
7 was 15.4%. At 2 years, the cumulative incidence of extensive cGVHD was 23.1%. In this
8 series, 23 (44%) patients were active or former smokers while 21 (40%) never smoked.
9 Smoker status data were missing for 8 patients (15%).

10

11 PFT and development of airflow obstruction and restrictive pattern

12 Pretransplantation PFT were performed at a median of 17 (range, 10-76) days before allo-
13 SCT. Subsequently, PFT were performed at a median of 101 (range, 77-119), 365 (range,
14 251-490) and 717 (range, 588-846) days after transplantation. The proportion of surviving
15 patients with available PFT was 85%, 89% and 82% at day 100, 1 year and 2 years,
16 respectively. PFT data before transplantation and at day 100, 1 year and 2 years
17 posttransplantation are summarized in **Table 2**. Before stem cell transplantation, lung function
18 was normal in 83% (n=43) of patients, while 6 patients met the criteria for obstructive lung
19 disease defined as FEV1/FVC <70, and 3 patients had restrictive lung disease, defined as
20 TLC <80%. Restrictive lung disease was graded as mild for 2 patients and moderate for one.
21 Among patients with a pretransplantation obstructive pattern, only one patient had a FEV1
22 inferior to 75% predicted. DLCO was impaired (mean value <80%) in 83% of patients before
23 transplantation, and remained altered but stable from baseline up to 2 years post
24 transplantation (p=0.84). Furthermore, 60% (n=31) had a mild diffusion impairment, 19%
25 (n=10) a moderate diffusion impairment, and 4% (n=2) a severe diffusion impairment of
26 DLCO (**Figure 1 E**). FEV1, FEV1/FVC ratio, FVC and TLC remained stable from baseline

1 up to 2 years post transplantation ($p= 0.26$, $p=0.07$, $p=0.27$, $p=0.44$, respectively) (**Figure 1**
2 **A-D**). Evaluation of LuFS showed a mildly abnormal lung function (category 1) in 44 patients
3 (77%) at baseline. From baseline up to 2 years, LuFS score remained stable with most of
4 patients with normal or mildly abnormal lung function, and no patient had a severely
5 abnormal lung function (**Figure 2**). There was no statistical difference when comparing time-
6 points: before allo-SCT versus 100 days ($p=0.53$), before allo-SCT vs 1 year ($p=0.29$), and
7 before allo-SCT versus 2 years ($p=0.54$).

8

9 **Mortality, infectious and non-infectious pulmonary complications**

10 Of the 52 patients included in this study, a total of 19 patients died (36.5%) during the follow-
11 up period. Overall survival, cumulative incidences of relapse and NRM rates at 2 years after
12 allo-SCT were 65% (95% CI, 51-76%), 33% and 9.7% respectively. Four deaths (21%) were
13 related to GVHD, 1 (5%) death was directly related to a pulmonary cause (pleuro-
14 pericarditis), and 1 (5%) due to a secondary malignancy. The remaining 13 (69%) deaths were
15 caused by relapse or progression of original disease. In this series, 8 patients presented a
16 possible or probable invasive aspergillosis before transplantation (1 to 8 months before). After
17 transplantation, two patients presented a possible aspergillosis (3 months and one year after
18 transplantation) and one patient presented a probable aspergillosis 4 months after allo-SCT²².
19 None of the patients was diagnosed with a CMV disease within 2 years after transplantation.
20 At 2 years, the cumulative incidence of AFO and RP was 3.8% and 9.6% respectively. RP
21 was graded as mild for the majority of patients. The cumulative incidence of pulmonary
22 cGVHD at 2 years was 1.9%, and only one patient met the criteria for BOS diagnosis
23 according to the NIH consensus guidelines²⁰ during the follow-up period of interest.

24

25

1 **DISCUSSION**

2 In this study, we reported a stable pulmonary function with a low rate of pulmonary
3 complications including airflow obstruction, restrictive lung disease and BOS in the two years
4 following allo-SCT conditioned by fludarabine, i.v. busulfan and ATG. It is well established
5 that pulmonary complications are a major cause of morbidity and mortality after allo-SCT and
6 occur in 30 to 60% of cases, and up to 80% in autopsy studies ^{2, 23}. Infectious complications
7 are the more frequent, especially in the early phase after allo-SCT, however, many non-
8 infectious pulmonary complications can occur after allo-SCT: restrictive lung disease,
9 impaired gas exchange or obstructive lung disease in particular in patients with concomitant
10 cGVHD ²¹.

11 The advent of RIC regimen allowed to perform allo-SCT in older patients or young patients
12 with severe comorbidities, including pulmonary comorbidities. The type of agents used as
13 part of the RIC regimens is a crucial determinant for the occurrence of pulmonary
14 complications. In the current study, we analyzed the results of a well-established RIC regimen
15 combining fludarabine, intermediate dose of i.v. busulfan and ATG (Thymoglobulin®) used
16 at a total dose of 5 mg/Kg. Such regimen combines an effective disease control with low
17 NRM and an acceptable toxicity profile ²⁴⁻²⁶. In our study, RP and AFO cumulative
18 incidences remained very low, at 3.8% and 9.6% respectively, suggesting that such regimen
19 does not induce a significant pulmonary toxicity. Indeed, fludarabine is known to be less toxic
20 to the pulmonary system than the traditional cyclophosphamide ²⁷. On the other hand, high
21 dose busulfan, along with cGVHD are the main risk factors identified for spirometric
22 obstruction ^{21, 28-30}. Furthermore, low dose TBI which is another component of RIC protocols,
23 remains an important risk factor of airflow decline, despite changes in TBI techniques aiming
24 to limit pulmonary toxicity ³¹. Regarding ATG, previous data from the standard
25 myeloablative setting already suggested a potential protective role of this agent on lung

1 function. The GITMO randomized trials³² showed that in patients receiving ATG, FEV1 and
2 FVC values remained stable at 2 years after allo-SCT (Δ FEV1, -3% and Δ FVC, +3%),
3 whereas there was a significant decrease of FEV1 and FVC and an increase of cGVHD in the
4 non-ATG group. Our results in the RIC setting are in accordance with these findings, further
5 supporting the value of ATG towards reducing the incidence and severity of GVHD³³. Here,
6 we reported a low cumulative incidence of extensive cGVHD at 2 years (23.1%). Such
7 protective role of ATG on lung function is likely mediated (at least in part) by its
8 effectiveness in reducing overall cGVHD. Indeed, pulmonary damage occurs during cGVHD,
9 and BOS is well linked to cGVHD. According to previous studies, BOS incidence ranges
10 from 6 to 20% in long term survivors³⁴. This important variability is probably related to
11 many parameters, including the nature of conditioning regimen, stem cell source, type of
12 donor etc. Furthermore, different definitions of airflow obstruction have been used over the
13 years to define BOS, contributing to this variability. We chose to apply the most recent NIH
14 criteria²⁰, and reported results according to the cumulative incidence procedure which is more
15 appropriate. In our cohort, despite the use of busulfan, the cumulative incidence of BOS was
16 very low (1.9%), supporting a protective role of ATG in the occurrence of cGVHD and BOS.
17 In addition, cGVHD might be responsible for indirect lung damage: severe chronic
18 scleroderma GVHD can lead to true RP. Thus, one may reasonably conclude that ATG can
19 contribute to the low cumulative incidence of RP (9.6%) observed in our study. One classical
20 argument against the use of ATG is the higher risk of opportunistic infections and disease
21 relapse. However, in our study, the use of ATG did not result in an increased incidence of
22 relapse, in contrast to the study by Soiffer et al³⁵. This difference may be explained by the
23 lower dose of ATG we used (5 mg/Kg total dose). Likewise, whereas higher doses of ATG
24 are known to favor infections, there were very few infectious pulmonary complications in our
25 cohort, in line with our previously published findings³⁶. Furthermore, low cumulative

1 incidence of extensive cGVHD and NRM at 2 years (23.1% and 9.7% respectively), compare
2 favorably with long term follow-up of the German randomized ATG study³⁷: at 3 years, the
3 cumulative incidence of extensive cGVHD and NRM were 12.2% and 19.4% respectively in
4 the ATG group and 45.0% and 33.5% respectively in the non ATG group. Thus ATG seems
5 to exert a strong protective effect against severe cGVHD, leading to a low NRM incidence,
6 indicating a good quality of life, since extensive cGVHD is well known to be responsible for
7 a worsened quality of life³⁸.

8 In the current series, a significant percentage of patients had DLCO impairment before allo-
9 SCT. After allo-SCT, DLCO remained impaired, but without evidence of worsening, as
10 previously described in the paediatric setting³⁹. The baseline impairment of DLCO in these
11 patients is likely multifactorial reflecting previous bacterial and viral infections, or toxicities
12 related to prior chemotherapy.⁴⁰ The impact of baseline DLCO impairment on outcome is
13 still controversial. However, a few studies have suggested a significant impact of DLCO
14 values on transplant outcome^{41, 42 43}.

15 Unfortunately, in the current study, we were not able to compare the results obtained using
16 the fludarabine, i.v. busulfan and ATG-based RIC regimen with a similar regimen not
17 containing ATG, because this is not common practice in our centre. Likewise, one may argue
18 that lung function measurements performed during the first 2 years after allo-SCT may not be
19 sufficient as lung function decline could appear after 2 years, and up to 18 years after allo-
20 SCT^{1, 21, 28, 44}. However, one must acknowledge that reduction in lung volumes and diffusing
21 capacity often occurred early within 12 months after allo-SCT, followed by an incomplete
22 recovery within the next two years^{21, 45}.

23 In conclusion, we report a low rate of pulmonary complications and lung function impairment
24 in patients undergoing a RIC regimen including fludarabine, i.v. busulfan and low dose of
25 ATG. These results further support the use of ATG as part of the so-called reduced-toxicity

1 regimens aiming to decrease long-term toxicities and to improve patients' quality of life.

2

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13

1 Author contributions

2 S. Dirou: collected, assembled and analyzed PFT data and wrote the manuscript;

3 F. Malard: helped in collecting, assembling and analyzing data, performed statistical analyses
4 and wrote the manuscript;

5 A Chambellan: performed and analyzed PFT data, helped in collecting, assembling and
6 analyzing PFT data;

7 P Chevallier, T Guillaume, J Delaunay, P Moreau, and S. Le Gouill: recruited patients, and
8 commented on the manuscript;

9 P Germaud: helped in collecting PFT data, and commented on the manuscript;

10 B. Delasalle: helped in analyzing PFT data and performed statistical analysis;

11 P Lemarchand: analyzed data and wrote the manuscript;

12 M Mohty: recruited patients, supervised research, analyzed data, and wrote the manuscript;

13 All authors approved submission of the manuscript for publication purposes.

14

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18

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1 **FIGURE LEGENDS**

2 **Figure 1.** Changes in PFT parameters from baseline up to 2years post allo-SCT. Data are
3 represented by boxplot. FEV₁, FEV₁/FVC, FVC, TLC, DLCO are expressed as percentage of
4 predicted value.

5

6 **Figure 2.** Lung Function Score (LuFS) before allo-SCT, 100 days, 1 year and 2 years after
7 allo-SCT. A separate score was assigned to relative values of FEV₁ and DLCO (>80% = 1,
8 70-79% = 2, 60-69% = 3, 50-59% = 4, 40-49%=5, <40%=6), these scores were then summed
9 and divided into four categories: LuFS 2 = category 0, LuFS 3-5 = category 1, LuFS 6-9 =
10 category 2, LuFS 10-12 = category 3. No patient had severely abnormal lung function. There
11 were no statistical differences in changes of LuFS before and after allo-SCT (Before allo-SCT
12 vs 100 days (p=0.53), vs 1 year (p=0.29), vs 2 years (p=0.54)).

13

1 **Table 1.** Demographic characteristics of patients and transplant-related events

Characteristic (%)	Study population (N=52)
Patient age, median (range)	59 (23-70)
Patient gender	
Male	32 (62)
Female	20 (38)
Smoker	
Yes	23 (44%)
No	21 (40%)
Data missing	8 (15%)
CMV serologic status	
Seronegative donor-recipient pair	23 (44%)
Diagnosis	
AML	22 (42)
MDS	10 (19)
NHL	13 (25)
Other*	7 (14)
Stem cell source	
Bone marrow	2 (4)
PBSC	50 (96)
Donor type	
Matched related donor (MRD)	29
Unrelated donor (UD)	23
CD34 ⁺ cell infused, × 10 ⁶ /Kg, median (range)	6.22 (1.15-16.3)
GVHD prophylaxis	
CsA alone	31 (60)
CsA + MMF	21 (40)
Grade 3-4 aGVHD at day 100 (cumulative incidence)	15.4%
Extensive cGVHD at 2 years (cumulative incidence)	23.1%

2 Abbreviations : CMV indicates cytomegalovirus; AML acute myelogenous leukemia; MDS myelodysplastic
3 syndrome; NHL, non-Hodgkin lymphoma; CsA, Ciclosporine A; MMF, mycophenolate mofetil.

4 *Others: 3 Hodgkin's disease, 3 multiple myeloma and 1 acute lymphoblastic leukemia.

5

1 **Table 2.** PFT Data Obtained Pretransplantation and at 100 Days, 1 Year, and 2 Years
 2 Posttransplantation (Median expressed as percentage of predicted value).

	FEV1, Median [range]	FVC, Median [range]	FEV1/FVC, Median [range]	TLC, Median [range]	DLCO, Median [range]
Pretransplantation (n = 52)	109.8 [68.5-137.3]	108.2 [66.5-138.4]	80.9 [55.3-98.1]	104.5 [65.2-137.1]	69 [37.5-96.1]
Day 100 (n = 40)	105.1 [71.5-135.1]	105.8 [68.1-136.3]	78.48 [55.5-91.1]	105.8 [77.9-138.7]	69.8 [43.3-106.3]
1 year (n = 32)	103.4 [56.1-143.7]	106.7 [59-139]	76.86 [62.8-89.9]	103.7 [76.2-132.2]	70 [37.4-94.4]
2 years (n = 28)	100.6 [63.8-118.1]	102.7 [63.9-117.8]	76.2 [58.7-90.7]	104.4 [79-144.9]	68.1 [34.4-86.2]

4 Abbreviations: FEV1 indicates forced expiratory volume in 1 second; FVC, forced vital capacity;
 5 TLC, total lung capacity; DLCO, lung carbon monoxide diffusing capacity.

6

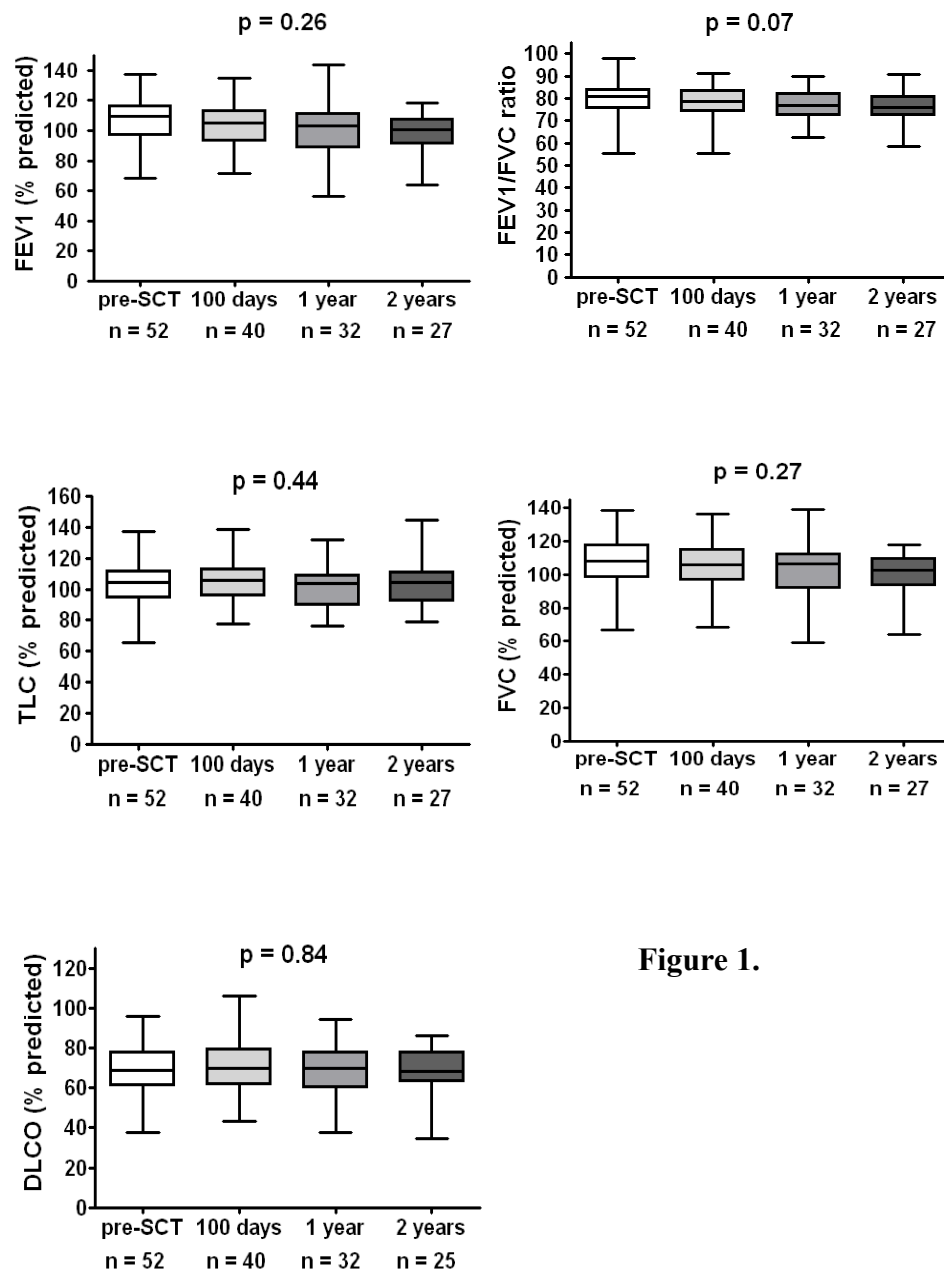


Figure 1.

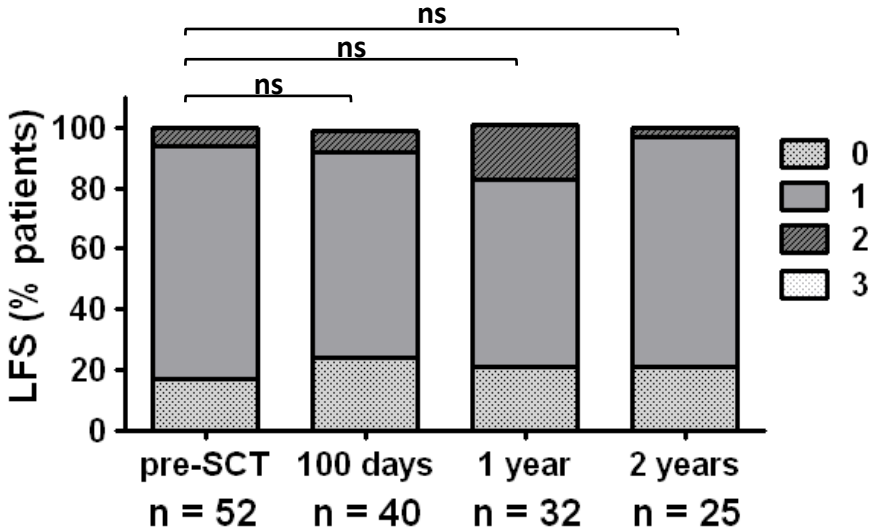


Figure 2.