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Supportive Care

Whole-Body Lung Function Test–Derived Outcome Predictors in Allogenic Stem Cell Transplantation

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A B S T R A C T

Despite clinical advances, late onset pulmonary complications in adult recipients of allogenic stem cell transplantation are a major cause of morbidity and mortality. Reported incidence and risk factors in the literature vary broadly and are partly contradictory. Identification of pretransplant factors associated with major complications would be helpful to define individual treatment strategies and early initiation of preventive measures.

To evaluate incidence and risk factors of late onset noninfectious pulmonary complications, with special regard to small airways disease (SAD) and bronchiolitis obliterans syndrome (BOS), indicating graft-versus-host disease, following myeloablative versus nonmyeloablative allogenic stem cell transplantation.

We reviewed the clinical records and assessed the course of lung function and pulmonary complications in adults who underwent allogenic stem cell transplantation for hematological malignancies between 1999 and 2015 using nonmyeloablative (n = 179) or myeloablative (n = 130) conditioning at the Division of Hematology of the Medical University of Graz. All patients underwent body plethysmography pulmonary function test (PFT), diffusion capacity for carbon monoxide, and arterial blood gas analysis before and repeatedly after transplant. SAD was defined as maximal expiratory flow at 50% and 25% of forced vital capacity <70% predicted.

Ventilatory disorders and gas transfer abnormalities were common before and after allogenic stem cell transplantation, independent of conditioning regimen. SAD was common in the nonmyeloablative (34%) and myeloablative (29%) groups. The 100-day post-transplant mortality was significantly associated with reduced pretransplant total lung capacity <80%. Mortality 100 days post-transplant was significantly associated with pretransplant SAD and a pretransplant smoking history. In this subset, a smoking history was independently associated with increased mortality, with a 5-year mortality of 45% compared with 26% in never-smokers. Pretransplant SAD was not predictive for the later development of BOS.

Smoking history, pretransplant restrictive PFT, and pre-existing SAD are important risk factors for death following allogenic stem cell transplantation. However, pretransplant SAD is not a predictor of long-term complications, including BOS.

INTRODUCTION

Allogenic stem cell transplantation (alloTX) is indicated for the treatment of various hematological diseases. Pulmonary complications after alloTX are frequent [1]. These complications include infections, neoplasia, and idiopathic and iatrogenic disorders [2–7], and are a major cause of morbidity and mortality in adult alloTX recipients [8–11]. Advances in antimicrobial prophylaxis, treatment of infections, and alloTX techniques, such as reduced-intensity conditioning, have decreased the risk of early post-transplant complications over the years. As a result, late onset pulmonary complications occurring more than 3 months after transplant are of increasing interest due to their impact on morbidity and mortality. It has been shown that 26% of alloTX patients develop airflow impairment in the post-transplant course [12,13], and in longtime survivors, the incidence for pathologic pulmonary function test (PFT) results ranges from 20% to 50% [14–20]. These pathologies can present as an obstructive ventilatory disorder, such as bronchiolitis obliterans syndrome (BOS), characterized by its nonresponsiveness to treatment and irreversibility, as a restrictive lung function impairment, such as organizing pneumonia, or as a combination of both [21]. In a retrospective analysis, the 2-year cumulative incidence of delayed

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onset noninfectious pulmonary complications was 10% among 438 patients surviving for more than 3 months [22]. In patients surviving for more than 2 years, Bathia et al. [23] found a 15.1-fold increased risk of late mortality due to ventilatory impairment compared with the general population, and several studies have reported a 30% to 60% lifetime risk of chronic pulmonary dysfunction in long-term alloTX survivors [24–26]. A precise identification of pretransplant factors associated with worsening PFT would allow the identification of high-risk patients and those who might benefit from preventive strategies.

Over the past years, numerous reports have been published on incidence, prevalence, and possible risk factors of pulmonary disorders following alloTX, however, with heterogeneous results and many open questions. A prevalent small airways disease (SAD) has been discussed as a possible indicator for later deterioration [27], but the evidence for this is sparse. We tested this hypothesis by comparing serial lung function tests of patients with myeloablative versus nonmyeloablative alloTX with regard to the development of pulmonary function test impairment with special regard to SAD. The study was approved by the local ethics committee of the Medical University of Graz (EK.Nr.: 29-028 ex 16/17).

METHODS

Between 1999 and 2015, anthropometrics, medical history, and PFT including blood gas analysis (BGA) of 309 of 380 consecutive patients undergoing alloTX at the Division of Hematology of the Medical University of Graz were obtained. Seventeen cases were excluded from analysis because they were transplanted more than once, and 54 patients were excluded because no or not enough clinical data were available.

In this retrospective analysis we consider the underlying hematological disease, concomitant diseases, smoking history, PFT, diffusion capacity for carbon monoxide (DLCO), and BGA, as well as anthropometrics and other functional data. We also analyze the presence of acute or chronic graft-versus-host disease (GVHD). To analyze comorbidities, we defined 7 types of major disease entities and assessed them in all patients.

Conditioning Regimen

The majority of patients receiving myeloablative conditioning were treated with cyclophosphamide/total body irradiation (cyclophosphamide 120 mg/kg on 2 days, and fractionated total body irradiation with 12 Gy in 6 fractions at 2 Gy). A small number of patients received oral busulfan/cyclophosphamide (busulfan 16 mg/kg 4 times daily on 4 days, and cyclophosphamide 120 mg/kg on 2 days). Beginning in 2013, patients receiving myeloablative conditioning were treated with cyclophosphamide and i.v. busulfan (i.v. busulfan .8 mg/kg 4 times daily on 4 days, and cyclophosphamide 120 mg/kg on 2 days).

Patients receiving nonmyeloablative conditioning were treated with fludarabine/total body irradiation (fludarabine 150 mg/m^2, and fractionated total body irradiation with 4 Gy in 2 fractions at 2 Gy) or fludarabine/melphalan (fludarabine 150 mg/m^2, and melphalan 140 mg/m^2).

Patients with matched unrelated donor additionally received antithymocyte globulin with 5 mg/kg on 4 days.

PFT and BGA

PFT and BGA were routinely performed before alloTX, after 3, 6, 9, and 12 months, and then yearly for up to 15 years. In cases of de novo lung function impairment, PFT and BGA were performed at 3-month intervals throughout. Forced expiratory volume in 1 second (FEV1), forced vital capacity (FVC), ratio of FEV1 to FVC (FEV1/FVC), maximal expiratory flow at 75% of FVC (MEF75), maximal expiratory flow at 50% of FVC (MEF50), maximal expiratory flow at 25% of FVC (MEF25), total lung capacity (TLC), residual volume (RV), and DLCO corrected for hemoglobin (DLCO single breath [$DLCO_{SB}$] and DLCO divided by alveolar volume [DLCO/VA]) were determined by standard procedures via whole-body plethysmography. All measurements conformed to the guidelines of the European Community for Steel and Coal, and for each individual, values were expressed as percentage of predicted values. BGA was determined from arterialized earlobe capillary blood at rest including partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2), oxygen saturation, and alveolar-arterial oxygen difference ($AaDO_2$). PFT was defined as pathologic when FEV1 was <80% predicted, FVC was <80% predicted, FEV1/FVC was <70% predicted, MEF75 was <70% predicted, MEF50 was <70% predicted, MEF25 was <70% predicted, $DLCO_{SB}$ was <80% predicted, DLCO/VA was <80% predicted, TLC was <80% predicted, RV was >120% predicted, and RV/TLC was >100% predicted. BGA was defined as pathologic when pCO_2 <35 mm Hg or pCO_2 >45 mm Hg, $AaDO_2$ >25, pH <7.36, or pH >7.44. BOS was diagnosed when the following criteria defined by the National Institutes of Health Consensus Report 2014 were present: FEV1/FVC <.7, FEV1 <75% of predicted with ≥10% decline over <2 years, absence of infection in the respiratory tract, radiological evidence (air trapping, small airway thickening, bronchiectasis) or evidence of air trapping by PFTs (residual volume >120% of predicted or RV/TLC elevated outside the 90% confidence interval) [28]. SAD was defined as pathologic readings in MEF50 and MEF25, with both values <70%. Restriction was defined as both TLC and FVC <80% predicted.

STATISTICS

SPSS 24.0.0.0 (IBM Corporation, Armonk, NY) was used for data analysis. A value of $P < .05$ was considered significant. Continuous variables are presented as mean ± SD or median (interquartile range), as appropriate. Categorical variables are presented as absolute and relative frequencies. For baseline values categorical variables were compared between groups (nonmyeloablative versus myeloablative patient) using chi-square test or Fisher's exact test and continuous variables using *t* test or Mann-Whitney *U* test. Further group comparisons were made for patients (1) with and without obstructive ventilatory disorder, (2) with and without a pathologic DLCO as defined by the hematopoietic cell transplantation-comorbidity index (HCT-CI) [29], (3) who died within the first 100 days after alloTx versus those who were alive after 100 days, (4) who died after the first 100 days after alloTx versus those who were alive at the last follow-up or lost to follow-up.

To identify possible predictors for BOS the following parameters were analyzed using univariate logistic regression analysis: PFT parameters, pre-alloTX conditioning regimen, sex, age, body mass index (BMI), and smoking history. Significant predictors were included in a stepwise multivariate logistic regression.

Five year survival rate was calculated for the whole group. The impact of PFT parameters, pre-alloTX conditioning regimen, sex, age, BMI, smoking history, comorbidities, and any combination of comorbidities as well as underlying hematologic disease (acute myelogenous lymphoma [AML], chronic myelogenous leukemia [CML], acute lymphoblastic leukemia [ALL], chronic lymphocytic leukemia [CLL], multiple myeloma [MM], anemia) on (1) overall survival and (2) event-free survival, defined as nonoccurrence of BOS, SAD, or death, was analyzed using univariate log-rank test or univariate Cox regression analysis. Afterward, a stepwise multivariate Cox regression analysis included those variables that showed a *P* value of ≤.05 in the univariate analysis was performed.

Exploratory analysis was performed for the course of MEF25/50 within patients with BOS, restriction, de novo SAD, SAD, SAD/chronic obstructive pulmonary disease (COPD) and patients without such conditions. Therefore, the course of each patient was plotted separately. Missing values were interpolated.

RESULTS

For anthropometrics, smoking habits, comorbidities, underlying disease, and donor source of 309 patients: 179 patients received nonmyeloablative conditioning and 130 patients myeloablative conditioning before alloTX. Anthropometrics, comorbidities, underlying hematologic disease, and donor source are given in Table 1.

In both groups, men were more frequently transplanted than women with an overall male/female ratio of 1.3:1. As shown in Table 1, 14% of all transplanted patients died within the first 100 days, with no significant difference between the nonmyeloablative and myeloablative groups ($P = .461$). With an overall median follow-up of 24.1 months (range, 0 days to 18.9 years), and median follow-up for patients without

Table 1
Baseline Anthropometrics, Smoking Status, Comorbidities, Underlying Hematologic Disease, and Donor Source of All Patients

	Nonmyeloablative Therapy, Baseline			Myeloablative Therapy, Baseline		
	All Patients	Alive ≤100 d	Alive >100 d	All patients	Alive ≤100 d	Alive >100 d
n	179 (100)	27 (15)	152 (85)	130 (100)	18 (14)	112 (86)
Age, yr	55 (48-61)*	53 (45-61)	55 (48-61)	40 (32-48)*	43 (33-51)	40 (31-48)
Male/female	100/79	15/12	85/67	72/58	9/9	63/49
BMI, kg/m^2	24.7 (22.2-27.2)	25.5(22.8-27.2)	24.6 (22.0-27.2)	23.7 (21.1-26.2)	25.1 (21.8-28.3)	23.3 (21.0-26.1)
Smokers	77 (43)	11 (41)	66 (44)	47 (36)	4 (22)	43 (38)
PY	4 (0-15)	4 (0-12)	4 (0-15)	0 (0-10)	0 (0-2)	0 (0-10)
Nonsmoker	50 (28)	7 (26)	43 (28)	51 (39)	7 (39)	44 (39)
Unknown	52 (29)	9 (33)	43 (28)	32 (25)	7 (39)	25 (22)
Comorbidities						
Renal	28 (16)	8 (30)	20 (13)	25 (19)	1 (6)	24 (21)
Cardiovascular	48 (27)*	6 (22)	42 (28)	22 (17)*	4 (22)	18 (16)
Pulmonary	22 (12)*	2 (7)	20 (13)	7 (5)*	1 (6)	6 (5)
Endocrine	48 (27)*	5 (19)	43 (28)	17 (13)*	1 (6)	16 (14)
Tumors	25 (15)	5 (19)	20 (13)	10 (8)	2 (11)	8 (7)
Surgery	13 (7)	0 (0)	13 (9)	4 (5)	2 (11)	5 (4)
Depression	10 (6)	0 (0)	10 (7)	2 (2)	0 (0)	2 (2)
Acute GVHD	49 (27)	9 (33)	40 (26)	41 (31)	5 (28)	36 (32)
Chronic GVHD	30 (17)	1 (4)	29 (19)	26 (20)	1 (6)	25 (22)
AML	109	21	88	76	13	63
CML	13	0	13	10	0	10
ALL	13	1	12	30	2	28
CLL	26	4	22	6	2	4
MM	13	0	13	4	1	3
Aplastic anemia	5	1	4	4	0	4
Donor CB	0	0	0	10	2	8
Donor M	111	19	92	69	11	58
Donor S	68	8	60	51	5	46

Values are n (%), median (interquartile range), or n.
PY indicates pack-years; CB, cord blood; M, matched; S, sibling.
* $P < .05$ for comparison of both groups.

documented death of 63.0 months (range, 23 days to 18.9 years), the overall 5-year survival rate was 52%.

The rate of smokers versus nonsmokers showed a tendency to be higher in the nonmyeloablative patient group than in the myeloablative patient group ($P = .062$), with an overall male/female ratio of 1.3:1, and with no significant difference in smoking history between the 2 groups ($P = .057$). Smoking was defined by a subject stating to be an active cigarette smoker or having smoked at least 1 pack-year. All others were classified as never-smokers, even if they occasionally smoked pipe or cigar. Smoking history was not available in a relatively large subset of our patients. To assess the effect of this missing information, we compared the group of patients with and without information regarding their smoking history. This revealed that these 2 groups did not differ significantly in any baseline characteristic (Supplementary Table S1). Therefore, we believe that these missing data had no significant effect on our conclusions.

Baseline PFT and BGA in both groups and in the subgroup of survivors versus nonsurvivors >100 days revealed significantly more impairment in lung function and gas exchange (FEV1/FVC,

Table 2
Comparison of PFT and BGA of Patients Undergoing Nonmyeloablative and Myeloablative Conditioning before alloTX

	Nonmyeloablative Therapy				Myeloablative Therapy			
	Baseline			Last Follow-Up	Baseline			Last Follow-Up
	All Patients	Alive ≤100 d	Alive >100 d	Alive >100 d	All Patients	Alive ≤100 d	Alive >100 d	Alive >100 d
n	179 (100)	27 (15)	152 (85)	71†	130 (100)	18 (14)	112 (86)	63‡
FEV1, %pred	93 ± 19	89 ± 22	94 ± 18	92 (79-102)	92 ± 14	89 ± 12	93 ± 14	89 (77-98)
FVC, %pred	95 ± 16	91 ± 21	96 ± 15	96 ± 19*	93 ± 15	91 ± 14	93 ± 15	89 ± 18
FEV1/FVC, %pred	80 (77-84)*	80 ± 9	80 ± 6§	78 (72-81)*	83 (80-89)	85 ± 7	84 ± 7	81 (75-86)
MEF50, %pred	87 ± 29	82 ± 38	88 ± 27	76 ± 32	92 ± 24	90 ± 25	93 ± 24	83 ± 35
MEF25, %pred	65 ± 25*	48 (38-83)	65 (50-74)§	53 (33-72)	80 ± 31	74 (53-95)	85 (62-101)	67 (36-85)
RV, %pred	110 (91-129)	113 (90-132)	109 (92-129)	116 (101-139)	102 (90-125)	106 (78-123)	101 (91-130)	121 (93-138)
TLC, %pred	103 ± 17	101 ± 24	103 ± 15	106 ± 17*	99 ± 14	92 ± 13	101 ± 14	99 ± 13
RV/TLC, %pred	95 (83-103)	95 (81-109)	96 (83-103)	98 (86-114)	95 (82-107)	101 (79-118)	94 (81-108)	102 (88-119)
DLCO/VA, %pred	82 (67-96)	85 ± 26	82 ± 19	84 ± 19	78 (72-95)	76 ± 11	83 ± 14	81 ± 14
$DLCO_{SB}$, %pred	76 ± 20	78 (49-93)	78 (65-84)	80 ± 21	79 ± 18	71 (62-78)	82 (66-92)	74 ± 16
pO_2, mm Hg	81 ± 10*	81 ± 8	81 ± 10	82 (76-88)	85 ± 9	85 ± 10	85 ± 9	85 (77-91)
pCO_2, mm Hg	36 (34-38)	36 ± 4	36 ± 3	34 (31-37)*	36 (34-39)	67 ± 4	36 ± 4	36 (34-38)
pH	7.4 ± .03	7.4 ± .02	7.4 ± .03	7.43 (7.42-7.44)	7.4 ± .03	7.4 ± .04	7.4 ± .04	7.42 (7.40-7.44)
$AaDO_2$, mm Hg	20 ± 10*	22 ± 10	19 ± 11§	23 (15-27)*	15 ± 7	15 ± 7	15 ± 7	16 (12-23)

Values are n (%), mean ± SD, or median (interquartile range).
* $P < .05$ for comparison of patients following nonmyeloablative versus myeloablative conditioning.
† Median follow-up 36 (interquartile range, 12-36) months.
‡ Median follow-up 24 (interquartile range, 12-36) months ($P = .375$).
§ $P < .05$ for comparison of patients ≤100 days versus >100 days alive within a group.

FVC, TLC, MEF25, pO_2, and $AaDO_2$) in the nonmyeloablative group (Table 2).

SAD and BOS

Obstructive airflow limitation including SAD was frequently seen in our patients. Four different "patterns" of obstruction were discerned, based on onset, etiology, and severity. SAD could be (1) pre-existing, based on a history of COPD or asthma; (2) due to unknown mechanisms and remaining stable throughout the observation period; (3) developing after alloTX never meeting criteria for diagnosis of BOS; or (4) meeting BOS criteria as defined by the National Institutes of Health Consensus Report 2014 [28]. Taken together, from all 309 patients, 99 (32%; 61 nonmyeloablative versus 38 myeloablative) met our definition of SAD at some point in time. In 68 of these patients (69%) SAD criteria were already present before alloTX, and in 41 of these patients (60%; 28 nonmyeloablative versus 13 myeloablative), SAD criteria were present before alloTX and could be attributed to an obstructive pulmonary disease. In another 27 patients (40%; 15 nonmyeloablative versus 12 myeloablative), SAD criteria were also met before alloTX, but without identifiable cause, and only in 2 of these patients (1 nonmyeloablative versus 1 myeloablative, both never-smokers) BOS developed in the further course. In 31 patients (31%), SAD developed de novo after alloTX. In 16 of these patients (52%; 12 nonmyeloablative versus 4 myeloablative), SAD developed after alloTX with an average delay of 30 months and remained stable throughout the observation period, never meeting the BOS criteria. In 15 patients (48%; 6 nonmyeloablative versus 9 myeloablative), SAD developed de novo after alloTX and resulted in BOS as defined, resulting in a total of 17 BOS cases (17%). Patients developed BOS after an average of 18 months (nonmyeloablative; range, 12 to 58 months; n = 7) and 15 months (myeloablative; range, 2 to 116 months; n = 10) after transplant. The only predictor of BOS was a smoking history (odds ratio, 1.32; 95% confidence interval, 1.15 to 12; P = .028). MEF25 <70% (P = .061) and elevated BMI (P = .064) showed a trend for an increased BOS risk.

Within the subgroup of patients with an obstructive ventilatory disorder, the severity of obstruction was graded according to SAD/COPD versus BOS versus pre-SAD versus de novo SAD. This was true for nearly all measures of PFT, including FEV1, FEV1/FVC, MEF 75, MEF50, and MEF25. These differences were more pronounced in the nonmyeloablative group, and were comparable between patients who lived more or less than 100 days. The myeloablative versus nonmyeloablative alloTX groups with de novo SAD, pre-SAD, SAD/COPD or BOS showed no significant differences concerning baseline PFT and BGA and also increasing age was not significantly associated with the development of SAD or BOS. In both groups, emphysema and elevated residual volume were present in approximately 43%.

Impairment of DLCO, pO_2, pCO_2, and $AaDO_2$

When applying a cutoff for a pathologic DLCO at <80% predicted, as recommended by the HCT-CI [29], a reduction of $DLCO_{SB}$ and DLCO/VA, reflecting impairment of diffusion capacity, was very frequent in both groups. Post-alloTX, significantly more patients in the myeloablative group showed a decline in $DLCO_{SB}$ as compared with the nonmyeloablative group. However, this difference was not significant in DLCO/VA (Supplementary Table S2).

Before alloTX, reduced $AaDO_2$ and pO_2, reflecting impairment in gas exchange, were significantly more common in the nonmyeloablative group. This difference between the groups remained stable in the later time course, although it was no longer statistically significant. In contrast, for the rate of patients with an elevated pCO_2, a marker for ventilatory impairment, the difference between the groups became significant only post alloTX (Supplementary Table S2).

Restriction

Only 10 patients (3%; 6 nonmyeloablative versus 4 myeloablative) had a restrictive ventilatory disorder post alloTX: 1 patient had a pseudorestriction due to severe emphysema, 2 patients had severe sclerodermiform GVHD of the skin, 2 patients had undergone surgical lung-volume reduction, 1 patient had a transient restriction due to pulmonary embolism, 2 patients suffered from chronic heart failure with pleural effusion, and in 2 patients the restriction was only attributable to pulmonary involvement of the hematologic disease. No interstitial lung diseases such as late onset (cryptogenic) organizing pneumonia or late onset pulmonary toxicity syndrome were observed.

Overall Survival

For both groups combined, SAD before alloTX was predictive for death in the later course (primary endpoint, univariate log rank test: P = .03; Cox regression analysis: P = .032; hazard ratio, 1.67; 95% confidence interval, 1.04 to 2.67) (Figure 1). Other PFT parameters, pre-alloTX conditioning regimen, sex, age, BMI, smoking history, comorbidities, or any combination of comorbidities, as well as underlying hematologic disease (AML, CML, ALL, CLL, MM, anemia), had no significant impact on survival time.

Less than 100 Days Alive

A reduction of TLC <80% predicted (ie, restrictive ventilatory pattern) (P = .006) and a reduction of MEF75 <70% predicted (P = .037) before alloTX were associated with death within 100 days after alloTX in the univariate analysis (n = 41; female = 20, male = 21). The same trend was seen for a pathologic pO_2 value in the BGA (P = .077). No other PFT parameter or any other factor including sex, or underlying hematologic disease, was predictive for early death. In the multivariate analysis, a reduction of MEF <70% predicted (HR: 3.08 95%CI: 1.18 to 8.03; P = .022) and TLC <80% predicted (hazard ratio, 4.01; 95% confidence interval, 1.54 to 10.44; P = .005) remained significant predictors of poor survival.

More than 100 Days Alive

In patients who lived more than 100 days, and therefore had a potential to develop a late onset pulmonary complication, the 5-year survival rate was 59%. Survival was independent of conditioning regimen (P = .549), underlying hematologic disease (AML: P = .723; ALL: P = .489; CLL: P = .664), sex (P = .132), age (P = .470), BMI (P = .483), or PFT (P > .200). Smokers had a significantly reduced survival (univariate log rank test: P = .018; Cox regression analysis: P = .020; hazard ratio, 1.80; 95% confidence interval, 1.10 to 2.95), with a 5-year survival rate of 55% compared with 74% in never-smokers (Figure 2).

Event-Free Survival

An increasing number of pack-years (P = .040) significantly reduced event-free survival, defined as nonoccurrence of SAD, BOS, or death. Smokers also had a shorter event-free survival concerning BOS and SAD (secondary endpoint, P = .096) as compared with never-smokers. Other PFT parameters, pre-

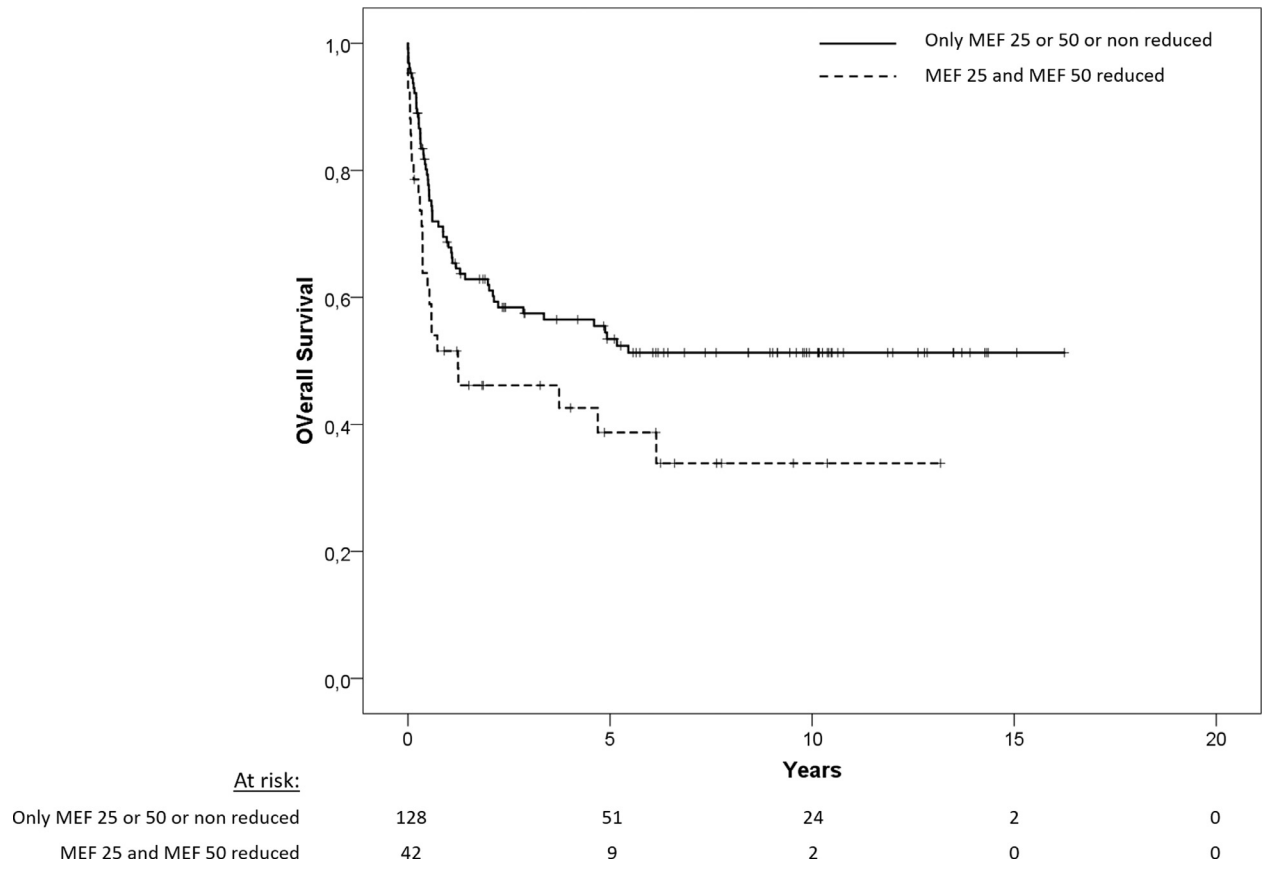

Figure 1. Kaplan-Meier statistics of overall survival function of patients with SAD before alloTX.

alloTX conditioning regimen, sex, age, BMI, comorbidities, or any combination of comorbidities (Figure 3) as well as the underlying hematologic disease (AML, CML, ALL, CLL, MM, anemia) had no significant impact on event-free survival.

DISCUSSION

Impairment of the PFT following alloTX, reflected by either decreased TLC, FVC, DLCO, or FEV1, is frequent [30,31], is associated with higher mortality and morbidity [32,33], and has been linked to cGVHD [34–36], Airflow limitation may present either as an obstruction, as typically seen in BOS, or as a restriction. In the past, several studies have searched for predictors of later pulmonary deterioration, primarily of BOS. SAD, defined as reduction of MEF50 and MEF25 <70%, assessed at baseline has been suggested as a predictor of later outcome [27]. We present the results of long-term PFT follow-up in a cohort of patients after alloTX with a special focus on SAD.

Patients undergoing nonmyeloablative alloTX were older and more frequently affected by ventilation disorders and other comorbidities, suggesting that these factors determined the choice between a myeloablative and a nonmyeloablative approach. I

n our cohort, 99 of 309 patients (32%) met our SAD criteria. In 69% of these patients, SAD was already present before alloTX, and in most of these cases (60%) SAD could be related to smoking/COPD or asthma. Interestingly none of our COPD/asthma patients developed BOS, so maybe the current definition of BOS is not sensitive enough to detect BOS in COPD patients. In 40% of patients with SAD before alloTX, no such association could be found, including 2 patients who developed BOS in the further course. Almost one-third (31 patients) developed de novo SAD, with a mean delay time of 30 months. These patients were characterized by a stable PFT in their follow-up, and none of these patients ever met National Institutes of Health criteria for BOS. The majority of patients with de novo SAD were found in the nonmyeloablative group (12 versus 4 myeloablative), possibly reflecting the older age and reduced health status of this group. It is also possible that this PFT impairment was a result of epithelial injury, induced by previous conditioning, or represented a subclinical BOS. We found that SAD, independent of hematologic disorder, anthropometric aspects, smoking history, comorbidity, or conditioning regimen, was a predictor of mortality, although it was not a predictor for BOS or other late noninfectious pulmonary complications. BOS is the only pulmonary complication currently considered diagnostic of cGVHD [37], and is characterized by the new onset of an obstructive PFT and a lack of reversibility. With a mean delay of 18 (nonmyeloablative) and 15 (myeloablative) months, 17 patients (6%) developed BOS (7 of 10; 4%/8%), as defined by the National Institutes of Health Consensus Report of 2014. This is in agreement with reported incidences of BOS in previous studies [38,39]. In a previous study, reduced FEV1 [40] before alloTX was significantly associated to the later development of BOS. We could not reproduce this finding. The only significant predictor for later BOS was a smoking history. There were only nonsignificant associations with a reduced MEF25 and an elevated BMI with BOS development.

When the pulmonary function is assessed for risk stratification before alloTX, the main focus is usually on FEV1; however, this does not give information on SAD. For early detection of lung disease and more precise risk stratification, FEV1 might not be sensitive enough. As we could show, SAD, as defined by

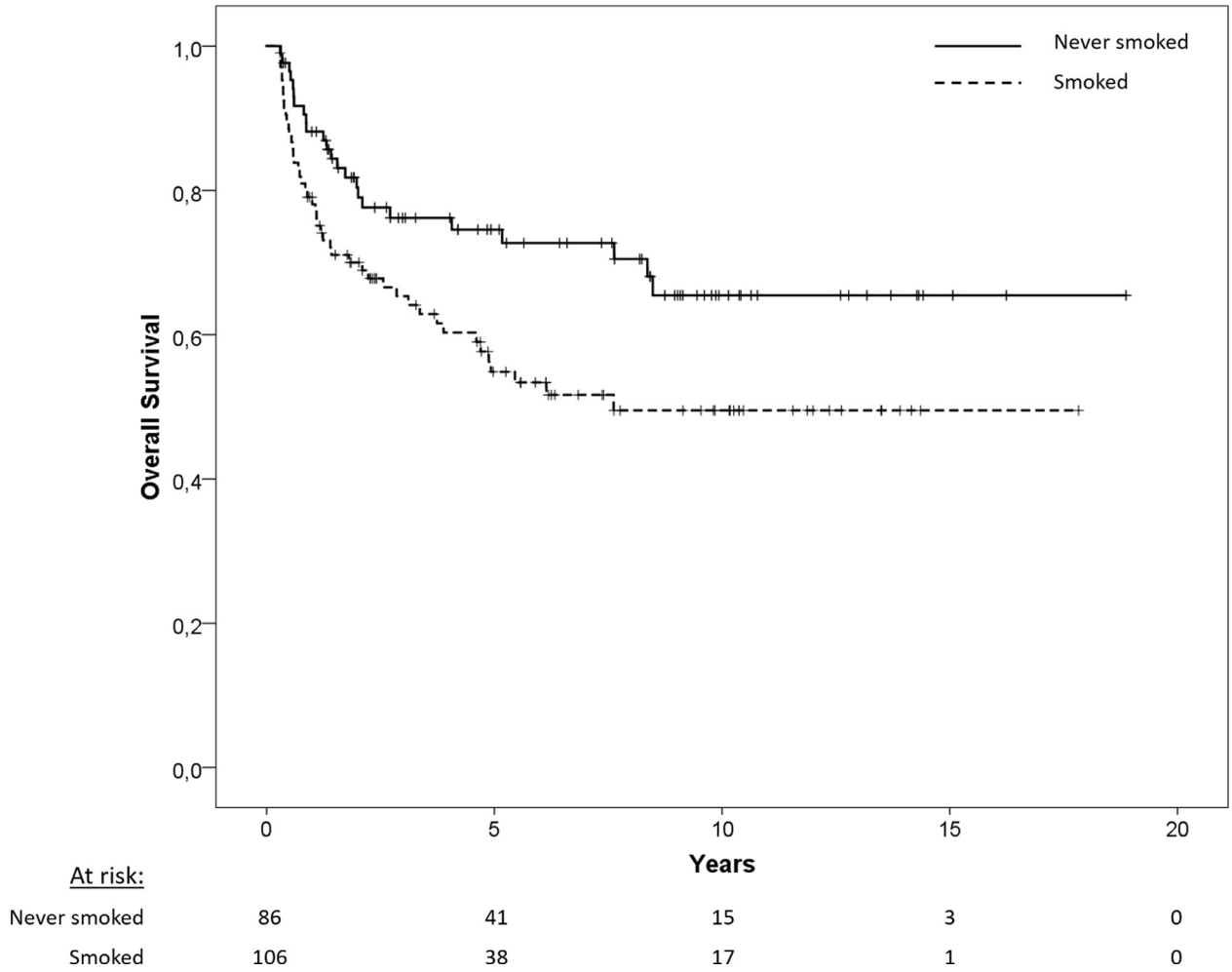

Figure 2. Impact of smoking history on survival in patients surviving for more than 100 days.

a significant reduction of both MEF50 and MEF25, is significantly associated with mortality after alloTX. Therefore, our data suggest to assess MEF50 and MEF25 before alloTX, ideally with a whole-body plethysmography. In case of SAD before alloTX, of course smoking cessation is mandatory. Additionally we suggest to further evaluate for possible underlying disease (ie, asthma or COPD), and to treat according to current guidelines.

Pulmonary restriction following alloTX has been reported in up to 36% of patients receiving alloTX [41]. In our study, population-restrictive PFT after day 100 was only seen in 3%. This discrepancy may be explained by the heterogenous origin of restrictive ventilatory patterns, which are reversible in many cases. In previous studies, cryptogenic organizing pneumonia and idiopathic pneumonitis syndrome, often diagnosed at autopsy, have been described as very frequent, and very early pulmonary complications following alloTX. Unfortunately, the cause of death in patients who lived less than 100 days was not determined in our study. This might explain the low overall incidence rate of pulmonary restriction in our study. Another cause of pulmonary restriction is therapy-induced diffuse parenchymal lung disease, triggered by busulfan, bleomycin, and radiation, which have become less frequent in recent years. In many cases, restrictive PFTs are transient, as the underlying cause can be treated effectively (effusion, pulmonary edema, pneumothorax, atelectasis). In some cases, restriction may be secondary to chronic GVHD of the skin (encasing, scleroderma-like chronic GVHD), lobectomy, neuromuscular disease, spine alteration, steroid treatment–related myopathy, lack of cooperation, frailty, or technical problems. Interestingly, in our study group, patients with a restrictive ventilatory disorder before alloTX (TLC <80%), independent of the conditioning regimen, had a higher risk of early death, which might be another explanation for the low rate of patients with a restrictive PFT in the long-term follow-up. This is in line with a recent study in bilateral lung transplant recipients, in which a restrictive PFT was associated with a significantly worse survival [42].

As we could show, a reduced TLC before alloTX was associated to early death. As TLC can only be determined via whole body plethysmography, this suggests the importance of performing whole body plethysmography in all patients before alloTX.

A frequently discussed issue is the value of DLCO. DLCO measures the ability to exchange gases at the alveolar capillary interface and reflects capillary surface area, and membrane properties, and is sensitive to heterogeneity in perfusion and ventilation. DLCO is also affected by the hemoglobin level and by CO-hemoglobin (recent smoking). A decreased DLCO has been reported in up to 80% of alloTX survivors, and has been associated with decreased survival and improved survival, or has no association to survival [8,20,33,43]. In our study, DLCO measurements were corrected for hemoglobin and are given

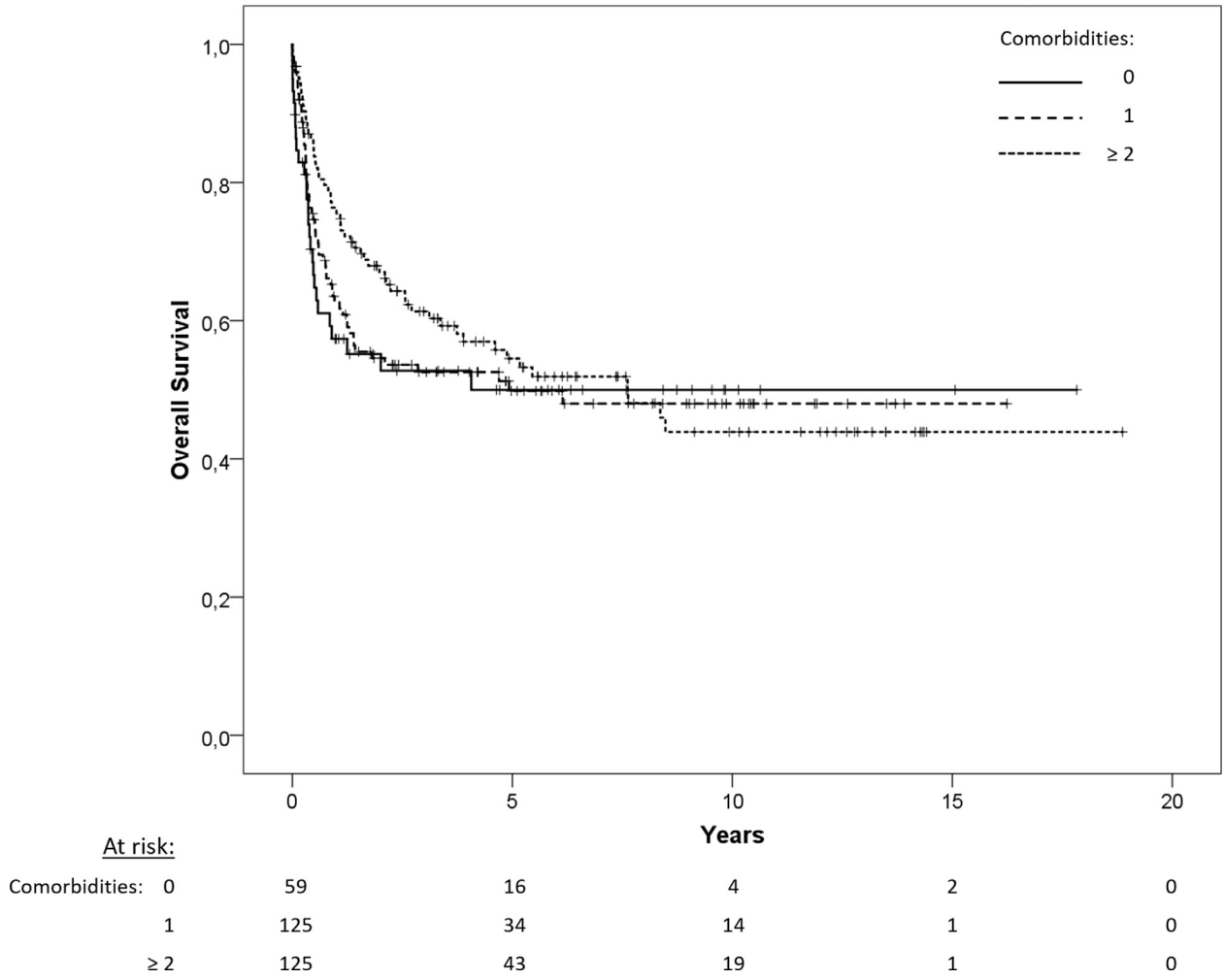

Figure 3. Survival function of comorbidities and combinations of comorbidities.

as both $DLCO_{SB}$ and DLCO/VA. With a pathologic cutoff at 80% predicted, as recommended by the HCT-CI, before alloTX, $DLCO_{SB}$ was impaired in 54% of all patients in both groups. Following alloTX, the reduction of $DLCO_{SB}$ was more pronounced in the myeloablative group, although these patients were younger and had less comorbidities. In the myeloablative group, DLCO/VA was more affected both before and after alloTX. This suggests more pulmonary toxicity of the myeloablative therapy. The cause of the DLCO decrease remains unclear, as it may reflect alveolar-endothelial damage, ventilation or perfusion heterogeneity, or subclinical lung fibrosis. Based on our results, $DLCO_{SB}$ and DLCO/VA with a cutoff at 80% predicted, alone or in combination, were predictive of neither the development of late onset noninfectious pulmonary complications nor death following alloTX. The same is true for respiratory insufficiency, defined as pathologic pO_2, pCO_2, and $AaDO_2$, which was more pronounced in the nonmyeloablative group, and most probably reflects the slightly reduced general health status and more distinct smoking habits as compared with the myeloablative group.

Our data show that smoking is an independent risk factor for SAD, BOS, and mortality. This suggests that smoking status should be evaluated in every patient and that patients be introduced into a smoking cessation program as early as possible.

Our study has several limitations: a nonrandomized, retrospective design; differences in baseline patient characteristics between the groups; and small patient numbers. However, despite heterogeneity among the investigated patients and therapy regimens, our analysis revealed significant predictors of mortality.

CONCLUSION

PFT by means of whole-body plethysmography is a noninvasive and easy approach to assess pulmonary function pre- and post-alloTX in adults. Restrictive PFT and obstructive airflow limitation before alloTX are significant risk factors for early and late mortality, although they are not predictive for BOS. Smoking is an independent risk factor for mortality and the development of both SAD and BOS. Our study emphasizes the importance of PFT before alloTX and the importance of smoking cessation programs before alloTX. If SAD and smoking history are suitable as additional parameters of a new prognostic index, they need further evaluation.

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SUPPLEMENTARY DATA

Supplementary data related to this article can be found on line at http//doi:org/10.1016/j.bbmt.2018.07.036.

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