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Survival Impact of Lung Transplantation for Chronic Obstructive Pulmonary Disease

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ABSTRACT

Chronic Obstructive Pulmonary Disease (COPD) is the primary indication for lung transplantation (LTx), but survival benefit is still debated. We analysed the survival impact of LTx in COPD with a new approach using the BODE index.

We retrospectively reviewed 54 consecutive LTx performed for COPD. Pre-transplant BODE score was calculated for each patient and a predicted survival was derived from the survival functions of the original BODE index validation cohort. Predicted and observed post-transplant survival was then compared.

In the subgroups with a BODE ≥7 and BODE <7, a majority of patients (66 and 69% respectively) lived longer after LTx than predicted by their individual BODE index. The median survival was significantly improved in the entire cohort and in the subgroup with a BODE ≥7. Four years after LTx, a survival benefit was apparent only in patients with a pre-transplant BODE score ≥7.

In conclusion, while a majority of COPD patients had an individual survival benefit from LTx regardless of their pre-transplant BODE score, a global survival benefit was seen only in patients with the more severe disease. This supports the use of the BODE index as a selection criteria for LTx candidates.

Abstract word count: 193

Keywords: BODE index, chronic obstructive pulmonary disease, lung transplantation, patient selection, survival analysis

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a leading cause of morbidity and mortality around the world, making it one of the major challenges for the health-care community. The primary management remains medical treatment, including smoking cessation, bronchodilators, oxygen administration, adequate diet and pulmonary rehabilitation. However, these are often insufficient in patients with advanced disease. For selected patients, surgical options include bullectomy, lung volume reduction surgery and lung transplantation (LTx) [1]. LTx for COPD has been first reported in 1970, but used on a larger scale only since the late 1980s, coinciding with improvement of surgical technique and immunosuppressive therapy. COPD is presently the main indication for LTx, accounting for more than one third of the procedures [2].

Although lung transplantation for COPD improves lung function [3], exercise capacity [4] and quality of life [5], the controversy remains regarding survival benefit. Studies conducted so far, whether showing a survival benefit [6-8] or not [9,10], have compared the survival of patients who underwent transplantation with patients remaining on the waiting list. Despite having used different approaches to take into account differences between patients on waiting list and those who underwent the procedure, bias cannot be excluded.

In COPD patients, several univariate survival prognostic factors have been identified [11,12]. However, the pathophysiology of COPD is complex and none of these factors alone is an accurate predictor of the survival of COPD patients. In 2004, Celli and co-workers identified from a large multicenter cohort of COPD patients, a combination of four variables which showed a strong association with survival in COPD: body-mass index (B), airflow obstruction (O), dyspnea (D) and exercise capacity (E) [13]. These variables were used to create the BODE index, a multidimensional scoring system that was shown to be a better predictor of survival than the spirometric staging system developed by the American Thoracic Society (ATS) [14]. The BODE index assigns a score from 0 to 10, with the higher score indicating more severe disease and predicting a poorer outcome.

Thus, the BODE index offers an opportunity to evaluate the natural history of COPD patients enrolled in a lung transplantation program, by using criteria that are free of the selection bias introduced by the decisions of the transplantation team. This was recently emphasized by the introduction of a BODE score ≥7 as a new recommended transplant criteria for COPD patients [15].

The primary goal of our study was to analyse the survival impact of lung transplantation in end-stage COPD patients, by comparing the effective post-transplant survival with the survival predicted by the BODE index as measured during pre-transplant clinical evaluation. The results were then applied to refine the selection criteria of LTx candidates.

MATERIAL AND METHODS

Study subjects

We retrospectively reviewed all consecutive subjects who underwent single (SLT) or bilateral LTx (BLT) for COPD at Lausanne and Geneva University Hospitals, Switzerland, from the start of the program in 1993 until the end of 2007, with a follow-up until the 30th June 2009. The diagnosis of COPD had been verified by a global assessment in every patient before listing, simultaneously with assessment of suitability for LTx and potential cardiovascular, infectious or psychiatric contra-indications to the procedure. Subjects with COPD related to alpha-1 antitrypsin deficiency were excluded from the study.

Data collection

Demographic and clinical characteristics collected during the pre-transplant assessment period were recorded from the patient's chart, as well as the time to LTx and the type of procedure. The date of death, when appropriate, was collected through centre-specific database.

BODE index calculation

The pre-transplant BODE index score was calculated for each patient as described by Celli et al. [13], using data obtained during the pre-transplant assessment: body mass index in kilograms per square meter, post-bronchodilator FEV_1 as percentage of the predicted value, score on the modified Medical Research Council (MMRC) dyspnea scale and 6-min walking distance (6MWD). Spirometry measurements and equations used to determine the predicted normal values for FEV_1 were according to the Official Statement of the European Respiratory Society for Standardized Lung Function Testing [16]. MMRC was collected or retrospectively evaluated from patient's chart when necessary. Six-minute walk tests without encouragement were performed. Missing 6MWD (3 subjects) were derived from maximum oxygen consumption value (VO_2 max) measured during the pre-transplant assessment, using the equations developed by Cahalin and al. in transplant candidates with end-stage lung disease [17]. A zero meter 6MWD was assigned to the 2 patients who were not able to perform the 6-min walk test or the VO_2 max test because of their respiratory condition.

Data analysis

We used the baseline survival function derived from the original BODE index cohort and provided by the authors [13]. The 95% confidence interval (CI) of the hazard ratio was used to calculate lower boundary, intermediate and upper boundary of life expectancy for each BODE level. The predicted survival with lower and upper estimates of each patient was then individually calculated as derived from their BODE score, and compared to their effective post transplant survival. Patients who were still alive at the end of the follow-up but had not yet achieved the upper boundary of their predicted survival were excluded from the analysis, as the survival impact of LTx could not be evaluated. The survival effect of the procedure on the entire cohort was then assessed by comparing the predicted survivals with the effective survival, and by determining the number of patients who individually benefited from the procedure. The same analysis was repeated in the subgroups with a pre-transplant BODE score <7 and ≥ 7. The survival after SLT versus BLT, and the difference between transplant periods were also analysed.

Statistical analysis

Student's T-test and chi-square test were used when appropriate to compare patient's characteristics. The survival effect of LTx on the entire cohort and on BODE score subgroups were assessed by a Wilcoxon signed ranks test. Kaplan-Meier survival estimates were used to describe the post-transplant survival of the entire cohort and log rank test was used to compare the survival between types and periods of transplant, and between pre-transplant BODE subgroups. Statistical analyses were performed with SPSS 17.0 for Windows (SPSS Inc. Chicago, IL, USA).

RESULTS

A total of 54 patients with COPD unrelated to alpha-1 antitrypsin deficiency underwent LTx from June 1993 until the end of 2007. No COPD patients listed for transplantation died during the waiting period. Twenty-six procedures (48%) were performed at Geneva University Hospitals and 28 (52%) in Lausanne, using a similar surgical and medical approach. Thirty-five patients (65%) underwent BLT whereas 19 (35%) had SLT. At the end of the follow-up, 29 patients (54%) were still alive. Six of these patients had not yet achieved the upper boundary of their predicted survival according to their pre-transplant BODE index, and were excluded from survival analysis. The patient's flow chart with life status at the end of the follow-up is shown on Figure 1.

The cohort included a patient with a low BODE score of 2, where the estimated half-life could not be calculated according to the data from the BODE original survival function [13]. Instead, the half-life was conservatively estimated according to the survival curve of the cohort of COPD patients described by Martinez et al [18]. One patient was retransplanted during the studied period and his survival time was calculated from the first LTx to death. Baseline characteristics of the transplanted patients are shown in Table 1. Excluded patients did not differ significantly from the cohort used for

survival analysis with respect to baseline characteristics. The mean follow-up was 5.7±4.5 (SD) years.

The comparison between observed post-transplant survival and expected survival according to pre-transplant BODE index is shown in Table 2. For the whole cohort, the median survival was significantly improved after LTx. This survival benefit was seen in the subgroup with a BODE score ≥7, but not in the subgroup with a BODE score <7, although a trend toward better survival with LTx was present. An individual survival benefit was seen in two third of the lung recipients, regardless of their BODE score subgroup. The detailed survival loss or gain for each patient is shown in Figure 2. It appears that a majority of patients lived much longer than expected while others, mainly in the BODE score <7, experienced a potential survival loss.

A sensitivity analysis on the effect of the exclusion of 6 patients from the survival analysis was performed. A pessimistic, intermediate, and optimistic survival were assigned to each of these excluded patients, using respectively the quartile 1, median and quartile 3 of the survival observed in the other patients who reached at least the same post-transplant survival. These 6 patients were then included in the analysis. In the entire cohort (n=48+6), the median post-transplant survival (pessimistic: 5.4 years; intermediate: 6.3 years; optimistic: 6.3 years) was significantly higher than the expected survival (lower boundary: 2.8 years; intermediate: 3.5 years; upper boundary: 4.2 years) in all scenarii. In the BODE ≥ 7 subgroup (n=35+2), the significant survival benefit of LTx was strengthened when compared to the lower boundary and intermediate expected survivals, and there was a trend towards benefit when compared to the upper boundary of predicted survival. The BODE < 7 subgroup (n=13+4) had a significant survival benefit from LTx only when compared to the lower boundary of the expected survival.

We found no significant survival difference between SLT and BLT subgroups, which had no between groups pre-transplant differences. The period of transplant (1993-1999 versus 2000-2007) was not associated with a survival difference.

The Kaplan-Meier post-LTx survival was not different between pre-transplant BODE score subgroups (Figure 3). This allowed us to compare the predicted survival at each step of the BODE index with the effective Kaplan-Meier post-transplant survival of the entire cohort (Table 3). This theoretical analysis showed that 4 years after LTx, the survival benefit is limited to patients with a pre-transplant BODE score ≥7.

DISCUSSION

This study showed a significant survival benefit of LTx in our cohort of COPD patients, with a median survival time significantly higher than expected before transplant. Considering that almost half of the patients were still alive at the end of the follow-up (see Figure 1), these results are particularly relevant, as the importance of the survival benefit may have been underestimated due to a limited follow-up period. Moreover, a majority of patients had an individual benefit from the intervention in terms of survival.

These results support two previous studies that have shown a global survival benefit after 260 [6] and 369 days [7], as well as a recent complex statistical simulation on the United Network for Organ Sharing database which showed a survival benefit in a majority of transplanted patients [8]. Two other studies did not demonstrate a survival benefit after 48 [9] and 24 months [10] of follow-up, but the follow-up time of the latter was too short to allow meaningful comparisons.

Methodologically, we used the pre-transplant BODE index to predict a theoretical survival at time of LTx. In contrast, the five studies published so far compared, either directly or with a statistical model, the survival of transplanted patients with patients staying on waiting list. This way of comparing survival is susceptible to potential bias against LTx. Indeed, the starting assumption is that all patients on the waiting list need a lung transplant at the time of listing. However,

considering the usual duration of the waiting time (often beyond 2 years) [6,19], transplant centres may register their patients early [20], which would improve the survival rate of the waiting list population. Furthermore, if patients on the waiting list are good candidates for transplantation at the time of listing, progression of the disease and ageing during waiting time make them potentially worse candidates, as older recipients have a significantly worse survival rate [2]. In contrast, high-risk patients have an increased probability of dying while on the waiting list, compared with low-risk patients who can survive long enough on the waiting list to undergo LTx. This could bias the results in favour of LTx. The likely different type of care received by patients on the waiting list compared to those not considered or denied for lung transplantation is another major potential bias. By assigning a BODE score-based predicted survival time, post-LTx survival can be compared with the predicted "natural" survival of the same patients, thus avoiding such risk of bias.

Our cohort's post-LTx survival rates, 77% at 1 year, 71% at 2 years and 65% at 4 years, are in accordance with previous studies in COPD patients [2, 21-23]. The short mean waiting time (6±4 months) and the absence of death on waiting list in our cohort may differ from other transplantation centres. However, our centres apply standard surgical and medical procedures, and the model used in this study is independent of any waiting list consideration. Our findings are therefore applicable to other lung transplantation centres.

Survival benefit is not the sole criteria to consider when evaluating the benefit of LTx in COPD patients, as LTx leads to a dramatic improvement of quality of life [5]. However, owing to the chronic shortage of lung donors, it is well accepted that LTx for COPD patients should be limited to a subset of those having the worst survival probability without intervention.

The presence of a FEV_1 < 25% of predicted value, a PaCO2 ≥ 55 mmHg (7.3 kPa), or pulmonary arterial hypertension with progressive deterioration has been used for many years as standard guidelines for the selection of COPD lung transplant candidates [24]. Nathan et al. [25] were the first to recommend the additional use of BODE index, and proposed a BODE score ≥ 7 as a new

transplant criteria. In 2006, the International Society of Heart and Lung Transplantation formalized the use of BODE score in the guidelines for the selection of lung transplant candidates [15], by adding a BODE index score ≥7 for transplantation and ≥5 for referral.

We found that the post-transplant mortality risk did not depend on the pre-operative BODE index. Based on our cohort's observed survival, the theoretical comparison with the survival predicted by each score of the BODE index showed a significant benefit at 4 years only with a pre-transplant BODE score ≥7. Moreover, in our cohort, we found that LTx improved the median survival only in the subgroup with a BODE score ≥7. In the subgroup with a BODE score <7, the mortality related to the intervention is higher than the long term expected benefit. Thus, these patients should not be transplanted at this stage of the disease or the indication should at least be carefully re-examined. Our results highlight the need for BODE index to become part of all pre-transplant assessments in COPD patients and provide support to the official recommendation to use a cut-off BODE score of 7 as transplant criteria.

Our cohort's baseline BODE scores repartition was significantly higher than in the original BODE index validation cohort [13] (Fig 4), reflecting the severity of COPD. The BODE index has not been specifically validated in a population listed for transplantation such as our cohort, but several factors suggest that this does not contraindicate its use. Not only did all our patients meet the inclusion criteria of Celli and co-worker's study [13], but almost 50% of the BODE index validation cohort had BODE scores ≥5 and therefore could have been referred for LTx as presently recommended [15]. More importantly, the BODE index has already proved its ability to predict mortality in severe COPD patients included in the National Emphysema Treatment Trial study [18]. These patients were likely to be selected and followed as closely as patients listed for LTx. Moreover, the use of the 95%CI of BODE index's predicted survival is likely to have accounted for most of the differences between patients which are not evaluated by the BODE index, such as age, or presence of pulmonary hypertension or other comorbidities. Nevertheless, the possibility that,

due to a positive selection bias, BODE index might be less accurate to predict mortality in a cohort listed for transplantation has to be considered when interpreting the results of our study.

The determination of BODE index scores from data collected during pre-transplant assessment is another limitation that should be recognized. Consequently, the calculated theoretical survival was not identical to the one at the time of LTx. However, considering the short waiting time (6±4 months), a significant worsening of patients conditions during this time is unlikely. The absence of deaths during this period reinforces this hypothesis. In any case, it would result in an underestimation of BODE index scores at the time of transplant and thus an overestimation of the predicted survival time. Consequently, we would have found a higher survival benefit of LTx.

In summary, the results of this study showed a significant survival benefit of LTx in our cohort of COPD patients. Importantly, not only the median survival was improved with LTx, but a significant majority of patients had an individual survival benefit from this procedure. Although the latter was independent from pre-transplant BODE score, the former was seen in the entire cohort and in the subgroup with a BODE score ≥7, but not in the subset of patients with a BODE score <7. Moreover, in a theoretical analysis, we found that 4 years after LTx a survival benefit can be expected only in the patients with a pre-transplant BODE score ≥7. For those with low BODE scores, the risk of the procedure outweighs the survival benefit. These results support the current recommendation to use a BODE score ≥ 7 as transplant criteria for patients with COPD.

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TABLES

Table 1. Patients baseline characteristics

	All n=48	BODE score <7 n=13	BODE score ≥7 n=35	p value*
Sex, male, n (%)	30 (63)	8 (62)	22 (63)	0.93
Age at LTx, years (mean ± SD)	55 ± 6	54 ± 5	56 ± 6	0.41
BMI, kg/m2 (mean ± SD)	22.4 ± 4.2	23.0 ± 4.1	22.2 ± 4.3	0.53
FEV_1, % of predicted value (mean ± SD)	23 ± 7	29 ± 8	22 ± 4	<0.001
MMRC dyspnea scale				
Class 2, n	5	5	0	
Class 3, n	28	8	20	<0.001
Class 4, n	15	0	15	
6MWD, m (mean ± SD)	242 ± 121	358 ± 106	199 ± 97	<0.001
BODE index (mean ± SD)	7.2 ± 1.5	5.3 ± 1.2	7.9 ± 1.0	<0.001
Time on waiting list, months (mean ± SD)	6 ± 4	5 ± 4	7 ± 4	0.09
Bilateral lung transplantation, n (%)	30 (63)	8 (62)	22 (63)	0.93
Transplant period				
1993-1999, n	22	7	15	0.50
2000- 2007, n	26	6	20	

*comparisons between BODE score < 7 and BODE score ≥ 7 subgroups. LTx: lung transplantation; BMI: body mass index, FEV_1: forced expiratory volume in 1 s; MMRC: Modified Medical Research Council; 6MWD: 6-min walk distance.

Table 2. Observed post-transplant survival versus cohort's expected survival at enrolment according to BODE index score

	All Patients (n=48)				BODE score <7 (n=13)				BODE score ≥7 (n=35)			
	Observed post LTx survival	Expected survival at enrolment			Observed post LTx survival	Expected survival at enrolment			Observed post LTx survival	Expected survival at enrolment		
		lower boundary	intermediate	upper boundary		lower boundary	intermediate	upper boundary		lower boundary	intermediate	upper boundary
Median survival, yrs (interquartile range)	5.4 (1.6-7.9)	2.8 (2.3-3.4)	3.5 (3.3-4.0)	4.2 (3.8-4.6)	7.7 (0.8-11.0)	3.4 (3.4-4.0)	4.6 (4.6-4.7)	4.0 (4.0-4.4)	5.0 (1.8-7.4)	2.3 (1.8-2.8)	3.3 (2.5-3.5)	3.8 (3.4-4.2)
p value*	–	0.0002	0.002	0.06	–	0.08	0.15	0.31	–	0.0009	0.009	0.15
Death occurrence before/after predicted, n; patients alive at the end of follow-up (n)	–	15 / 10 (23)	16 / 9 (23)	17 / 8 (23)	–	4 / 3 (6)	4 / 3 (6)	4 / 3 (6)	–	11 / 7 (17)	12 / 6 (17)	13 / 5 (17)
Patients with individual survival benefit	–	69%	67%	65%	–	69%	69%	69%	–	69%	66%	63%

* Observed vs expected survival (Wilcoxon signed rank test). LTx: lung transplantation

Table 3. Post- transplant observed Kaplan-Meier survival and expected survival according to BODE index score

	Observed Kaplan-Meier post transplant survival (95% CI) **(n= 48)**	Expected survival according to BODE score (95% CI)						
		BODE score 4	**BODE score 5**	**BODE score 6**	**BODE score 7**	**BODE score 8**	**BODE score 9**	**BODE score 10**
1 year	**0.77** (0.65 - 0.89)	0.97 (0.96-0.98)	0.96 (0.95-0.97)	0.95 (0.93-0.96)	0.93 (0.90-0.95)	0.91 (0.86-0.94)	0.88 (0.81-0.93)	0.85 (0.74-0.91)
2 years	**0.71** (0.58 - 0.84)	0.89 (0.87-0.91)	0.86 (0.81-0.89)	0.82 (0.75-0.87)	0.76 (0.66-0.83)	0.70 (0.56-0.80)	0.61 (0.44-0.75)	0.52 (0.31-0.70)
3 years	**0.67** (0.54 - 0.80)	0.81 (0.77-0.85)	0.76 (0.69-0.81)	0.69 (0.59-0.77)	0.61 (0.47-0.72)	0.52 (0.34-0.66)	0.41 * (0.22-0.60)	0.31 * (0.12-0.31)
4 years	**0.65** (0.51 - 0.79)	0.66 (0.59-0.72)	0.57 (0.47-0.66)	0.47 (0.34-0.59)	0.37 * (0.22-0.52)	0.26 * (0.12-0.44)	0.17 * (0.05-0.35)	0.09 * (0.01-0.27)
10 years	**0.39** (0.21 - 0.57)	ND	ND	ND	ND	ND	ND	ND

* Significant survival benefit (chi-square test). CI: confidence interval; ND: not determined

FIGURE LEGENDS

Figure 1: **Patient's flow-chart with life status at the end of the follow-up.**

Figure 2: **Individual survival impact of lung transplantation on each patient.**

Individual survival loss or gain was obtained for each patient by comparing the observed post-transplant survival with the 95% CI's upper boundary of predicted survival according to pre-transplant BODE score. Patients are separated in 2 subgroups based on their pre-transplant BODE score (BODE < 7 and BODE ≥ 7). Patients still alive at the end of the follow-up are presented differently to highlight their potentially longer survival gain.

Figure 3: **Observed post-transplant survival: difference between pre-transplant BODE score subgroups.**

Figure 4: **BODE index repartition: studied transplanted cohort versus original BODE index validation cohort** [13]**.**

FIGURE 1.

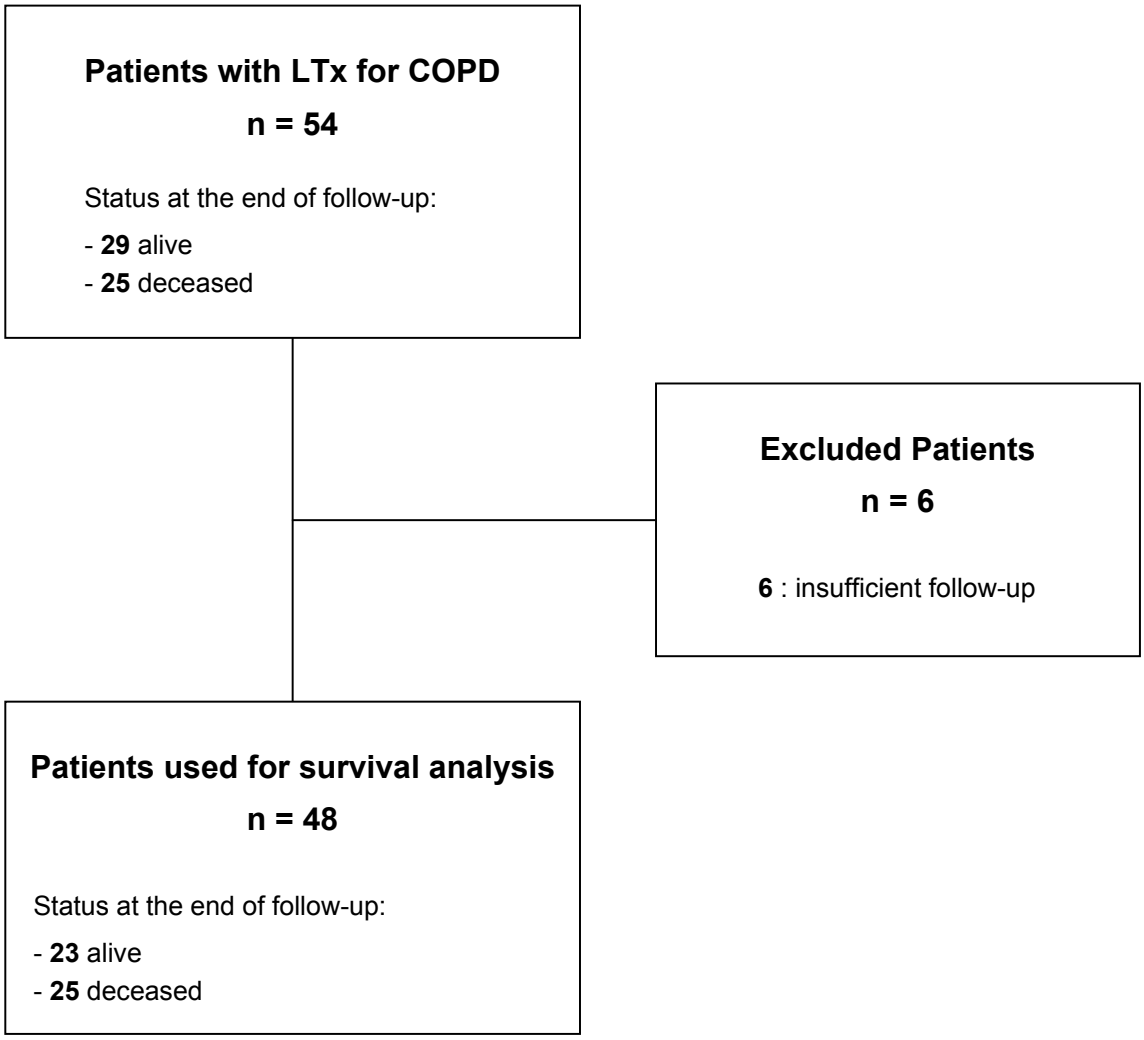

Patients with LTx for COPD
n = 54
Status at the end of follow-up:
- 29 alive
- 25 deceased
Excluded Patients
n = 6
6 : insufficient follow-up
Patients used for survival analysis
n = 48
Status at the end of follow-up:
- 23 alive
- 25 deceased

FIGURE 2.

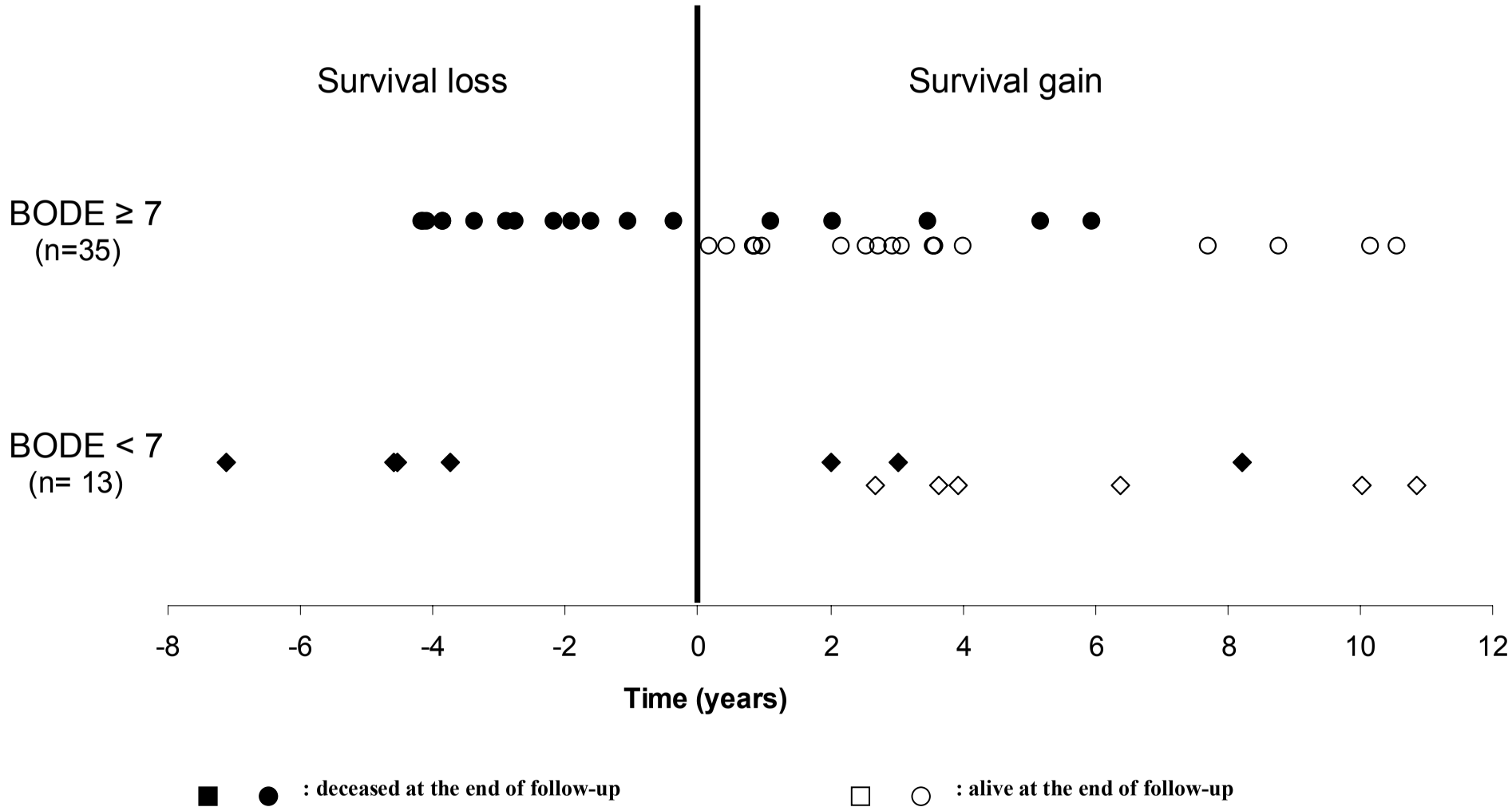

Survival loss
Survival gain
BODE ≥ 7
(n=35)
BODE < 7
(n= 13)
-8
-6
-4
-2
0
2
4
6
8
10
12
Time (years)
: deceased at the end of follow-up
: alive at the end of follow-up

FIGURE 3.

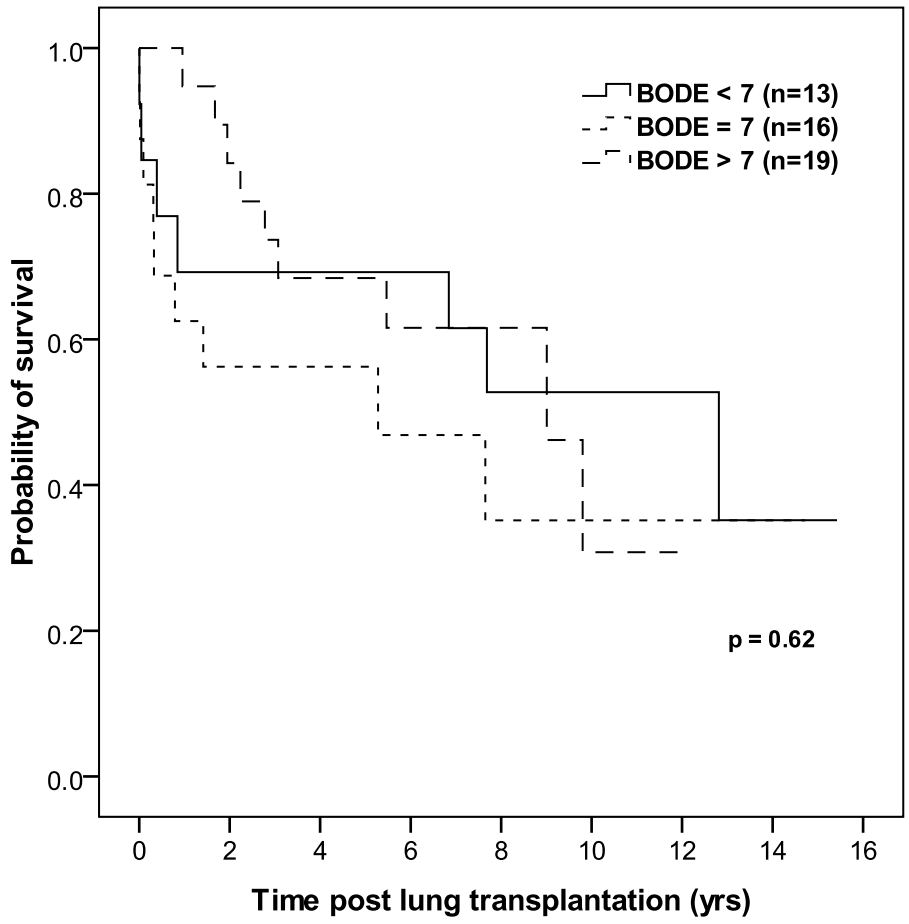
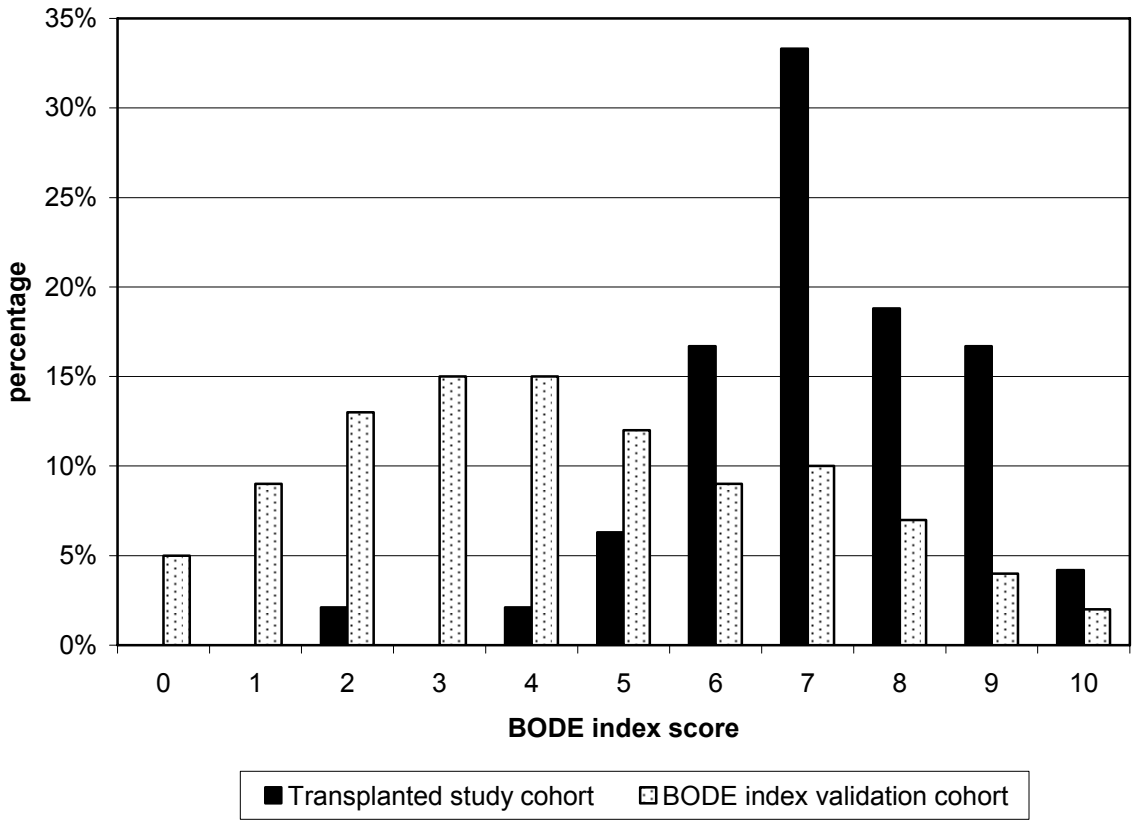

1.0
0.8
0.6
0.4
0.2
0.0
Probability of survival
BODE < 7 (n=13)
BODE = 7 (n=16)
BODE > 7 (n=19)
p = 0.62
0
2
4
6
8
10
12
14
16
Time post lung transplantation (yrs)

FIGURE 4.


35%
30%
25%
20%
15%
10%
5%
0%
percentage
0
1
2
3
4
5
6
7
8
9
10
BODE index score
Transplanted study cohort
BODE index validation cohort