Performance of the BODE index in patients with α_1-antitrypsin deficiency-related COPD

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ABSTRACT The BODE (body mass index, airflow obstruction, dyspnoea and exercise capacity) index is used to decide on referral and transplantation of patients with chronic obstructive pulmonary disease (COPD). The BODE index has not been validated in patients with α_1-antitrypsin deficiency, who account for 15% of COPD patients undergoing lung transplantation. We sought to validate the BODE index in α_1-antitrypsin deficiency-related COPD.

We assessed the prognostic value of the BODE index in 191 patients followed from 2006 to 2012 in a French prospective cohort of patients with α_1-antitrypsin deficiency.

20 patients died during follow-up and 22 underwent lung transplantation. Survival (95% CI) was 93.0% (91.7–94.3%) at 3 years and 76.0% (72.9–79.1%) at 5 years. The 3-year survival was 97.4% (96.6–98.2%), 98.0% (96.7–99.3%), 87.7% (84.5–90.9%) and 75.3% (66.0–84.6%) for patients with BODE index 0–2, 3–4, 5–6 and 7–10, respectively. Survival discrimination of the BODE index was better than with both forced expiratory volume in 1 s and Global Initiative for Chronic Obstructive Lung Disease classification. Regarding calibration, expected survival by BODE index was noticeably lower than observed survival.

The BODE index showed very good survival discrimination in patients with α_1-antitrypsin deficiency-related COPD. Larger studies are needed to support its use to drive patient referral for lung transplantation.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a common disease characterised by an incompletely reversible limitation in airflow [1]. Up to one-quarter of adults aged >40 years have mild and more airflow obstruction [2, 3]. Although mortality related to other leading causes of death, such as cardiac disease and stroke, has decreased from 1970 to 2002, that related to COPD doubled over the same period; COPD is currently the fourth leading cause of death, but the World Health Organization predicts that it will become the third leading cause by 2030 [4, 5].

α_1-antitrypsin (α_1-AT) deficiency is an under-recognised genetic condition that predisposes to COPD and liver disease [6]. α_1-AT deficiency is inherited as an autosomal-codominant condition for which more than 120 alleles have been identified. α_1-AT deficiency is thought to be involved in ~2% of COPD [7].

Several predictors of mortality have been described in patients with COPD [8]. Although forced expiratory volume in 1 s (FEV_1) remains the most important physiologic indicator of severity of airflow obstruction in COPD, its predictive value for mortality is weak, especially when it is >50%. The multidimensional BODE index, which combines body mass index (BMI), degree of airflow obstruction, dyspnoea and exercise capacity into a single index, has been widely validated in COPD [9]. This index was derived from analysis of a cohort of 207 patients and then prospectively validated in a cohort of 625 patients. Further studies have shown that the BODE index could distinguish patients who will and will not die, and that its evolution over time or after a therapeutic intervention was associated with survival [10]. The BODE index is now largely used in clinical practice, and current guidelines for lung transplantation indicate the BODE index as a measure for patient referral and transplantation, even in patients with α_1-AT deficiency, the fourth leading indication for lung transplantation worldwide [11, 12]. According to the 2012 report of the International Society for Heart and Lung Transplantation (ISHLT) registry, α_1-AT deficiency currently accounts for 7% of all lung transplants performed worldwide and 16% of COPD patients who undergo lung transplantations [13].

However, patients with α_1-AT deficiency-related COPD are likely to have a different prognosis than those without the deficiency: they tend to be younger and have less tobacco-smoking exposure, and as many as 20% may experience serious liver disease leading to liver transplantation or death [14].

The aim of this study was to validate the BODE index in a population of patients with AAT deficiency-related COPD, with survival as the outcome.

Methods

Study design and patients

The French cohort of α_1-AT deficiency-related COPD (CONEDAT), launched in January 2006, aimed to describe the natural history of patients with this condition and to figure out associated prognostic factors. This is an open, ongoing, prospective cohort aiming to include all patients living in France who fulfil the following criteria: 1) α_1-AT level below 0.5 $g \cdot L^{-1}$; 2) emphysema diagnosed on computed tomography; and 3) FEV_1/forced vital capacity <0.7 [15, 16]. After the baseline visit, patients return to their study centres for follow-up assessments every 6 months for 10 years. At each visit, the severity of COPD is assessed by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria [1]. Data were prospectively collected for the four components of the BODE index: BMI, post-bronchodilator FEV_1 as a percentage of predicted value, score on the modified Medical Research Council (mMRC) dyspnoea scale and 6-min walking distance [17]. Spirometry measurements and equations used to determine the predicted normal values for FEV_1 agreed with the official statement of the European Respiratory Society for standardised lung function testing [18]. α_1-AT protein concentration was assessed by an immunoturbidimetric or immunonephelometric method, using commercially available kits (normal range 0.90–2.0 $g \cdot L^{-1}$). In most patients, α_1-AT phenotype was assessed by isoelectric focusing electrophoresis on ready-to-use agarose gels with immunological detection, using a commercially available kit (Hydragel 18 AAT Isofocusing; Sebia, Evry, France). Alternatively, α_1-AT genotype was determined using DNA amplification by PCR with specific primers for detection of the PI S and PI Z mutations in the *SERPINA1* gene. The investigators at each centre determined the cause of death after reviewing the medical records. The list of all investigators involved in the study can be found in the Acknowledgements section. All patients gave their informed consent to be included in the study, which was approved by the institutional review board (IRB Paris Nord – Paris 7). This study is registered at www.clinicaltrials.gov as NCT00700934.

Statistical analysis

The aim of this study was to investigate the survival discrimination and calibration of the BODE index in patients with α_1-AT deficiency-related COPD. The BODE index has four categories of scores as originally described by Celli *et al.* [9]: 0–2, 3–4, 5–6 and 7–10. The end-point was patient survival. Because some

patients underwent lung transplantation during follow-up, survival estimation by the traditional Kaplan–Meier estimator, which assumes that patients censored because of lung transplantation share the same risk of death as patients still under observation, would have led to biased estimates (informative censoring). Therefore, we used an inverse probability of censoring weighted (IPCW) survival estimator [19]. With this method, each observation is weighted according to the inverse of the probability of remaining uncensored, which is computed by fitting a Cox model for censoring that incorporates the BODE index (which varies over time) and age at inclusion. The same weights were used in Cox models assessing the relationship between BODE and survival. Because augmentation therapy has been associated with emphysema progression and survival in several studies [20–23], all models were adjusted for augmentation therapy and stratified by centre. We used smoothing splines to explore the correct functional form of the covariates [24].

We also tested whether BODE index evolution over time was associated with survival. Because BODE evolution over time and survival are two inter-related processes, a model for the joint distribution of the longitudinal and survival outcomes was used [25–27]. In this model, BODE evolution over time was fitted by using a linear mixed-effects model that included age, sex and augmentation therapy as fixed effects. In the random-effects design matrix, we included an intercept and a time term. Using the same approach, we also tested whether the slope of BODE evolution over time was associated with survival.

Model discrimination

We used the area under the time-dependent receiver operating characteristic (ROC) curve (AUC$_t$) to assess the survival discrimination of the baseline BODE index on survival [28]. At a given time, this approach measures the ability of the BODE index to distinguish between patients who died before that time and those who were still alive beyond that time (*i.e.* the probability that the BODE index of the former would be greater than that of the latter). The c-statistic, which is commonly used as a discrimination index in prognostic studies [29], can be expressed as a weighted average of AUC$_t$ [30]. To account for loss to follow-up, the AUC$_t$ is estimated by an IPCW approach. In this study, we computed the AUC$_t$ every 30 days from 1 to 5 years.

Model calibration

To assess the BODE index calibration in our patients, we compared expected survival and observed survival for the four subgroup scores of the BODE index. Expected survival according to BODE value was computed according to baseline survival of patients as defined by CELLI *et al.* [9] and LAHZAMI *et al.* [11].

Statistical software

Data management involved use of Stata MP v12.0 (StataCorp, College Station, TX, USA) and data analyses R 2.15.2 (R Foundation for Statistical Computing, Vienna, Austria). The following R packages were used: *survival*, *timeROC*, *cmprsk* and *JM*. A routine was developed by two of the authors (R. Porcher and G. Thabut) to compute the weights used for the IPCW survival estimator. The statistical code used for these analyses is available on request from the first author (G. Thabut).

Results

Patient characteristics

215 patients were included in our cohort and prospectively followed by the end of the study, on December 31, 2012. The BODE index could not be computed for 24 patients, mostly because of missing 6-min walking distance values, thus 191 patients in 40 centres were analysed. The number of patients by centre ranged from 1 to 36. All patients had α_1-AT blood level <0.5 g·L^{-1}; α_1-AT genotype was PI ZZ in 170 (89%) patients, PI SZ in 12 (6.3%), PI null/Z in three (1.6%) and was not available in six (3.2%). The main characteristics of patients are presented in table 1. Mean $\pm$ SD age was 50.8 $\pm$ 10.9 years and baseline FEV$_1$ was 42.5 $\pm$ 19.9% of the predicted value. According to the GOLD staging of COPD, 140 patients (73.3%) had severe or very severe COPD (stage III or IV, respectively).

The baseline BODE index was 3.6 $\pm$ 2.3 (range 0–10). The BODE index was 0–2 for 66 (34.6%) patients, 3–4 for 61 (31.9%), 5–6 for 41 (21.5%) and 7–10 for 23 (12%). The values of the BODE index components by the four stages of the GOLD classification are presented in table 2.

Follow-up and outcome

Median follow-up time was 31.4 months (range 1–91.3 months). During follow-up, 20 patients died, 22 underwent lung transplantation, five withdrew from the study and four were lost to follow-up, giving 140 patients alive at the end of the study period. Among the 20 patients who died, only one was registered for a lung transplant. Among the 22 patients who underwent a lung transplant, five died during follow-up.

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TABLE 1 Baseline characteristics of 191 patients with α_1-antitrypsin deficiency-related chronic obstructive pulmonary disease

Age years	50.8±10.9
Age distribution	
⩽50 years	96 (50.3)
51–55 years	30 (15.7)
56–60 years	26 (13.6)
>60 years	39 (20.4)
Females	72 (37.7)
Smoking status	
Never-smokers	21 (11.0)
Current smokers	7 (3.7)
Smoking history pack-years	18.2±16.3
mMRC dyspnoea score	
0	8 (4.2)
1	65 (34.0)
2	72 (37.7)
3	36 (18.9)
4	10 (5.2)
Body mass index kg·m^{-2}	22.9±4.0
GOLD stage	
I[#]	10 (5.3%)
II[¶]	41 (21.6%)
III[+]	57 (29.8)
IV[§]	83 (43.5)
Exacerbations	
In the year before study inclusion	1.4±1.8
At least one exacerbation in the year before inclusion	108 (56.5)
History of wheezing	109 (57.7)
Chronic bronchitis	68 (35.9)
FEV1 % of predicted	42.5±19.9
TLC % of predicted	127.9±24.4
Charlson index[f]	2.7±1.3
6-min walking distance m	433.1±135.7
Treatment	
Inhaled corticosteroids	157 (82.6)
Long-acting β_2-agonists	171 (90.0)
Long-acting anticholinergic agents	142 (75.6)
Augmentation therapy	97 (50.8)
Oxygen required at rest	62 (32.6)

Data are presented as mean±SD or n (%). mMRC: modified Medical Research Council; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV1: forced expiratory volume in 1 s; TLC: total lung capacity. [#]: mild; [¶]: moderate; [+]: severe; [§]: very severe; [f]: scores on the Charlson index can range from 0 to 33, with higher scores indicating more coexisting conditions.

TABLE 2 BODE index components for patients with α_1-antitrypsin deficiency-related chronic obstructive pulmonary disease by GOLD stage

	GOLD stage			
	I	**II**	**III**	**IV**
Severity	Mild	Moderate	Severe	Very severe
Subjects n	10	41	57	83
FEV1 % of predicted	97.4±16.8	61.4±8.1	40.6±5.9	27.5±8.5
Body mass index kg·m^{-2}	21.9±3.2	22.9±2.7	24.2±4.3	22.2±4.2
mMRC dyspnoea score	2.1±0.7	2.3±0.6	2.6±0.8	3.5±0.9
6-min walking distance m	461.0±109.0	503.6±136.3	466.6±117.6	369.7±124.3
BODE index	0.8±0.8	1.3±1.7	3.2±1.3	5.4±1.7

Data are presented as mean±SD, unless otherwise stated. BODE: body mass index, airflow obstruction, dyspnoea and exercise capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; FEV1: forced expiratory volume in 1 s; mMRC: modified Medical Research Council.

The survival rates (95% CI) were 95.5% (71.9–99.3%) at 30 days, 85.9% (62.4–95.2%) at 1 year, 78.7% (51.7–91.7%) at 3 years and 70.9% (42.0–87.2%) at 5 years.

Survival

The cumulative incidence of death (95% CI) was 0.5% (0–1.6%), 4.7% (1.3–8.2%), 6.3% (2.3–10.4%) and 17.2% (9.1–25.3%) at 1, 2, 3 and 5 years, respectively. The cumulative incidence of lung transplant was 5.5% (2.2–8.8%), 8.8% (4.5–13.1%), 12.9% (7.5–18.2%) and 15.1% (9.0–21.2%) at the same times (fig. 1). Using the IPCW survival estimator, the survival was 99.5% (99.0–100%), 94.8% (93.7–95.9%), 93.0% (91.7–94.3%) and 76.0% (72.9–79.1%) at 1, 2, 3 and 5 years, respectively (online supplementary fig. S1). Figure S2 displays the survival over time calculated with three different estimators: the traditional Kaplan–Meier estimator, the IPCW survival estimator, and a Kaplan–Meier estimator considering both death and transplantation events. The IPCW survival estimator gave survival data between the traditional survival Kaplan–Meier estimator and the Kaplan–Meier estimator of death or lung transplant.

The mean±SD baseline BODE score was lower among survivors than among those who died or underwent transplantation (3.1±2.1 *versus* 5.8±2.0 and 5.5±1.9, respectively). The baseline BODE score was higher for patients who died from respiratory causes than from other causes (6.6±1.6 *versus* 4.6±1.9, respectively; p=0.03). Figure 2 reports the survival of patients by baseline BODE index. The 3-year survival (95% CI) was 97.4% (96.6–98.2%), 98.0% (96.7–99.3%), 87.7% (84.5–90.9%) and 75.3% (66.0–84.6%) for patients with BODE index 0–2, 3–4, 5–6 and 7–10, respectively. In a Cox model with IPCW weights, adjusted for centre and augmentation therapy, baseline BODE index was associated with survival (hazard ratio (HR) for 1-point increase in BODE index 1.52, 95% CI 1.14–2.0; p=0.004). Plots based on smoothing splines supported a linear association of the BODE index (fig. S3) and three of its components (FEV_1, dyspnoea and 6-min walking distance) with the log hazard of death, but a U-shape association for BMI (fig. S4).

Figure 3 displays the discrimination, as assessed by AUC_t, of the BODE index, GOLD classification and FEV_1 for survival. The BODE index demonstrated very good discrimination, better than both FEV_1 and the GOLD classification.

BODE index over time

The mean±SD number of BODE assessments per patient was 3.6±2.7 (range 1–11). Slopes of BODE over time were calculated for each patient by using a joint model. According to this model, BODE increased over time at an average rate of 0.17±0.04 points per year. Slopes of BODE were associated with the BODE measured at baseline; the greater the baseline BODE, the greater the increase in BODE over time (p=0.002). In a joint model in which the risk of death depended both on the value and slope of BODE, only the value of BODE over time was associated with death (HR for 1-point increase in BODE 1.81, 95% CI 1.40–2.34; p<0.0001) but not the slope (p=0.78).

Calibration

Figure 4 compares the observed survival of our patients and expected survival (with data for patients used to validate the BODE index) by the four groups of BODE index measured at baseline. For the same level of baseline BODE, the observed survival was better than the expected survival.

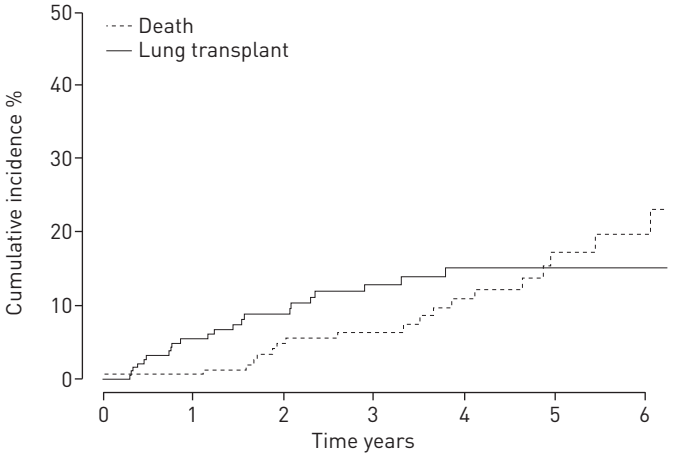

FIGURE 1 Cumulative incidence of death and lung transplant by time from inclusion in the cohort.

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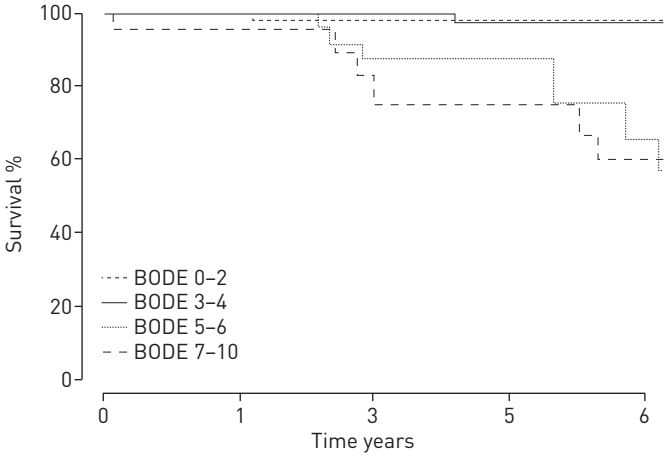

FIGURE 2 Inverse probability of censoring weighted estimates for survival according to four BODE (body mass index, airflow obstruction, dyspnoea and exercise capacity) index categories for the 191 patients with α_1-antitrypsin deficiency-related chronic obstructive pulmonary disease.

Causes of death

Among the 20 patients who died during follow-up, 12 (60%) died from respiratory failure, four (20%) from liver disease (two cancers and two from cirrhosis) and one from stomach cancer, one committed suicide, and the underlying cause of death was unknown in the remaining two patients.

Sensitivity analyses

The results regarding survival discrimination and calibration were largely unchanged when only patients with a documented PI ZZ genotype (n=170) were taken into account (data not shown).

Discussion

This study shows that the BODE index has very good survival discrimination in patients with α_1-AT deficiency-related COPD. However, our results also suggest that the observed survival is higher for patients with than without α_1-AT deficiency at the same BODE level. Our results remain to be validated in larger cohorts of patients.

The BODE index has gained widespread acceptance as a prognostic marker in COPD patients. It is easy to compute and has been largely validated in several cohorts of patients. The BODE index has shown better discriminant ability than other prognostic markers such as the FEV_1 or GOLD classification [8]. A recent study also demonstrated the association of BODE index evolution over time and risk of death [10]. Because the BODE index has been largely validated and is easy to compute, it is now used as a tool on which to base patient listing for transplantation. In the ISHLT guidelines for selection of lung transplant candidates [12], BODE >5 is an indication for patient referral and an index >7 is an indication for patient transplantation in recipients with COPD. These guidelines are in use in many countries including France.

α_1-AT deficiency-related emphysema accounts for 2% of all COPD patients and for 7% of all transplantations worldwide [1, 13]. Our results show that the discriminant power of the BODE index is

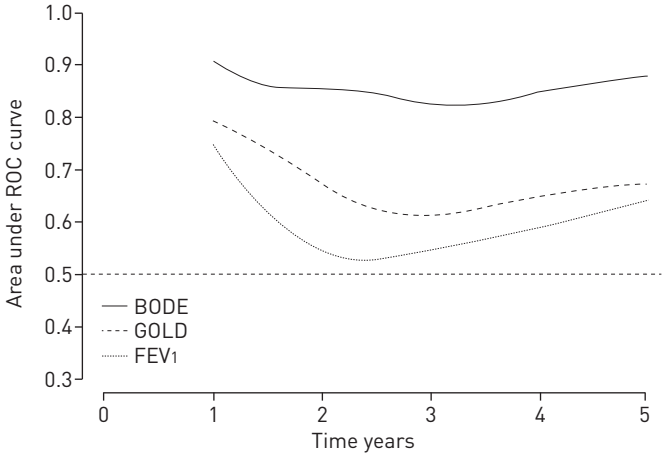

FIGURE 3 Survival discrimination of the BODE (body mass index, airflow obstruction, dyspnoea and exercise capacity) index, Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification and forced expiratory volume in 1 s (FEV_1) as assessed by time-dependent area under the receiver operating characteristic (ROC) curve.

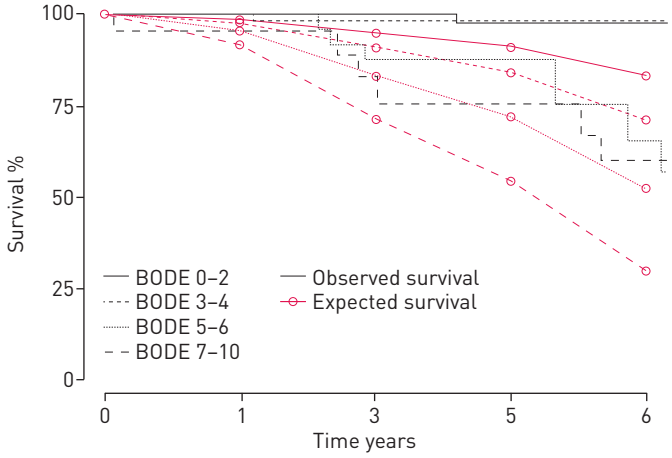

FIGURE 4 Expected and observed survival according to four BODE (body mass index, airflow obstruction, dyspnoea and exercise capacity) index categories for the 191 patients with α_1-antitrypsin deficiency-related chronic obstructive pulmonary disease. Observed survival is assessed by the inverse probability of censoring weighted survival estimator.

very good in these patients. All components of the BODE index except BMI were associated with survival. Regarding BMI, exploratory analyses suggested that the functional form of this variable may not be linear but may exhibit a U-shape, a functional relationship found in other settings [31], but unusual in COPD patients [32]. These results need to be confirmed in larger studies. We also found that BODE evolution over time was related to mortality, which reinforces the validity of the BODE index. Although the BODE index was good at ranking patients by their expected survival (discrimination), it considerably underestimated the survival of patients (calibration). Although survival prediction may not be the first goal of the BODE index (the seminal paper on the BODE index did not provide any tool for prediction), it is used in this way for patient referral for transplantation [11, 12], and interest is growing in predicting the survival of COPD patients to tailor management and treatment [33, 34]. In our study, patients with BODE index from 7 to 10 had a 60.2% (95% CI 50.5–69.9%) 4-year survival as compared with <25% in the original paper describing the BODE index [9]. These differences in outcome could be related to differences in the underlying condition; for instance, the mean patient age in the seminal paper by CELLI *et al.* [9] was 66 years as compared with 50.8 in our cohort. It could also be related to differences in comorbidities, as suggested by the low Charlson index of the patients enrolled in this study. In our study, besides respiratory failure, which was the cause of death in 60% of cases, 20% of patients died from complications of α_1-AT deficiency-related liver diseases. Although these results are in line with the conclusions of a recently published study showing severe fibrosis or cirrhosis present in 17.5% of patients [14], they must be viewed cautiously given the small study sample size.

We faced several methodological issues when designing this study. Assessing the survival of patients with competing events (here death and lung transplantation) is challenging. When the event of interest is death, the most widely used approach is the traditional Kaplan–Meier estimator in which patients undergoing lung transplantation are considered as if they were lost to follow-up (censored). This approach assumes that the distribution of survival times of patients who underwent transplantation is the same as that of patients who did not (uninformative censoring). This assumption is obviously untenable here, and this approach overestimates the ''true'' survival of patients because the sickest patients are removed from the database over time. Although this issue is common in studies assessing the prognosis of COPD, given the high number of COPD patients receiving a transplant worldwide, in general, it is largely overlooked and not even mentioned by investigators.

Here, we used an IPCW survival estimator to compute the survival of patients with α_1-AT deficiency-related COPD that accounts for transplantation. The basic idea is to weight observations based on their likelihood of being incomplete (because of lung transplanation); that is, to re-weight cases from underrepresented groups. This approach gives more weight to patients with a high probability of undergoing transplantation, to account for attrition of these patients over time because of transplantation. The use of this technique leads to noticeably lower and presumably more accurate estimates than the traditional Kaplan–Meier approach. Another approach, illustrated in figure S2, is to consider death or transplantation as an event. This approach may be viewed as a worst-case scenario because it assumes that patients would have died the day they underwent transplantation had they had not received the transplant. The same is true for the Cox model that assumes independent censoring given the covariates. Therefore, we used the same weights as we computed for the IPCW survival estimator in our Cox models.

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This study has several limitations. First, we could prospectively follow only 191 patients with α_1-AT deficiency-related COPD and only 20 deaths were recorded during follow-up, which further limits the statistical power of our study. Although this sample was large enough to demonstrate the discriminant ability of the BODE score in these patients, a larger sample size would have allowed for more precise estimates of the observed survival of patients according to their baseline BODE score. Second, we ascertained causes of recipient death without using an adjudication committee, and our findings must be interpreted cautiously. As others have shown, cause of death is difficult to assess reliably without the use of an adjudication committee [35].

In conclusion, the BODE index showed very good survival discrimination for survival in patients with α_1-AT deficiency-related COPD. Our data suggest that the capacity of the BODE index to predict survival in α_1-AT-deficient patients should be evaluated in larger studies to properly support the current recommendations for its use for lung transplant referral.

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