ORIGINAL ARTICLE
COPD

Survival benefit of lung transplantation compared with medical management and pulmonary rehabilitation for patients with end-stage COPD

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ABSTRACT

Background: COPD patients account for a large proportion of lung transplants; lung transplantation survival benefit for COPD patients is not well established.

Methods: We identified 4521 COPD patients in the United Network for Organ Sharing (UNOS) dataset transplanted from May 2005 to August 2016, and 604 patients assigned to receive pulmonary rehabilitation and medical management in the National Emphysema Treatment Trial (NETT). After trimming the populations for NETT eligibility criteria and data completeness, 1337 UNOS and 596 NETT patients remained. Kaplan–Meier estimates of transplant-free survival from transplantation for UNOS, and NETT randomisation, were compared between propensity score-matched UNOS (n=401) and NETT (n=262) patients.

Results: In propensity-matched analyses, transplanted patients had better survival compared to medically managed patients in NETT (p=0.003). Stratifying on 6 min walk distance (6 MWD) and FEV_1, UNOS patients with 6 MWD <1000 ft (~300 m) or FEV_1 <20% of predicted had better survival than NETT counterparts (median survival 5.0 years UNOS *versus* 3.4 years NETT; log-rank p<0.0001), while UNOS patients with 6 MWD ⩾1000 ft (~300 m) and FEV_1 ⩾20% had similar survival to NETT counterparts (median survival, 5.4 years UNOS *versus* 4.9 years NETT; log-rank p=0.73), interaction p=0.01.

Conclusions: Overall survival is better for matched lung transplant patients compared with medical management alone. Patients who derive maximum benefit are those with 6 MWD <1000 ft (~300 m) or FEV_1 <20% of predicted, compared with pulmonary rehabilitation and medical management.

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Lung transplantation offers a survival benefit for COPD patients with 6MWD <1000 ft (~300 m) or FEV_1 <20% of predicted compared to pulmonary rehabilitation and medical therapy. 6MWD and FEV_1 should be considered in the transplant patient selection process. http://bit.ly/2SlkTIo

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Introduction

Lung transplantation is the final therapeutic option for patients with end-stage lung disease. COPD has been the most frequent underlying disease for both single (44% of all single lung transplants) and double (32% of all double lung transplants) transplant recipients from 1995 to 2016 [1].

Despite recent improvements in early post-operative outcomes, the median survival time following lung transplantation is approximately 5–6 years. In contrast with other lung diseases, *e.g.* idiopathic pulmonary fibrosis and pulmonary arterial hypertension, in which lung transplantation is believed to prolong life, the survival benefit is controversial for COPD because advanced-stage COPD outcomes using medical management alone are better than those of other end-stage lung diseases [2–6]. Despite advances in treatment, COPD mortality and prognosis have not changed appreciably in the last three decades. COPD continues to be the fourth most frequent cause of death worldwide [7–10].

A forced expiratory volume in 1 s (FEV_1) <30% of predicted was associated with survival rates of 65% and 30% at 2 and 5 years, respectively [11–13], and FEV_1 below 30% was considered to be a threshold for lung transplant evaluation. Objective measurements like cardiopulmonary exercise test results or 6-min walk distance (6 MWD) were demonstrated to be consistent predictors of mortality [14, 15]. In an attempt to improve prediction of survival, the BODE index including body mass index (BMI), obstruction, dyspnoea and exercise capacity was developed by Celli *et al.* [16] in 2004.

Lung allocation scores (LAS) were implemented in May 2005 [17]. The models for survival after lung transplantation and wait list survival probability were combined to form a model in which the expected benefit of the transplant was calculated as the difference between predicted post-transplant survival and wait list survival [18]. The National Emphysema Treatment Trial (NETT) elucidated the risks and benefits of lung volume reduction surgery (LVRS) proposed as a therapy for advanced COPD in 2003 [19].

Our study compares COPD patient survival after lung transplantation with the survival of an independent series of severe emphysema patients who received only medical management (the control arm of NETT). We hypothesised that patients with severe COPD attain a survival benefit after lung transplantation and that parameters assessing the severity of disease, such as 6-min walk distance (6 MWD) and forced expiratory volume in 1 s (FEV_1), are determinants of transplant benefit.

Material and methods

The University of Maryland Baltimore Institutional Review Board granted the study an exemption (HP-00068606) from informed consent for review of data from UNOS (the United Network for Organ Sharing) and NETT.

We present patient characteristics for the following three groups obtained from the UNOS and NETT data files: UNOS patients listed for lung transplantation in the LAS era, UNOS patients transplanted in the LAS era and NETT patients randomised to the control arm of the trial (to receive only pulmonary rehabilitation and standard medical therapy).

For continuous variables, medians and interquartile ranges were compared with Wilcoxon rank-sum tests, as statistical tests for normality (including Shapiro–Wilk and Kolmogorov–Smirnov) rejected normality of distributions for several variables. Categorical variables, frequency distributions were analysed using chi-squared tests. We compared baseline characteristics of the UNOS transplanted patients and NETT control patients; we did not make a separate comparison of UNOS listed and NETT rehabilitation group patients' baseline characteristics because UNOS listed and UNOS transplanted patients had a large overlap and were very similar in the baseline characteristics we assessed.

We first compared transplant-free survival between all UNOS listed patients (censoring transplanted patients at the time of surgery) and NETT control patients. Our primary analyses compared post-transplant survival for UNOS transplanted patients to survival after randomisation for NETT control patients. Re-transplantation for UNOS patients and transplantation following randomisation for NETT patients were taken to be treatment failures. In UNOS, deaths of the study participants were ascertained *via* the US Social Security Death Index. Patients were followed for a maximum of 10 years after transplantation or randomisation and were censored if alive and free of subsequent transplantation at the end of follow-up. NETT patients underwent complete evaluations at 6 months, 12 months, and yearly thereafter.

A propensity score was computed for each patient in the UNOS COPD and NETT patient population, using a logistic regression model that included the following parameters, selected based on clinical relevance and literature review [11–16]: age, sex, percent predicted of FEV_1, percent predicted of forced vital capacity (FVC), 6 MWD, oxygen requirements, carbon dioxide tension (P_{CO_2}) and body mass index (BMI). UNOS patients were excluded if they had values outside ranges based on eligibility criteria for NETT and plausibility for COPD transplant patients: $18 \leqslant \text{age} \leqslant 80$ years, $5 \leqslant FEV_1 \leqslant 45\%$ predicted,

10⩽FVC⩽100% predicted, 6 MWD⩾140 m (459 ft.), 0⩽O_2 requirements⩽6 L per min., 25⩽Partial pressure of carbon dioxide (P_{aCO_2})⩽60 mmHg, mean pulmonary artery pressure (PAP)⩽35 mmHg, and 15⩽BMI⩽31.1 kg·m^{-2} for females and 32.2 kg·m^{-2} for males. A greedy matching algorithm implemented *via* the gmatch SAS macro was used to match patients between NETT and UNOS based on the propensity score, with one-to-many matching.

The log-rank test was used for survival analyses, and the Renyi test when survival curves crossed. Survival comparisons between UNOS transplanted and NETT patients were repeated after stratifying patients by 6 MWD and FEV_1, and post-transplant survival was compared between the full populations of "more severe" (6 MWD <1000 ft (~300 m) or FEV_1 <20% predicted) and "less severe" (6 MWD ⩾1000 ft (~300 m) and FEV_1 ⩾20% predicted) transplanted COPD patients in UNOS. The decision to use cut-offs of 20% for FEV_1 and 1000 ft (~300 m) for 6 MWD was based on clinical experience. The most recent ISHLT consensus document recommend a FEV_1 less than 15% to 20% predicted as criteria for lung transplant listing [20]. Similarly, a 6 MWD less than 1000 ft (~300 m) was associated with increased mortality in 1-year experience [21].

Analyses were conducted with SAS Software, version 9.4, and p<0.05 (two-tailed) statistically significant.

Results

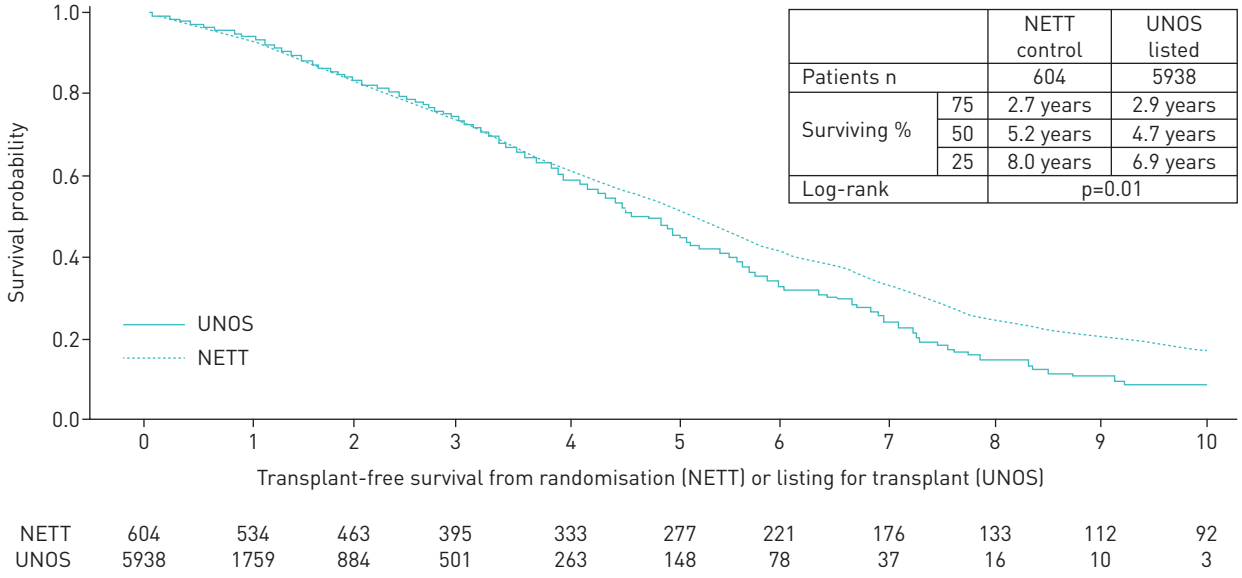
We identified 4521 COPD patients in the UNOS dataset who received a transplant between May 2005 and August 2016; 5938 COPD patients were listed for transplantation in this same era. 604 patients were randomised to pulmonary rehabilitation and medical treatment in the NETT between January 1998 and July 2002. Demographic and clinical characteristics for the three populations (UNOS listed, UNOS transplanted and NETT control) are shown in table 1.

A Kaplan–Meier plot comparing transplant-free survival between the UNOS listed (censoring transplanted patients at the time of surgery) and NETT control populations is shown in figure 1. Median survival

TABLE 1 Patient characteristics at baseline

	UNOS listed	Unmatched Patients UNOS transplanted	NETT control	p-value[¶]	Matched Patients UNOS transplanted	NETT control3	p-value
Subjects n	5938	4521	604		401	262	
Demographics							
Age years	61 (56–64)	61 (57–65)	67 (64–71)	<0.0001	64 (61–67)	65 (61–68)	0.02
⩾65	1445 (24)	1287 (28)	432 (72)	<0.0001	199 (50)	152 (58)	0.04
Female sex	3043 (51)	2182 (48)	219 (36)	<0.0001	177 (44)	109 (42)	0.52
Race				0.10			0.28
White	5462 (92)	4172 (92)	569 (94)		384 (96)	246 (94)	
Non-white	476 (8)	349 (8)	35 (6)		17 (4)	16 (6)	
BMI kg·m^{-2}	24 (21–28)[#]	24 (21–27)[#]	25 (22–27)[#]	0.12	25 (22–27)	24 (21–28)	0.76
Disease severity							
FVC % pred	54 (43–65)[#]	52 (41–64)[#]	58 (48–68)[#]	<0.0001	55(47–65)	55 (45–65)	0.92
FEV_1 % pred	20 (16–25)[#]	20 (16–25)[#]	24 (20–29)[#]	<0.0001	21 (18–25)	22 (18–26)	0.10
6 MWD ft	760 (497–984)[#]	770 (504–998)[#]	1229 (990–1413)[#]	<0.0001	1000 (810–1191)	1065 (860–1280)	0.01
6 MWD m	232 (151–300)[#]	235 (154–304)[#]	375 (302–431)[#]		305 (247–363)	325 (262–390)	
6 MWD <1000 ft (~300 metre) or FEV_1 <20% pred	4035 (86)[#]	4004 (89)[#]	238 (39)	<0.0001	269 (67)	151 (58)	0.02
O_2 requirements at rest L	3 (2–3)[#]	3 (2–4)[#]	1 (0–2)	<0.0001	2 (2–3)	2 (2–2)	0.04
P_{CO_2} mmHg	47 (42–54)[#]	49 (43–58)[#]	43 (39–46)	<0.0001	45 (40–50)	44 (40–49)	0.49
Mean PAP ⩾35 mmHg	555 (10)[#]	455 (11)[#]	0 (0)[+]		0 (0)[+]	0 (0)[+]	
Transplant characteristics							
Type of lung transplant							
Single	NA	1756 (39)[#]	NA		183 (46)	NA	
Double	NA	2764 (61)[#]	NA		218 (54)	NA	

Data are presented as median (interquartile range) or n (%), unless otherwise stated. UNOS: United Network for Organ Sharing; NETT: National Emphysema Treatment Trial; BMI: body mass index; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 s; 6MWD: 6-min walk distance; P_{CO_2}: carbon dioxide tension; PAP: pulmonary arterial pressure. NA: not applicable. [#]: At least one patient was missing data on this variable, so statistics are based on patients with available data; [¶]: p-value is for the comparison of the UNOS transplanted and NETT control groups; [+]: mean PAP⩾35 was an exclusion criterion for NETT, so prior to matching, we excluded patients with PAP⩾35.



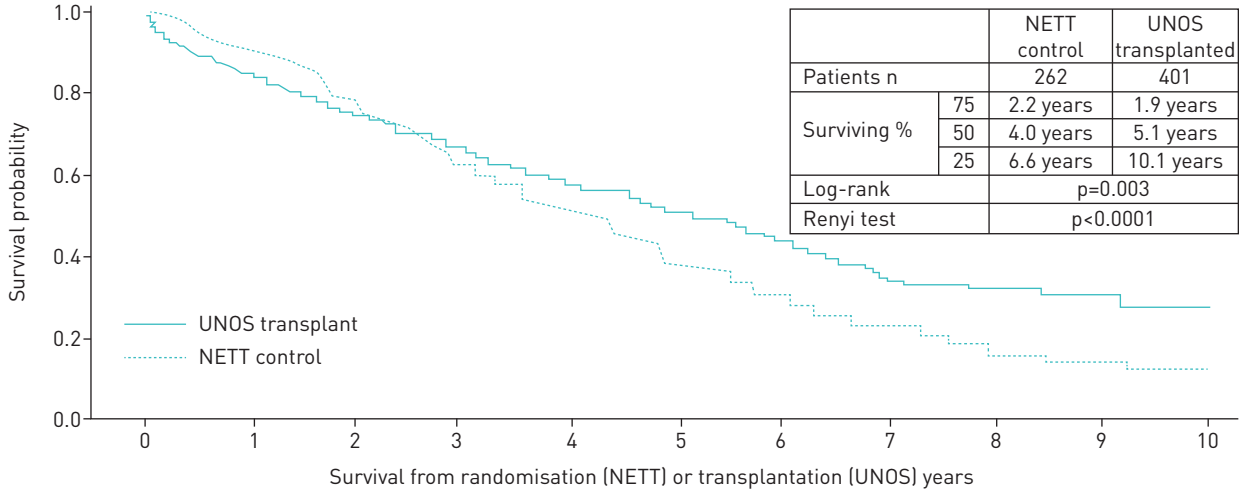
		NETT control	UNOS listed
Patients n		604	5938
Surviving %	75	2.7 years	2.9 years
	50	5.2 years	4.7 years
	25	8.0 years	6.9 years
Log-rank		p=0.01	

NETT	604	534	463	395	333	277	221	176	133	112	92
UNOS	5938	1759	884	501	263	148	78	37	16	10	3

FIGURE 1 Kaplan–Meier plot of transplant-free survival for United Network for Organ Sharing (UNOS) listed and National Emphysema Treatment Trial (NETT) patients.

without transplantation was 5.2 years in the NETT population and 4.7 years in the UNOS listed population (log rank p=0.01).

After excluding patients with missing data on one or more of the variables to be used for propensity score matching, excluding patients whose values on at least one of these variables were inconsistent with NETT eligibility criteria or untenable for a COPD transplant patient, and matching the remaining UNOS transplanted and NETT control patients, there were 262 patients from NETT and 401 patients from UNOS. Figure 2 contains a Kaplan–Meier plot comparing survival between the matched UNOS transplanted and NETT control patients. The median (IQR) survival free of subsequent transplantation was 4.0 years (2.2–6.6 years) in NETT, compared 5.1 years (1.9–10.1 years) in UNOS (log rank p=0.003). In the first 2 years after transplantation or randomisation, the probability of survival was similar for UNOS patients and NETT patients, (74% *versus* 77%; p=0.28). Around 2.5 years the survival curves cross. Since the survival crossed, the Renyi test was performed for comparison of survival between the two groups (p<0.0001).



		NETT control	UNOS transplanted
Patients n		262	401
Surviving %	75	2.2 years	1.9 years
	50	4.0 years	5.1 years
	25	6.6 years	10.1 years
Log-rank		p=0.003	
Renyi test		p<0.0001	

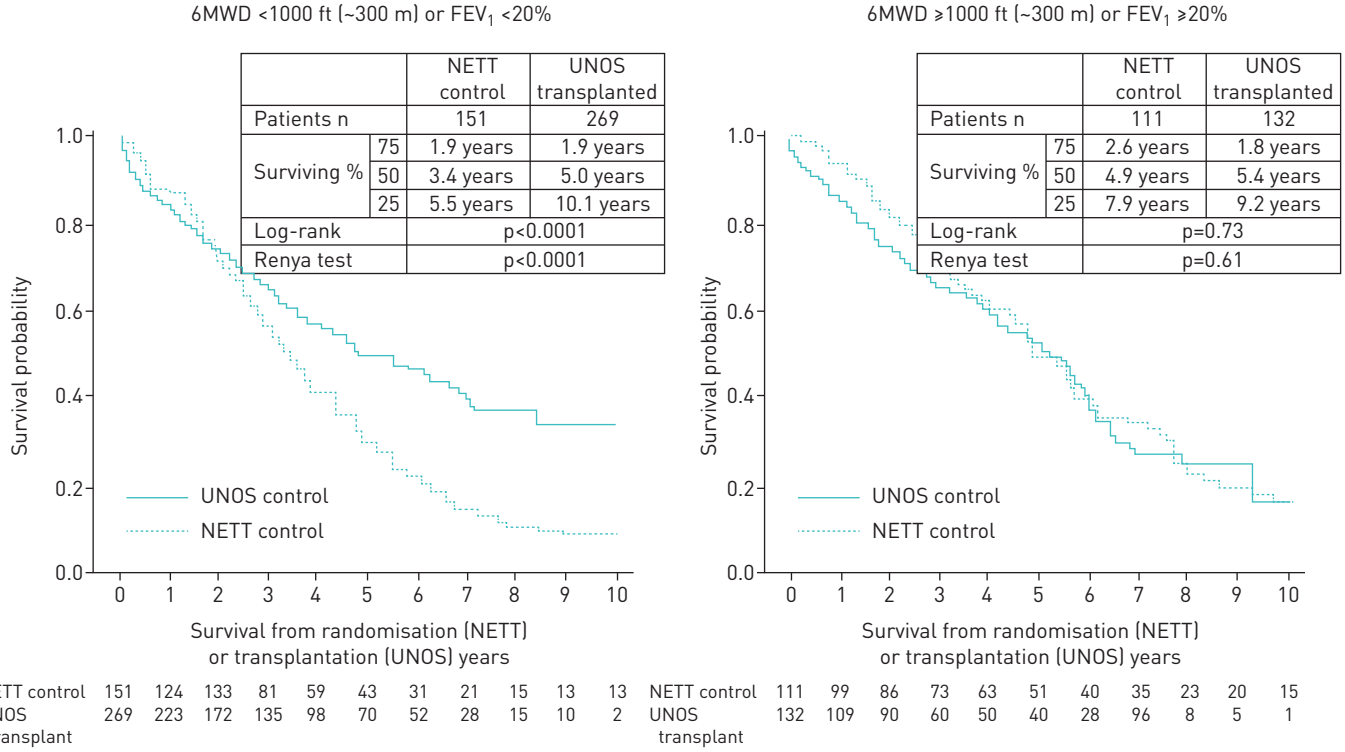
NETT control	262	226	189	154	122	94	71	56	38	33	29
UNOS transplant	401	332	252	195	148	110	80	44	23	15	3

FIGURE 2 Kaplan–Meier plot of survival curves for propensity-matched United Network for Organ Sharing (UNOS) transplant patients and National Emphysema Treatment Trial (NETT) patients.

The crossing NETT and UNOS survival curves suggest the possibility of heterogeneity in the benefit of transplant (*e.g.* a trade off of perioperative mortality against a long-term survival improvement). When we stratified patients according to disease severity as indicated by 6 MWD and FEV_1, out of the 4496 UNOS transplanted patients who had 6 MWD and FEV_1 data available, 89% (4004) were in the more severe stratum, and 11% (496) were in the less severe stratum.

Within each disease severity stratum, a Kaplan–Meier plot comparing survival between matched UNOS transplanted and NETT patients is shown in figure 3. In the more severe stratum, median (IQR) survival among the matched patients was 5.0 years (1.9–10.1 years) for UNOS transplanted patients and 3.4 years (1.9–5.5 years) for NETT patients; log-rank p<0.0001 and Renyi p<0.0001. In the less severe stratum, median survival was 5.4 years (1.8–9.2 years) for UNOS, and 4.9 years (2.6–7.9 years) for NETT; log-rank p=0.73, Renyi p=0.61. The test for heterogeneity between these two strata was significant at p=0.01.

Survival percentages at each year were calculated (fig. 3). For patients with a FEV_1 ⩽20% predicted and 6 MWD ⩽1000 ft (~300 m), a survival benefit of transplantation was apparent after 2 years, while for patients with FEV_1 >20% predicted and 6 MWD >1000 ft (~300 m), transplantation did not appear to confer a survival advantage.



Low 6MWD (<1000 ft (~300 m) or FEV_1 <20%) Survival %

Year	1	2	3	4	5	6	7	8	9	10
UNOS	85	73	66	57	50	47	39	37	34	34
NETT	87	74	56	42	30	22	15	11	9	9

High 6MWD (<1000 ft (~300 m) and FEV_1 <20%) Survival %

Year	1	2	3	4	5	6	7	8	9	10
UNOS	86	75	66	60	53	38	27	25	25	17
NETT	95	87	77	69	56	44	38	25	22	17

FIGURE 3 Kaplan–Meier plot of survival curves for propensity-matched United Network for Organ Sharing (UNOS) transplant patients and National Emphysema Treatment Trial (NETT) patients, within each disease severity stratum. FEV_1: forced expiratory volume in 1 s.

The finding of survival benefit in patients with low FEV_1 or 6 MWD undergoing lung transplantation is not unique to the <20% predicted FEV_1 and <1000 ft (~300 m) 6 MWD demarcations, as we found the benefit is even stronger among more severe patients with FEV_1 <15% predicted or <800 ft (~240 m) for the 6 MWD.

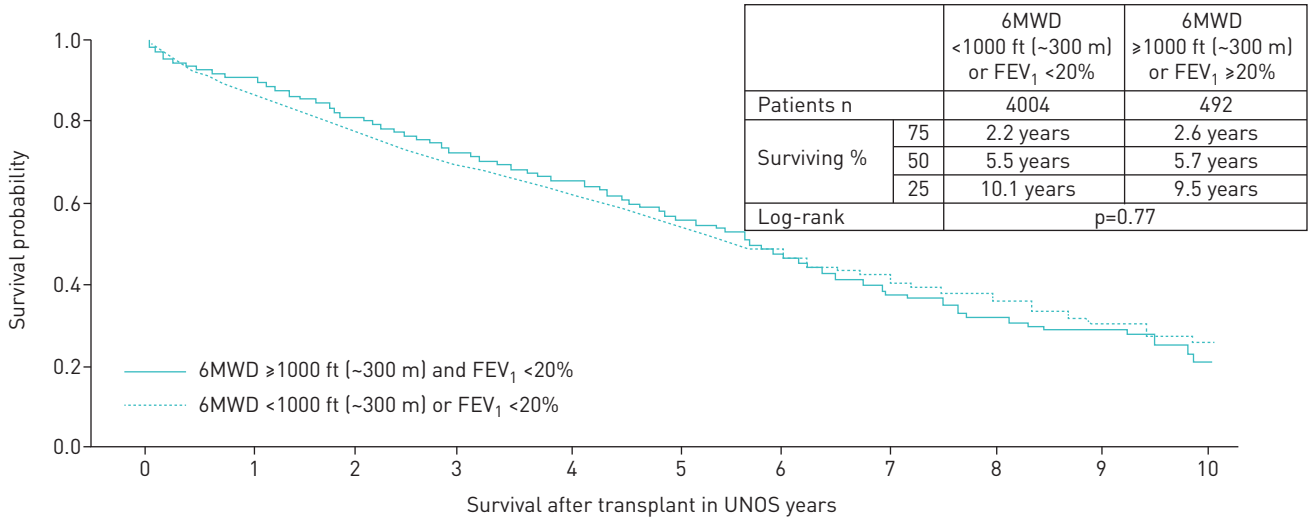
As shown in figure 4, there was little difference in post-transplant survival according to disease severity stratum. Among the 4496 transplanted UNOS patients: median survival was 5.5 years in the more severe stratum, compared with 5.7 years in the less severe stratum (p=0.77). The median (IQR) LAS differed by 1.2 units between patients in the more severe stratum (33.6 (32.6–35.4)) and the less severe stratum (32.4 (31.7–33.5)); p<0.0001. The same trend was observed within the transplanted patients who were propensity-matched to NETT patients. The median (IQR) LAS differed by only 0.5 units between transplanted patients in the more severe stratum (32.7 (31.9–33.7)) and the less severe stratum (32.2 (31.6–33.4)) indicating non-clinical significance for LAS but statistical significance; p<0.008.

Discussion

COPD is one of the most common indications for lung transplantation [1, 3], but there is a continuing controversy regarding the survival benefit of this intervention for COPD patients. Various studies have reported a clear impact on life expectancy after lung transplantation for idiopathic pulmonary fibrosis, cystic fibrosis and primary pulmonary hypertension [3, 22–25]; reports for COPD patients are inconsistent [26, 27].

A retrospective cohort study of 1997 patients transplanted in the UK demonstrated that transplantation confers survival benefit for patients with emphysema [25], results consistent with earlier European studies [23, 24]. In contrast, Hosenpud *et al.* [28], in a 1998 study reviewing the outcomes of 1274 lung transplant candidates found mortality for COPD patients on the waiting list was low; post-transplantation survival did not exceed waiting-list survival during the 2-year follow-up. Thabut *et al.* [29] in 2008 used the UNOS transplant and waitlist data to estimate the survival impact of lung transplant and reported that patients with an FEV_1 <16% of predicted will gain at least 1 year of survival after transplant. In these studies, mortality after lung transplant is compared to mortality of potential recipients with COPD on a lung transplant waiting list who are not operated or censored at the time of operation. Those analyses are subject to potential selection bias.

To clarify the survival benefit of lung transplantation for COPD patients without this selection bias, we analysed survival data from the UNOS Thoracic Registry and compared it to survival in the control group of NETT, an independent COPD population. Initially, we performed a survival comparison of all UNOS listed patients and the NETT control cohort, censoring UNOS listed patients at the time if transplantation,



		6MWD <1000 ft (~300 m) or FEV_1 <20%	6MWD ⩾1000 ft (~300 m) or FEV_1 ⩾20%
Patients n		4004	492
Surviving %	75	2.2 years	2.6 years
	50	5.5 years	5.7 years
	25	10.1 years	9.5 years
Log-rank		p=0.77	

6MWD <1000 ft (~300 m) or FEV_1 <20%	4004	2967	2353	1866	1451	1070	768	509	318	183	61
6MWD ⩾1000 ft (~300 m) and FEV_1 <20%	492	413	334	260	209	155	116	83	48	25	6

FIGURE 4 Kaplan–Meier plot comparing post-transplant survival between pre-operative disease severity strata. 6MWD: 6-min walking distance; FEV_1: forced expiratory volume in 1 s.

to establish that the two populations are comparable (5.2 years in NETT *versus* 4.7 years in UNOS). This analysis suggested that the populations of NETT and UNOS listed patients (censored at transplantation) are comparable for survival even though baseline characteristics indicated the NETT population was less severely ill; propensity score matched analysis seem reasonable.

Consistent with Hosenpud *et al.* [28], in the first 2 years following transplantation or NETT randomisation, we found a similar survival in the UNOS (74%) and NETT (77%) groups, a difference that was not statistically significant (p=0.28). Patients undergoing lung transplantation experience immediate risks related to the procedure in exchange for the possibility of relief of symptoms and survival gains. The "crossing" NETT and UNOS survival curves are difficult to interpret and suggest both the possibility of long-term benefit and heterogeneity in the benefit of transplant. Therefore, we stratified patients according to disease severity as indicated by 6 MWD and FEV_1.

Although the curves cross still for the "more severe" stratum in the stratified analysis, they are closer together. There was a survival advantage for UNOS lung transplant patients compared to NETT patients among those with "more severe" COPD, as defined by 6 MWD <1000 ft (~300 m). or FEV_1 <20% predicted. A large majority of transplanted patients in UNOS (89%) were in the "more severe" category.

Less severely affected patients (6 MWD ⩾1000 ft (~300 m) and FEV_1 ⩾20% of predicted), 11% of transplanted patients in UNOS, showed little if any increase in survival with lung transplantation. For these patients, on a case-by-case basis, there may be other clinical or functional reasons that suggest urgency of lung transplantation.

The difference in LAS scores between the "more severe" and "less severe" strata was small in spite of the clear difference in survival benefit of transplantation, suggesting that for COPD patients, the LAS score may not reflect post-transplant survival benefit. A composite index of clinical parameters able to predict post-transplant surgery survival is urgently needed.

There is a difference of a decade in the observation on NETT patients and the UNOS patients we report; but, COPD mortality and prognosis have not changed substantially in the last 3 decades. Specific therapies (like new inhalers or endobronchial valves placement) have had some impact on quality of life but none other than transplantation on survival [30].

UNOS does not contain quality of life information, and this outcome was not assessed in our study. Because UNOS does not quantify dyspnoea, we were not able to calculate the BODE (BMI, airflow obstruction, dyspnoea, exercise capacity) index for UNOS patients. However, the criteria of 6 MWD <1000 ft (~300 m) or FEV_1 <20% of predicted are consistent with the recent International Society for Heart and Lung Transplantation (ISHLT) consensus that proposes a BODE threshold⩾7, which represents a low FEV_1 and 6 MWD, for transplant listing [28].

The study has limitations associated with the retrospective nature of the UNOS data. A considerable proportion of transplanted patients had to be excluded because they did not meet the NETT inclusion criteria; *e.g.* patients with low 6 MWD (459 ft (~140 m)), severe pulmonary hypertension (>35 mmHg) or high oxygen requirements (>6 $L \cdot min^{-1}$).But our comparison in this limited population should generalise well because the more severely affected patients will almost surely benefit from surgery unless they are among the infrequent perioperative mortality cases and the less severely affected will do better than without surgery. Our results suggest that perioperative mortality is similar for the less severely affected COPD patients and the more severely affected patients who would sustain the most benefit from transplant.

Although the results could not be extended to all COPD patients listed for transplantation, our study suggests that more severe COPD cases are better candidates for lung transplantation when survival is the primary outcome measure not taking into account quality-of-life assessment. The retrospective nature of UNOS data does not allow quality-of-life assessment as this information is not recorded in UNOS database. A comparison of post-transplant survival between the more severe and less severe COPD patients indicated that post-transplant survival is similar regardless of disease severity among COPD patients, refuting the common argument that more severe patients are too high risk for transplantation with surgery increasing death risk in more ill patients. Differences in survival benefit between the disease severity strata are due to the favourable survival of less severely affected COPD patients even without transplantation treated with medical therapy and pulmonary rehabilitation according to NETT criteria. These results should be generalised with some caution because the NETT patients were selected to meet all enrollment criteria for that clinical trial.

Conclusion

We conclude that transplant surgery has a survival benefit in the more severely affected end-stage COPD patients (with 6 MWD <1000 ft (~300 m) or FEV_1 <20%), and, no appreciable benefit for the less severely

affected patients. 6 MWD and FEV_1 contributes to the clinical decision-making process for pulmonologists and thoracic surgeons evaluating end-stage COPD patients.

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