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Gait-speed and oxygen flow during six-minute walk test predicts mortality in patients with advanced lung disease

Irina Timofte[1], Adriano Tonelli[2], Montserrat Diaz-Abad[1], Avelino Verceles[1], Nicholas Ladikos[3], Aldo Iacono[4], Michael L. Terrin[5], Marniker Wijesinha[6], Olufemi Akindipe[2], Maher Baz[7]

[1]Department of Medicine, Division of Pulmonary and Critical Care, University of Maryland School of Medicine, Baltimore, MD; [2]Department of Pulmonary and Critical Care, Respiratory Institute, Cleveland Clinic, Cleveland, OH; [3]Department of Pharmacy, Johns Hopkins Medicine/Suburban Hospital, Bethesda, MD; [4]Department of Pulmonary and Critical Care, University of Maryland School of Medicine, Baltimore, MD; [5]Department of Epidemiology and Public Health, University of Maryland School of Medicine, Baltimore, MD; [6]Department of Epidemiology and Preventive Medicine, University of Maryland School of Medicine, Baltimore, MD; [7]Department of Lung Transplantation, University of Kentucky, Lexington, KY, USA States

Abstract

The six-minute walk test (6MWT) is a useful tool to predict outcomes in patients with advanced lung diseases. Greater distance walked has been shown to have independent prognostic value. We reviewed the medical records of 164 patients with advanced lung disease who underwent lung transplant evaluation. Results of the 6MWT (distance walked, oxygen required to maintain oxygen saturation >90%, and gait speed) were recorded and analyzed with respect to mortality. 6MWT mean oxygen (O_2) flow *via* nasal cannula was 3.5±3.7 l/min. The distance walked in meters (m) and percent predicted distance were inversely associated with mortality, hazard ratio (HR): 0.995 per meter (95% CI 0.992-0.998) for walk distance in meters and 0.970 per % predicted distance (95% CI 0.950-0.990). Patients who walked <200 meters [HR: 2.1 (95% CI 1.1-4.0)] or <45% of predicted, HR: 2.7 (95% CI 1.2-5.7) had higher mortality. O_2 flow during the test had a direct association with mortality (HR: 1.1 per L/min (95% CI 1.0-1.2). In multivariate analysis, O_2 flow >3.5 L/min remained predictive of mortality, HR: 1.1 per l/min (95% CI 1.0-1.2). Gait speed was higher in patients who survived through follow-up compared to patients who died (mean 0.83±0.35 m/s *vs* 0.69±0.33 m/s, p=0.03). Gait speed >0.8 m/s was a predictor of survival, HR 3.4 (1.1, 10.6). In summary, distance walked and O_2 flow during the 6MWT were predictors of mortality in patients with advanced lung disease. Patients who required more than 3.5 l/m of O_2 to maintain oxygen saturation >90% had a higher mortality. Faster gait speed during the 6MWT was also associated with better survival.

Correspondence: Irina Timofte, Department of Medicine, Division of Pulmonary and Critical Care, University of Maryland School of Medicine, 110 South Paca Street, 2nd Floor, Baltimore, MD 21201, USA.
Tel. +1.410.328 2864 - Fax: +1.443.462 3045.
E-mail: Irtimofte@SOM.umaryland.edu

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Introduction

The six-minute walk test (6MWT) is a simple functional test used in clinical practice and research for the assessment of exercise capacity in patients with moderate-to-severe cardiopulmonary disease. Since first being introduced by Butland in 1982 [1], this test has been particularly useful in assessing patients with chronic obstructive pulmonary disease (COPD) [2-4], pulmonary hypertension [5], interstitial lung disease [6], cystic fibrosis [7] and post-acute respiratory distress syndrome [8]. Lung transplantation is a therapeutic option for a broad spectrum of chronic, incapacitating pulmonary disease. The distance walked during the 6MWT is an important factor in guiding decisions about the time for lung transplant listing. More than three decades ago, Kadikar *et al.* showed that a 6MWT distance <400 meters was valuable in listing for lung transplantation [9]. Subsequently, the

6MWT distance was incorporated in the calculation of the lung allocation score [10]. But, there are few disease-specific predictors to guide listing [11].

In patients with chronic lung diseases gait speeds reflect the overall level of impairment and offers an integrated index of physical activity. There are limited data regarding the importance of gait speed and oxygenation saturation during 6MWT in lung transplant evaluation.

We hypothesized that 6MWT walked distance, gait speed, and/or oxygen flow requirements are prognostic for patients with advanced lung disease evaluated for lung transplantation. The purpose of the study is to assess these in predicting mortality among advanced lung disease patients.

Materials and Methods

This study was a retrospective review of the records of 164 patients who underwent lung transplant evaluation at the University of Florida between March 2001 and November 2008. Lung transplant evaluation consisted of history, physical examination, laboratory testing, chest X-ray imaging, pulmonary function tests, 6MWT, electrocardiogram, right heart catheterization and interviews with social and psychology services. We searched the U.S. Social Security Death Index for vital status outcomes. This study was approved by the University of Florida IRB.

Six-minute walk test

We recorded the data from each subject first, 6MWT performed as part of the initial lung transplant evaluation according to the American Thoracic Society guidelines [12]. The tests were supervised by respiratory therapists with patients on the same supplemental oxygen as the patients were using at home unless the baseline pulse oximetry (SpO_2) measurement was <90 %, for which oxygen flow was increased by 1 l/min every min until SpO_2 ≥90% was achieved.

Patients were instructed to walk the corridor from one end to the other, as many laps as comfortable within the permitted time. Tests were stopped at six min or earlier for chest pain, intolerable dyspnea, gait instability, or other signs of severe distress [12]. In addition to the total distance walked, the oxygen flow required to keep a SpO_2 ≥90% was recorded. Before, during and immediately after the test, heart rate, blood pressure, SpO_2 and Borg dyspnea scale were documented. Blood pressure was measured using an automated blood pressure monitor; heart rate was determined by a reliable waveform on pulse oximeter. The following formulas were used to predict walk distance for a calculation of percentage of predicted; for men, $6MWD = (7.57 \times height_{cm}) - (5.02 \times age) - (1.76 \times weight_{kg}) - 309$ m; and for women, $6MWD = (2.11 \times height_{cm}) - (2.29 \times weight_{kg}) - (5.78 \times age) - 667$ m [9].

Gait speed

The gait speed data were obtained from the data measured during the 6MWT. Gait speed was calculated for each participant using total distance (m) walked divided by total time walked in seconds.

Outcome variables

The outcome is mortality. Data regarding lung transplant listing, transplantation, and survival were obtained from a lung transplant database maintained by the institution and medical records. The U.S. Social Security Death Index [13] was queried when needed to confirm decease.

Statistical analysis

Continuous data are reported as mean ± standard deviation (SD). Chi-square and Student's *t*-test were used to compare categorical and continuous variables, respectively. Survival from the date of 6MWT was analyzed, censored at the time of transplant and was analyzed according to the method of Kaplan-Meier. Survivors, awaiting lung transplantation, were censored at the end of the study (03/13/2009). Univariate analysis was performed and multivariate analyses adjusted for age, gender and underlying disease (obstructive versus restrictive) were performed using Cox regression and expressed as hazard ratio (HR) with 95% confidence interval (CI). 6MWT distances were assessed as discriminator values using receiver operating characteristic (ROC) curves, with mortality as the dependent variable. Similar ROC analyses were performed for gait speed and oxygen flow used during the 6MWT. Maximum follow-up time was 8 years. All p values reported are two tailed. A p-value ≤0.05 was considered significant. The analyses were performed using the statistical packages SPSS, version 17 (SPSS Inc., Chicago, IL, USA) and SAS Software, version 9.4.

Results

Patient's initial characteristics

A total of 164 patients underwent lung transplant evaluation, age 51.8±0.9 years and 58% women. Underlying diagnoses included COPD (33%), idiopathic pulmonary fibrosis (22%), cystic fibrosis (11%), pulmonary fibrosis related to connective tissue disease (11%), sarcoidosis (7%), alpha-1 antitrypsin deficiency (6%), pulmonary arterial hypertension (4%), and others (6%). Most patients had airflow obstruction (54%) on spirometry. Right heart catheterization revealed mean pulmonary artery pressure 29.4±19.7 mm Hg, cardiac output 4.97±1.3 (l/min). Patient characteristics are presented in Table 1.

6MWT results

During the 6MWT a mean of 3.5±3.7 l/min of O_2 flow was required by the cohort to complete the test. The average 6MWD was 261±123 m, 44±21 % of predicted. Even with increasing O_2 flow, mean SpO_2 dropped 6.8±5.6 % from the beginning to the end of evaluation and heart rate increased 21±13 bpm during the test (Table 1).

6MWT parameters and survival

Survival probability (transplantation censored) from the time of initial 6MWT was 89% and 59% at one and five years, respectively. The distance walked and percent of predicted distance were associated inversely with mortality - HR: 0.995 per meter (95% CI 0.992-0.998) for walk distance in meters and 0.970 per % predicted distance (5% CI 0.950-0.990). Mortality was increased for patients who walked <200 m (HR: 2.1, 95% CI: 1.1-4.0) or <45% of predicted walk distance (HR: 2.7, 95% CI: 1.2-5.7). The distance walked was analyzed by receiver operating characteristic (ROC) (Figure 1). The area under the curve was 0.7 (95% CI 0.6-0.8, p=0.001). The O_2 flow (l/min) during the test had a direct association with mortality (HR: 1.1 for O_2 flow per l/min (95% CI 1.02-1.20)). The area under the curve (Figure 2) for the oxygen flow was 0.6 per l/min (95% CI 0.99-1.19, p=0.06). There was no association between the difference in heart rate or SpO_2 before and at the end of exercise and mortality. In multivariate analysis only the O_2 flow predicted mortality (HR: 1.1 for O_2 flow per l/min; 95% CI: 1.01-1.2). Patients who required >3.5 O_2 l/min had a higher one year and five-year mortality.

Gait speed results

Mean gait speed was 0.79 m/sec (SD 0.34). Details regarding gait speed are presented in Table 2. The histogram comparing the distribution of gait speed in patients who survived with patients who did not survived is presented in Figure 3 (p=0.01). Survival was associated with faster gait speed (mean 0.8±0.35 m/s *vs* 0.7±0.33 m/sec; p=0.03). The area under the curve for

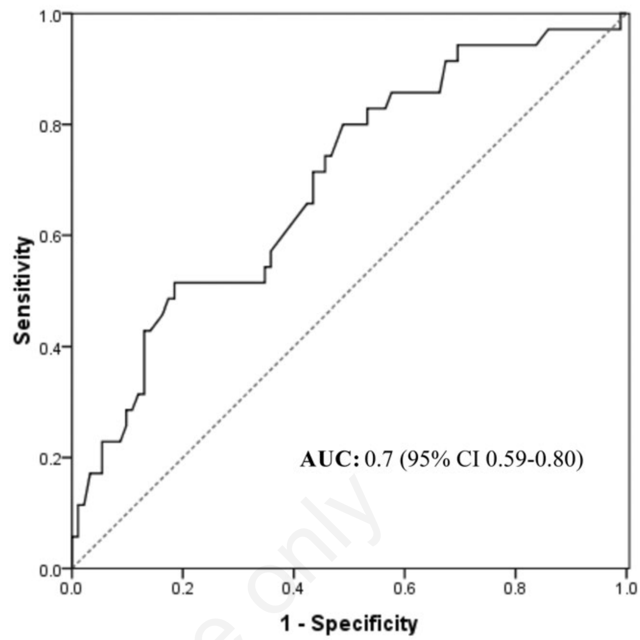

Figure 1. 6MWT distance Receiver operating characteristic (ROC) curve with mortality as outcome. AUC, area under the curve; CI, confidence interval.

Table 1. Patient characteristics at baseline.

		All patients n=164	O_2 in l/m O_2<=3.5 l n=94	O_2>3.5 l n=68	p-value	Gait speed Slow gait speed n=87	Fast gait speed n=77	p-value
Demographics								
Age, years	Mean (SD)	52(11.9)	50 (13)	54 (9)	0.05	54 (10.3)	50(13.4)	0.04
Gender	Female (%)	94 (57%)	50 (53%)	44 (65%)	0.14	50 (57%)	44 (57%)	0.96
Pulmonary function and six-minute walk test								
Forced vital capacity percent of predicted	Mean (SD)	46(14)	46(13)	46 (15)	0.92	47 (14)	46 (13)	0.69
Forced expiratory volume percent of predicted	Mean (SD)	35(19)	33(18)	38(20)	0.15	32 (19)	39(19)	0.013
Total lung capacity	Mean (SD)	90(43)	97(44)	81(37)	0.02	100.2 (44)	78(38)	0.014
Diffusion capacity for carbon monoxide	Mean (SD)	32 (19)	34(20)	29(14)	0.1	27 (15)	39(20)	<0.001
6-minute walk distance, meter	Mean (SD)	263 (123)	283 (132)	231 (102)	0.005	181 (74)	356 (100)	<0.001
6MWD <200 meter	Nr (%)	65(40%)	34 (36%)	31 (45%)	0.22	57 (66%)	8 (10%)	<0.001
Cardiac output, l/min	Mean (SD)	4.9 (1.3)	5.0 (1.2)	4.9(1.4)	0.41	4.8 (1.1)	5.1(1.4)	0.17
Mean pulmonary Artery pressure mmhg	Mean (SD)	20 (1)	27 (8)	32 (12)	0.02	30 (10)	28(9.5)	0.14
Ejection fraction	Mean (SD)	57 (8.5)	58(6.8)	57(10.3)	0.34	57 (8.7)	58(8.2)	0.8
Transplant characteristics								
Underlying disease (obstructive *vs* restrictive)	Obstructive (%)	88(53%)	57 (60%)	31(45%)	0.27	55 (63%)	34(38%)	0.014
Patient underwent transplant	Transplanted (%)	48(29%)	31 (%33)	17(25%)	0.27	22 (25%)	27(35%)	0.17
Patient died before transplant	Died (%)	31(19%)	15 (16%)	16(24%)	0.22	22 (25%)	9(12%)	0.026
Type of lung transplant								
	Single (%)	23(14%)	18 (58%)	5(29%)	0.06	8 (36%)	15 (64%)	0.11
	Double (%)	25(15%)	13 (42%)	12(70%)		14(63%)	11 (41%)	

dichotomized gait speed receiver operating characteristics (Figure 4) was 0.65 (95% CI 0.052-0.68, p=0.01).

Patient's outcomes

Twenty-nine (29) % of patients underwent lung transplantation of which 23 (14%) underwent single and 25 (15%) underwent double lung transplantation; 19% of patients died before lung transplantation.

The Kaplan-Meier plot displaying the survival censoring transplant for the full cohort is shown in Figure 5. The estimated survival at 5 years was 56% for the overall cohort. A Kaplan-Meier plot comparing the survival censoring transplant between the patients with fast gait speed (>0.8 m/min) and slow gait speed (≤ 0.8 m/min) is shown in Figure 6, at 5 years 65% in the fast gait speed and 49 % in the slow gait speed group.

Discussion

In the present study of patients with heterogeneous advanced lung diseases evaluated for lung transplantation, we found that the amount of oxygen required to maintain SpO_2 ≥90%, distance walked during 6MWT, and gait speed were associated with mortality. A distance of <200 m predicted increased mortality. In multivariate analysis baseline O_2 flow (>3.5 L/min) to maintain O_2 saturation >90% was an independent predictor of mortality.

Since the first successful human lung transplant in 1983, there have been increasing numbers of lung transplants performed every year. However, the list of potential candidates for lung transplantation exceeds the number of donors. Also, there is a critical balance between transplanting patients too early or too late. In an effort to direct lung transplantation to more urgently ill patients, the lung allocation score (LAS) system was implemented in 2005 and dramatically altered the way in which donor lungs were allocated in the United States. There has been a decrease in mortality on the wait list since 2005 [11,14,15].

Previous studies showed that 6MWD is an independent predictor of all-cause as well as pulmonary-related mortality. COPD patients who walked <300 m had a significantly greater mortality rate [16]. In patients with idiopathic pulmonary arterial hypertension (IPAH), 6MWD <300 m was associated with increased mortality [17]. In patients with idiopathic pulmonary fibrosis, 6MWD <200 m was associated with mortality [18], results similar to our study. Castleberry *et al*. reported the association between the 6MWD and survival after lung transplantation [19]. In his study, 6MWD is significantly associated with post-transplant survival,

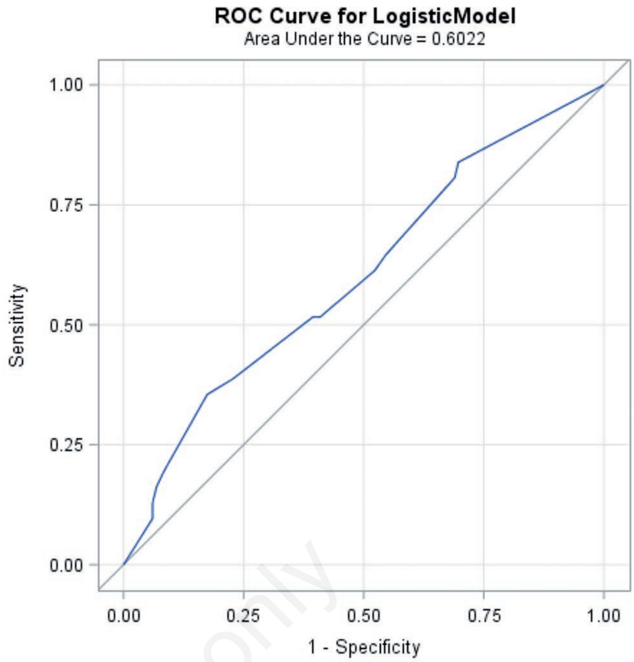

Figure 2. Receiver operating characteristic (ROC) curve for oxygen flow with mortality as outcome.

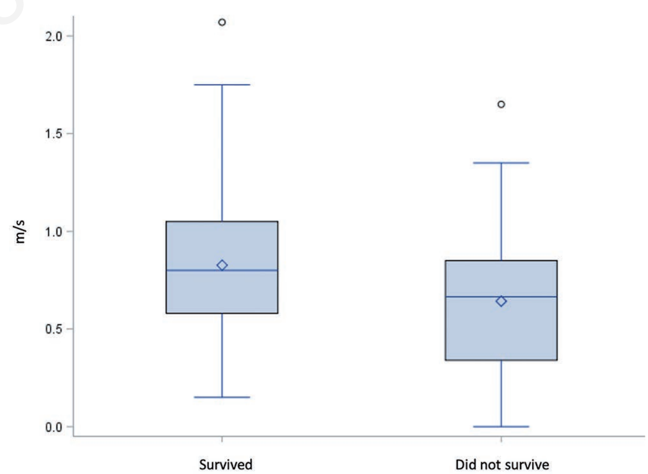

Figure 3. Box and whisker plot comparing the distribution of gait speeds in patients who survived with patients who did not survive.

Table 2. Gait speed characteristics.

		All patients n=164	Slow gait speed n=87	Fast gait speed n=77
Gait speed	Mean (SD)	0.79(0.34)	0.54(0.17)	1.08(0.22)
Outcomes				
Patient underwent transplant	Transplanted (%)	48 (29%)	22 (25%)	27 (35%)
Patient died before transplant	Died (%)	31 (19%)	22 (25%)	9 (12%)

and increasing 6MWD was associated with significantly lower overall hazard of death.

In the present study we also have shown that the maximum O_2 flow used during the 6MWT had a significant association with mortality. Patients who required >3.5 O_2 l/min to maintain O_2 saturation>90%, had reduced 1-year and the 5-year survival. Although mortality is related to use of oxygen therapy in patients with COPD [4], for patients with sarcoidosis awaiting lung transplantation [20] or patients with idiopathic pulmonary fibrosis complicated by pulmonary arterial hypertension [21], no specific cut off for O_2 flow is documented in the literature. The prognostic value of O_2 flow during 6MWT to maintain O_2 saturation >90% is a new predictor of mortality in patients with advanced lung disease undergoing lung transplant evaluation.

A recent article demonstrated that gait speed is independently associated with 6MWD in patients with severe chronic lung disease [22]. For COPD patients, gait speed had a strong correlation with pulmonary function, functional capacity, and health-related quality of life [23-25]. Though gait speed has been shown to predict survival in older adults [26], the association between gait speed and survival in patients with severe lung disease evaluated for lung transplantation has not been thoroughly evaluated. Our study demonstrates that gait speed predicts mortality in patients with advanced lung disease.

We are interested in gait speed because it is a simple method for patient testing, largely independent of time and setting. Our study shows that faster gait speed is associated with better survival and could substitute for the 6MWT.

The study has limitations associated with the retrospective nature of our database. Data regarding dyspnea and muscle fatigue at the end of the test are not included in our database; therefore, those outcomes were not analyzed. Although a previous study showed that decreases in SpO_2 during exercise has prognostic value [18], our design did not allow us to demonstrate an association between the change in SpO_2 before and at the end of exercise and mortality. A relatively small sample size in a single center cohort limits our generalizability.

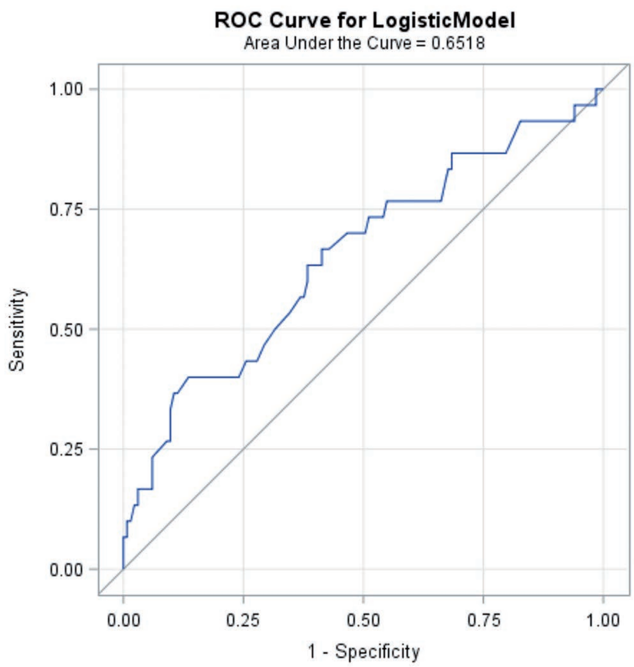

Figure 4. Receiver operating characteristic (ROC) curve for gait speed >0.8 m/s with mortality as outcome.

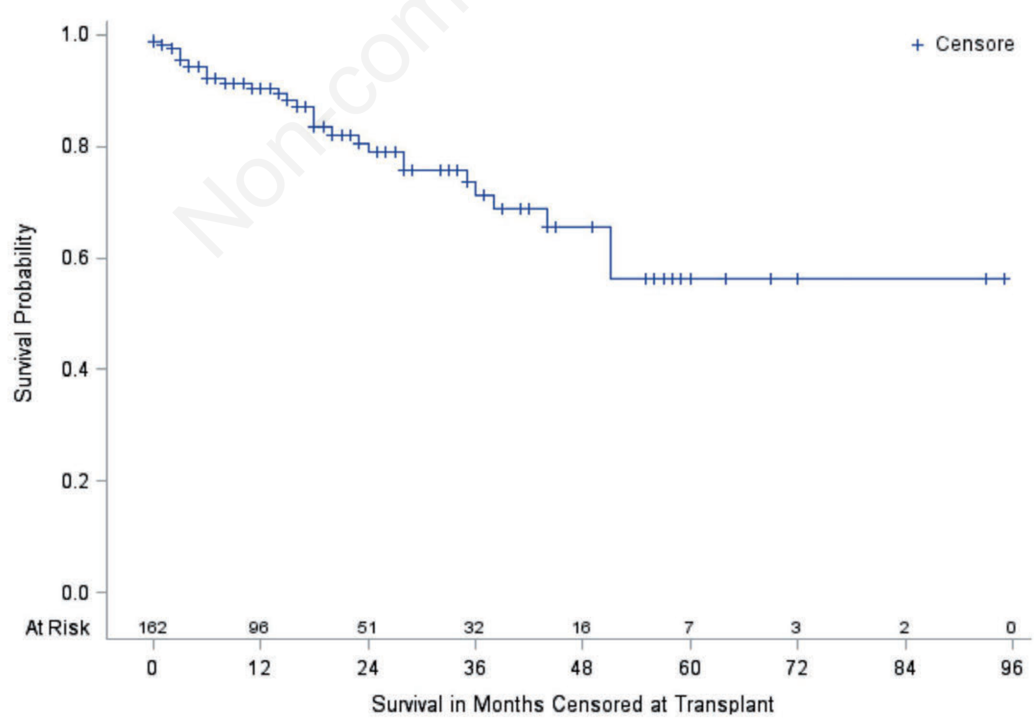

Figure 5. Survival for cohort censored at transplant.

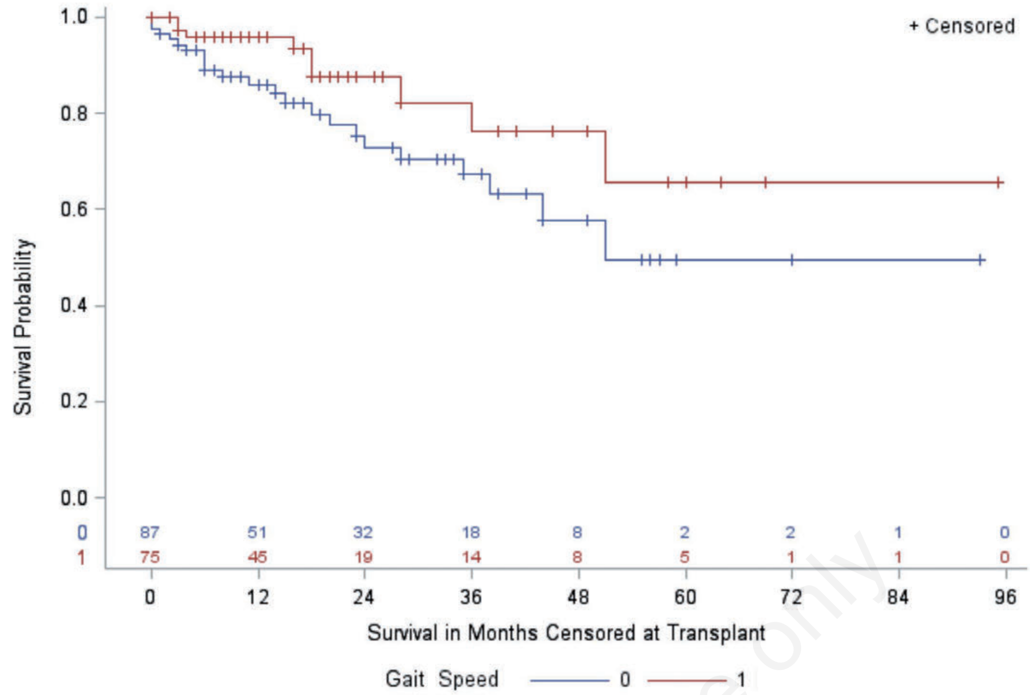

Figure 6. Transplant-free survival comparing patients with fast gate speed (>0.8 m/min) and slow gait speed (≤0.8 m/min).

Conclusions

Our study showed that oxygen flow to maintain O_2 saturation >90% during a 6MWT predicted mortality in a cohort of advanced lung disease patients evaluated for lung transplantation and may be valuable for predicting wait list mortality. Faster gait speed is associated with better survival.

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