Supplemental Material

Frailty after lung transplantation is associated with impaired health-related quality of life and mortality

Aida Venado MD MAS[1]*, Nicholas A. Kolaitis MD[1]*, Chiung-Yu Huang PhD[2], Ying Gao MS[1], David Glidden, PhD[2,] Allison Soong, MPH[1], Nicole Sutter, MPH[1], Patricia P. Katz PhD[1], John R. Greenland MD PhD[1,3], Daniel R. Calabrese, MD[1], Steven R. Hays MD[1], Jeffrey Golden, MD[1], Rupal J. Shah MD MSCE[1], MS, Lorriana E. Leard MD[1], Jasleen Kukreja MD MPH[4], Tobias Deuse MD[4], Paul J. Wolters, MD[1], Kenneth Covinsky MD MPH[1], Paul D. Blanc MD PhD[1], Jonathan P. Singer MD MS[1].

*Authors contributed equally

Methods

Clinical care protocol

All participants received a standardized immunosuppression regimen at our institution. Induction with basiliximab was administered intraoperatively and on post-operative day (POD)4.

Methylprednisolone was administered intraoperatively and in the first two days after transplant. Thereafter, prednisone was administered at a dose of 20mg daily during the first three months after transplant. Then, prednisone was gradually tapered over the four to twelve months after transplant to a maintenance dose of 0.1mg/kg.

A two-week steroid pulse with taper was used to treat both acute cellular rejection and infections with community-acquired respiratory viruses (CARV); methylprednisolone 500mg daily weaned down to prednisone 20mg daily for the former, and prednisone 60mg daily weaned down to 20mg daily for the latter. Then, patients resumed their previous prednisone dose.

Tacrolimus was started on POD1 and continued indefinitely after transplant with dose adjustments based on trough levels. The targeted tacrolimus trough levels decreased gradually, being 10-14 ng/ml, 10-12 ng/ml, 8-10 ng/ml, and 6-8 ng/ml, at 0-, 3-, 6-, and 12-months post-transplant, respectively.

Mycophenolate mofetil, 1000mg twice daily, was started on the day of transplant and continued indefinitely.

Everolimus or sirolimus was added in select cases of recurrent acute cellular rejection or development of chronic lung allograft dysfunction (CLAD) at the discretion of treating clinicians, or, in rare cases, replaced tacrolimus when patients developed chronic kidney disease.

Outcome variables

Health Related Quality of Life: HRQL is multidimensional by definition. HRQL instruments each assess a discrete set of conceptual health domains[1,2]. Furthermore, different disease states impact an individual person's HRQL in different ways. Since many different conceptual health domains may be important to lung transplant recipients, we leveraged multiple instruments to provide a more comprehensive assessment of HRQL. We evaluated HRQL across several conceptual health domains, including domains addressed by generic, respiratory-specific, and health-utility instruments. We assessed generic HRQL by the Medical Outcomes Survey Short Form-12 version 2 (SF12). We assessed respiratory-specific HRQL using the Airways Questionnaire 20-Revised (AQ20-R). In order to assess health-utility, we utilized the Euroqol 5D 3L (EQ5D).

The Medical Outcomes Survey Short Form-12 version 2 is a 12-item generic HRQL instrument, which was adapted from the longer Short Form-36. There are two summary scores in the SF12, a physical component score (SF12-PCS) and a mental component score (SF12-MCS). The SF12 instrument reproduces at least 90% of the variance of the Short Form-36. Both the SF12-PCS and the SF12-MCS range between 0-100 with a population mean of 50 and standard deviation of 10. Higher scores denote better HRQL. The SF12-PCS and SF12-MCS have a minimally important difference (MID) of 5[3,4].

The AQ20-R is a respiratory-specific HRQL instrument. The range of scores is 0-20 with higher scores indicating worse HRQL. We reverse coded the AQ20-R for the purpose of our analysis such that higher scores denote better HRQL across all instruments. There is no established MID for the AQ20-R, as such, we used one-half of the standard deviation (1.75) as a distribution based MID[5,6].

The EQ5D is a 5-item health-utility instrument. It ranges from -0.11 to 1. Higher scores reflect better health utility. A score less than zero reflects a health-utility is “worse than death”. The MID for EQ5D is 0.06[7].

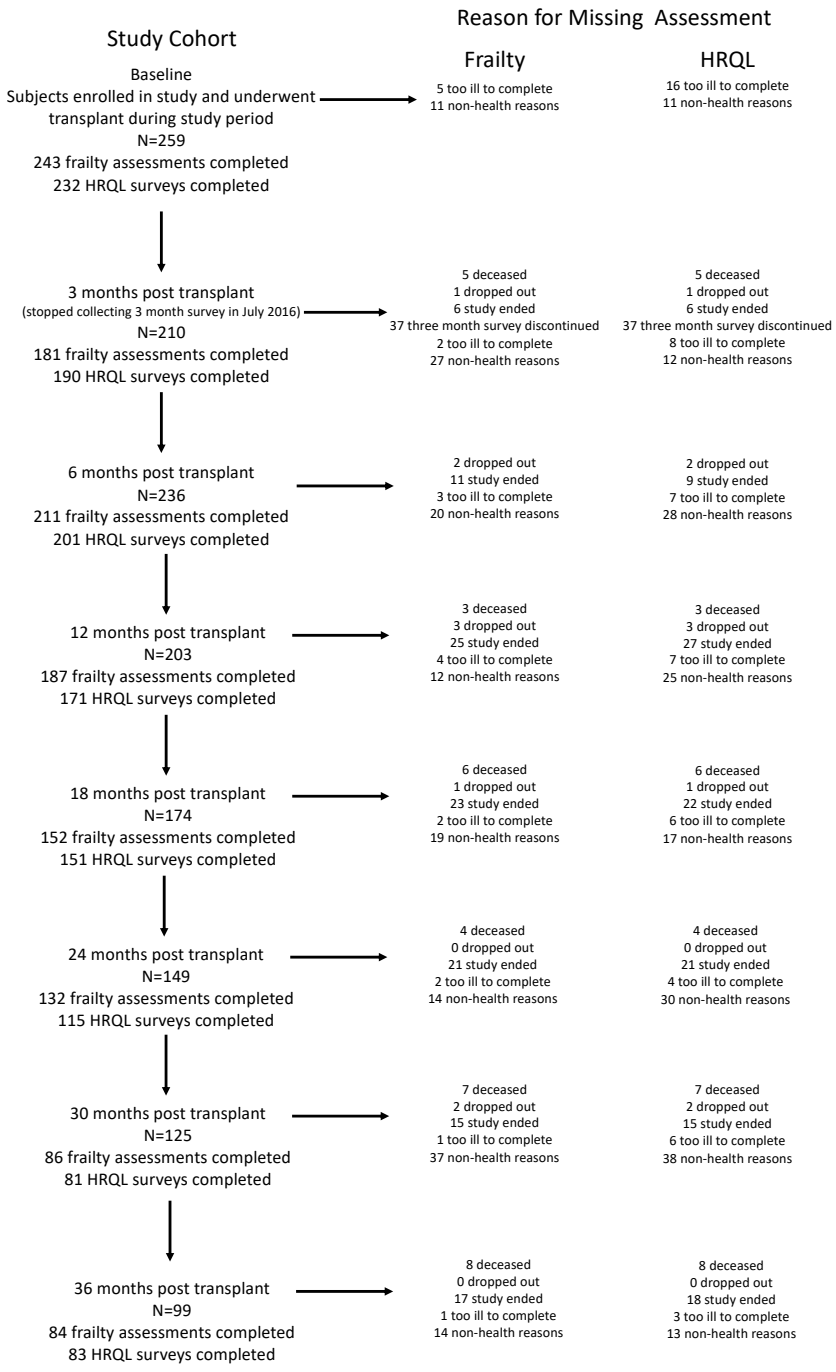

Figure 1: Consort diagram of subjects throughout the study.

The left column presents the number of participants providing data for analysis at each time point. The number of subjects at the 3-month post-transplant time point was less than 6-month time point, because the 3-month study visit was dropped after July, 2016. The right two columns detail the reasons for missing frailty or health-related quality of life (HRQL) assessments at each time point.

Table 1. Number of patients with at least one-point worsening in SPPB

Visit of evaluation	Compared with	Number of patients with at least one-point worsening in SPPB
3-month post-transplant	pre-transplant baseline	49
6-month post-transplant	3-month post-transplant	26
12-month post-transplant	6-month post-transplant	41
18-month post-transplant	12-month post-transplant	27
24-month post-transplant	18-month post-transplant	27
30-month post-transplant	24-month post-transplant	14
36-month post-transplant	30-month post-transplant	8
Total number of participants with at least one-point worsening of SPPB		129 (50% of cohort)
Note: missing data in SPPB were not imputed. The calculation of following numbers required non-missing SPPB at two continuous visits.		

The Short Physical Performance Battery (SPPB) ranges from 0 to 12, (minimal important difference = 1); lower scores denote worse frailty.

Table 2. Association of frailty (SPPB ≤9) as a time-dependent predictor with HRQL in lung transplantation

Predictor	Instrument	Instrument Type	Difference	95% CI	p-value
Frailty (SPPB ≤9)	SF12-PCS (MID=5)	Generic-Physical	-6.08	(-7.68, -4.47)	<0.01
	SF12-MCS (MID=5)	Generic-Mental	-1.22	(-2.68, 0.23)	0.10
	AQ20-R (MID=1.75)	Respiratory-Specific	-0.95	(-1.45, -0.44)	<0.01
	EQ5D (MID=0.06)	Health-Utility	-0.06	(-0.09, -0.04)	<0.01

Instruments: Short Physical Performance Battery (SPPB), range from 0 to 12; Short Form 12–Physical Component Score (SF12-PCS), range 0 to 100; Short Form 12–Mental Component Score (SF12-MCS), range 0 to 100; Airways Questionnaire 20–Revised (AQ20-R), range 0 to 20, which was reverse-coded for analysis; EuroQoL 5D (EQ5D), range -1.11 to 1, which measures health utility. Minimally important difference (MID). The association between frailty and HRQL was quantified by linear mixed-effects models considering frailty as a time-dependent predictor variable. All models were adjusted for pre-operative age, sex, race, diagnosis, as well as for BMI and FEV1 measured at each study visit.
Data are presented as mean effect estimates with 95% confidence intervals.

Table 3. Causes of death up to 48 months after lung transplant

Cause of death	Number of deaths
Chronic rejection	20
Acute Lung Injury	5
Other infection	4
Cancer	4
Pneumonia	3
Sepsis	3
Congestive Heart Failure	2
Pulmonary embolus	1
Renal Failure	1
Unknown Cause of Death	3

Cause of death occurring within the first 48 months after transplantation.

Table 4. Association of frailty, defined as SPPB ≤ 9, with 4-year mortality after lung transplant

Model	Time-dependent predictor from baseline to 36 months post-transplant	Baseline			
		Pre-transplant	3-months Post-transplant	6-months Post-transplant	12-months Post-transplant
Unadjusted	Frailty	4.26 (2.23, 8.15)	4.06 (2.06, 7.98)	3.83 (1.91, 7.68)	4.62 (2.27, 9.39)
Adjusted	Frailty	2.87 (1.53, 5.40)	2.60 (1.33, 5.07)	2.51 (1.27, 4.96)	3.13 (1.53, 6.42)

The Short Physical Performance Battery (SPPB) ranges from 0 to 12, (minimal important difference = 1); lower scores denote worse frailty. Frailty was defined as SPPB ≤ 9. Mortality risk was estimated by Cox's proportional hazards models with SPPB as a time-dependent predictor, including all SPPB measurements a participant had from baseline to 36 months post-transplant. Results when setting the baseline SPPB at different time points are shown side by side for comparison. All SPPB values before the specified baseline are excluded from the models. The number of participants alive at each of the baseline points is indicated. Models were adjusted for pre-operative age, sex, race, diagnosis, and BMI and FEV1 measured at each visit. Results represent hazard ratio for death with 95% confidence intervals noted in parenthesis.

Table 5. The association of muscle function, body composition, and malnutrition after transplantation with the development of frailty (SPPB ≤9) in lung transplant recipients

Model	Time-dependent predictor*		Odds Ratio frail versus not frail (95% CI)
1	Sarcopenia Component	Per 1.0 kg decrease in grip strength	1.24 (1.16, 1.32)
2		Weak grip ¶	6.66 (3.62, 12.25)
3	Body Composition	Underweight (BMI <18.5 kg/m^2)	6.55 (1.66, 25.90)
		Obesity (BMI ≥ 30 kg/m^2)	1.37 (0.72, 2.61)
4	Malnutrition	Per 1.0 g/dl decrease in albumin	3.19 (2.05, 4.96)
5		Albumin nadir <3.5 g/dl ¶	3.93 (2.20, 7.00)
6	Renal dysfunction	Per 10-ml/min/1.73m^2 decrease in eGFR	1.36 (1.18, 1.57)
7		CKD Stage 3 versus Stage 1 or 2	1.63 (0.88, 3.05)
		CKD Stage 4 or 5 versus Stage 1 or 2	4.82 (2.18, 10.6)

*Generalized linear mixed effects model with sarcopenia, body composition, malnutrition, and renal dysfunction as a time-dependent predictors and frailty as the "lagged" outcome.
Measures of frailty were obtained at study visits at 3-, 6-, 12-, 18-, 24-, 30-, and 36-months after lung transplantation. Measures of body composition, sarcopenia, nutrition, and renal function in the 3-6-month time period preceding each study visit were collected and used as time-dependent predictors of the subsequent, or "lagged" outcome of frailty.
Frailty was quantified using the Short Physical Performance Battery (SPPB), which ranges from 0-12 (minimal important difference = 1); lower scores denote worse frailty. Frailty was defined as a continuous measure and as a binary outcome (frail = SPPB ≤9).
Body composition was determined by the most extreme body mass index (BMI) in the interval prior to visit. Underweight and obesity were compared to a reference BMI of 18.5 to <30 kg/m^2.
Grip strength was used as a proxy for sarcopenia. A weak grip was defined as proposed by the European Working Group on Sarcopenia in Older People[8].
Malnutrition determined by the lowest serum albumin in the interval prior to visit, both as a continuous and a binary predictor.
Measures of renal function were calculated as the lowest estimated glomerular filtration rate (eGFR) and the worst chronic kidney disease stage in the time period preceding each study visit. eGFR calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[10].
Models 1-5 were adjusted for study visit, age, sex, and race. Models 6 and 7 were adjusted for study visit.
Results represent the effect of sarcopenia, body composition, malnutrition, and renal dysfunction on SPPB score and odds ratio for frailty; 95% confidence intervals are noted in parenthesis.
¶ Denotes that predictor is binary

Table 6. The association of immunosuppression after transplantation with the development of frailty in lung recipients

Time-dependent predictor*	Change in SPPB frailty (95% CI)	Odds Ratio frail versus not frail (95% CI) Frail=SPPB ≤7	Odds Ratio frail versus not frail (95% CI) Frail=SPPB ≤9
1 ng/ml increase in trough tacrolimus level	0.02 (-0.04, 0.09)	0.88 (0.70, 1.10)	0.95 (0.84, 1.08)
Use of prednisone pulse and taper ¶	-0.51 (-1.23, 0.22)	1.90 (0.18, 19.64)	1.94 (0.60, 6.29)

*Generalized linear mixed effects model with immunosuppression as a time-dependent predictor and frailty as the "lagged" outcome. Analytically, measures of frailty were obtained at study visits at 3-, 6-, 12-, 18-, 24-, 30-, and 36-months after lung transplantation. Measures of immunosuppression in the 3-6-month time period preceding each study visit were collected and used as to develop our time-dependent predictors of the subsequent, or "lagged" outcome. Frailty was quantified using the Short Physical Performance Battery (SPPB), which ranges from 0 to 12, (minimal important difference = 1); lower scores denote worse frailty. Frailty was defined a continuous measure, and as a binary outcome with two different cut points (frail = SPPB ≤7) and (frail = SPPB ≤9). Predictor of tacrolimus immunosuppression was the average daily tacrolimus trough participants were exposed to in the interval prior to visit. Predictor of prednisone immunosuppression quantified by use of a prednisone pulse and taper in the interval prior to visit. Pulses of prednisone are typically employed for episodes of acute rejection or community acquired upper respiratory viral infections. Models were adjusted for study visit, age, sex, and race. Results with SPPB as a binary outcome represent odds ratio for frailty with 95% confidence intervals noted in parenthesis. Results with SPPB as a continuous measure represent the effect of immunosuppression on SPPB score with 95% confidence intervals noted in parenthesis.

¶ Denotes that predictor is binary

Table 7. Association of pre-operative characteristics with frailty six months after lung transplant

	Odds ratio for being frail six months after transplant (95% CI)		P value
Univariate analysis			
Frail pre-transplant	3.54	(1.15, 10.90)	0.03
Female sex	3.70	(1.14, 12.02)	0.03
Age at transplant (per 1-year older)	1.00	(0.96, 1.05)	0.95
Diagnosis			
COPD vs ILD	3.21	(0.98, 10.55)	0.05
PH vs ILD	2.25	(0.25, 20.25)	0.47
CF vs ILD	1.06	(0.12, 8.99)	0.96
LAS at transplant (per 1-point increase)	0.98	(0.95, 1.01)	0.16
Non-white vs white race	1.29	(0.42, 3.95)	0.65
Multivariate analysis with predictors with P ≤ 0.05			
Frail pre-transplant	3.42	(1.05, 11.14)	0.04
Female gender	3.04	(0.90, 10.34)	0.08
Diagnosis			
COPD vs ILD	2.74	(0.73, 10.36)	0.14
PH vs ILD	2.37	(0.25, 22.45)	0.45
CF vs ILD	0.74	(0.08, 6.80)	0.79

Univariate and multivariate logistic regression models for odds of being frail at 6-months after transplantation using select pre-operative characteristics. Frailty was quantified using the Short Physical Performance Battery (SPPB). Frailty was defined as a binary outcome (frail = SPPB ≤7). Results with SPPB as a binary outcome represent odds ratio for frailty at 6-months after transplantation with 95% confidence intervals noted in parenthesis. Multivariate models adjusted for predictors found to be significant (P≤ 0.05) in univariate analysis. These included being frail prior to transplantation, female gender, and diagnosis.

Table 8. Proportion of frailty after transplant stratified by age at surgery

Age (years)	3-months post-transplant N = 180					6-months post-transplant N = 211					12-months post-transplant N = 186				
	N	SPPB ≤ 7		SPPB ≤ 9		N	SPPB ≤ 7		SPPB ≤ 9		N	SPPB ≤ 7		SPPB ≤ 9	
<40	22	1	(5%)	3	(14%)	24	2	(8%)	5	(21%)	21	1	(5%)	2	(10%)
40 to <50	25	5	(20%)	8	(32%)	29	1	(3%)	6	(21%)	26	1	(4%)	4	(15%)
50 to <60	50	7	(14%)	21	(42%)	61	6	(10%)	16	(26%)	55	8	(13%)	13	(24%)
≥ 60	83	18	(22%)	39	(47%)	97	6	(6%)	23	(24%)	84	11	(11%)	19	(23%)
P value			0.25		0.03			0.71		0.95			0.43		0.51

Frailty was quantified using the Short Physical Performance Battery (SPPB), which ranges from 0 to 12, (minimal important difference = 1); lower scores denote worse frailty. Frailty was defined a continuous measure, and as a binary outcome with two different cut points (frail = SPPB ≤7) and (frail = SPPB ≤9).

References

1. Singer JP, Chen J, Blanc PD, Leard LE, Kukreja J, Chen H. A Thematic Analysis of Quality of Life in Lung Transplant: The Existing Evidence and Implications for Future Directions. *American Journal of Transplantation.* Apr 2013;13(4):839-850.

2. Seiler A, Klaghofer R, Ture M, Komossa K, Martin-Soelch C, Jenewein J. A systematic review of health-related quality of life and psychological outcomes after lung transplantation. *Journal of Heart and Lung Transplantation.* Feb 2016;35(2):195-202.

3. Ware JE, Kosinski M, Keller SD. A 12-item short-form health survey - Construction of scales and preliminary tests of reliability and validity. *Medical Care.* Mar 1996;34(3):220-233.

4. Beaton DE, Boers M, Wells GA. Many faces of the minimal clinically important difference (MCID): a literature review and directions for future research. *Current Opinion in Rheumatology.* Mar 2002;14(2):109-114.

5. Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life - The remarkable universality of half a standard deviation. *Medical Care.* May 2003;41(5):582-592.

6. Chen H, Eisner MD, Katz PP, Yelin EH, Blanc PD. Measuring disease-specific quality of life in obstructive airway disease - Validation of a modified version of the airways questionnaire 20. *Chest.* Jun 2006;129(6):1644-1652.

7. Williams A. Euroqol - a New Facility for the Measurement of Health-Related Quality-of-Life. *Health Policy.* Dec 1990;16(3):199-208.

8. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age Ageing.* Jul 2010;39(4):412-423.

9. Stevens LA, Schmid CH, Greene T, et al. Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m2. *Am J Kidney Dis.* Sep 2010;56(3):486-495.

10. Stevens LA, Schmid CH, Greene T, et al. Comparative performance of the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD) Study equations for estimating GFR levels above 60 mL/min/1.73 m2. *Am J Kidney Dis.* 2010;56(3):486-495.