

Idiopathic Pulmonary Fibrosis

Gender-Age-Physiology Index Stage for Predicting Future Lung Function Decline

Margaret L. Salisbury, MD; Meng Xia, MS; Yueren Zhou, MS; Susan Murray, ScD; Nabihah Tayob, ScD; Kevin K. Brown, MD; Athol U. Wells, MD; Shelley L. Schmidt, MD; Fernando J. Martinez, MD; and Kevin R. Flaherty, MD

CHEST 2016; 149(2):491-498

Online supplements are not copyedited prior to posting and the author(s) take full responsibility for the accuracy of all data.

© 2016 AMERICAN COLLEGE OF CHEST PHYSICIANS. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians. See online for more details. DOI: 10.1378/chest.15-0530

e-Appendix 1.

MATERIALS

Statistical Methods

In this study, we use mixed models methodology to estimate FVC and DLCO trajectory over time in a group of patients stratified by GAP stage. This model uses all available PFTs in estimation, allowing for staggered measurements over time with no loss of information. We elected to summarize results over time using splines to allow for trajectory changes at yearly intervals. “Slope” of the trajectory for a given group of patients (GAP stage) is summarized as absolute change in FVC or DLCO during a given year; we also display at each follow-up year a point estimate of relative change from baseline. We found the best model fit (using AIC criteria) for our groups when stratified by GAP stage using yearly splines; we also tested 6-month splines but this did not improve model fit. The model was also evaluated when adjusting for baseline age (continuously), gender, and FVC (continuously), but adjustment for these parameters (which are incorporated into the GAP score regardless) did not improve model fit.

Notably, it is expected that a number of patients will have missing follow up data due to lack of follow up PFT in a given time interval or loss due to attrition or death. Mixed models also account for missing data by assuming that the missing data would be similar in nature and on the same trajectory as the data observed on a patient up to that point. We elect to display PFT trajectory through 2 years of follow up as the sample size available for inference decreased beyond that point.

e-TABLES

e-Table 1. Patient characteristics for all included patients and those excluded due to missing FVC or DLCO data.

Characteristic	Included Patients	PFT Missing	p-value
Total No.	657	77	
Mean Age (SD), y	62.9 (10.0)	64.4 (10.5)	0.21
Male gender, %	70	62.3	0.17
Mean FVC (SD), %-Predicted	68.0 (17.0)	65.9 (17.3)	0.31
DLCO (SD), %-Predicted	45.7(16.0)	n/a	n/a
3-year Transplant-Free Survival, %	53.3	82.5	<0.0001

e-Table 2. Relative change in FVC from baseline at 6-month intervals

	GAP 1 n=306	GAP 2 n=288	GAP 3 n=63	p ¹	p ²	p ³
6-months	-4.17 (-5.46,-2.88) n=248	-4.89 (-6.30,-3.49) n=192	-0.45 (-3.87,2.96) n=31	0.46	0.05	0.02
12-months	-7.10 (-9.43,-4.77) n=216	-12.11 (-14.76,-9.46) n=124	-10.27 (-17.04,-3.50) n=19	0.01	0.39	0.62
18-months	-11.41 (-14.87,-7.96) n=177	-13.48 (-17.63,-9.34) n=93	-10.72 (-21.34,-0.10) n=15	0.45	0.90	0.63
24-months	-13.73 (-18.45,-9.02) n=146	-17.64 (-23.39,-11.89) n=71	-25.16 (-39.59,-10.72) n=12	0.30	0.14	0.34

Data are shown as % decline (CI 95%).
p¹ compares GAP 1 vs GAP 2, p² GAP 1 vs GAP 3, and p³ GAP 2 vs GAP 3.
No. of patients indicates number with data available at the indicated time point.

e-Table 3. Relative change in DLCO from baseline at 6-month intervals

	GAP 1 n=306	GAP 2 n=288	GAP 3 n=63	p ¹	p ²	p ³
6-months	-7.01 (-9.11,-4.90) n=233	-4.43 (-6.75,-2.10) n=184	-6.34 (-11.99,-0.69) n=31	0.11	0.83	0.54
12-months	-12.66 (-16.38,-8.94) n=201	-14.85 (-19.16,-10.54) n=113	-25.60 (-36.33,-14.87) n=19	0.45	0.03	0.07
18-months	-19.59 (-24.88,-14.30) n=169	-18.96 (-25.39,-12.54) n=87	-24.77 (-40.40,-8.15) n=15	0.88	0.59	0.55
24-months	-22.43 (-29.16,-15.70) n=136	-29.77 (-37.87,-21.68) n=67	-47.09 (-66.83,-27.36) n=12	0.17	0.02	0.11

Data are shown as % decline (CI 95%).
p¹ compares GAP 1 vs GAP 2, p² GAP 1 vs GAP 3, and p³ GAP 2 vs GAP 3.
No. of patients indicates number with data available at the indicated time point.

e-Table 4. Mixed models outputs for relative FVC decline from baseline before and after adjusting for baseline age, gender, and FVC.

	GAP 1	GAP 2	GAP 3	p ¹	p ²	p ³
Year 1 Unadjusted	-7.68 (-9.80,-5.56)	-10.95 (-13.31,-8.59)	-5.05 (-10.81,0.71)	0.04	0.40	0.06
Adjusted	-7.69 (-9.85,-5.54)	-11.10 (-13.49,-8.71)	-5.59 (-11.48,0.30)	0.04	0.51	0.09
Year 2 Unadjusted	-14.04 (-18.68,-9.83)	-16.68 (-22.35,-11.02)	-21.72 (-35.91,-7.54)	0.48	0.31	0.52
Adjusted	-16.09 (-21.38,-10.80)	-16.03 (-21.91,-10.15)	-28.15 (-46.33,-9.97)	0.99	0.22	0.21

Data are shown as % decline (CI 95%).
p¹ compares GAP 1 vs GAP 2, p² GAP 1 vs GAP 3, and p³ GAP 2 vs GAP 3.
No. of patients indicates number with data available at the start of each time interval.

e-Table 5. Mixed models outputs for relative DLCO decline from baseline before and after adjusting for baseline age, gender, and FVC.

	GAP 1	GAP 2	GAP 3	p ¹	p ²	p ³
Year 1						
Unadjusted	-13.48 (-16.83,-10.13)	-11.98 (-15.76,-8.20)	-18.35 (-27.48,-9.23)	0.56	0.33	0.21
Adjusted	-13.54 (-16.95,-10.12)	-12.15 (-15.99,-8.30)	-18.12 (-27.42,-8.82)	0.60	0.36	0.24
Year 2						
Unadjusted	-22.98 (-29.57,-16.39)	-27.62 (-35.51,-19.72)	-42.06 (-61.26,-22.85)	0.38	0.07	0.17
Adjusted	-23.45 (-30.84,-16.06)	-26.39 (-34.90,-17.88)	-25.76 (-72.79,21.27)	0.62	0.92	0.98

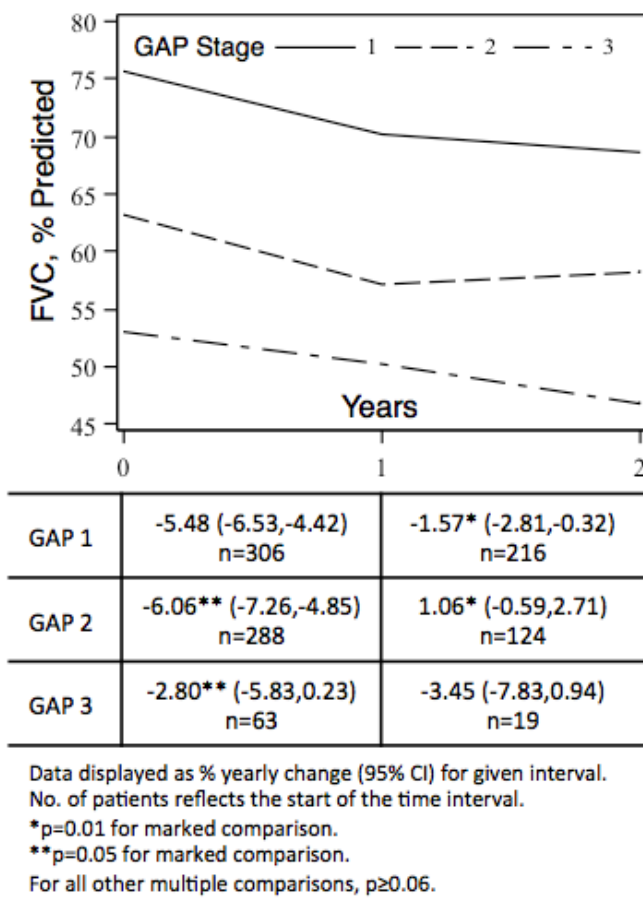
Data are shown as % decline (CI 95%).
 p¹ compares GAP 1 vs GAP 2, p² GAP 1 vs GAP 3, and p³ GAP 2 vs GAP 3.
 No. of patients indicates number with data available at the start of each time interval.

e-Table 6. Multivariable analysis with 10% FVC and 10% DLCO decline inserted separately into model to avoid data loss.

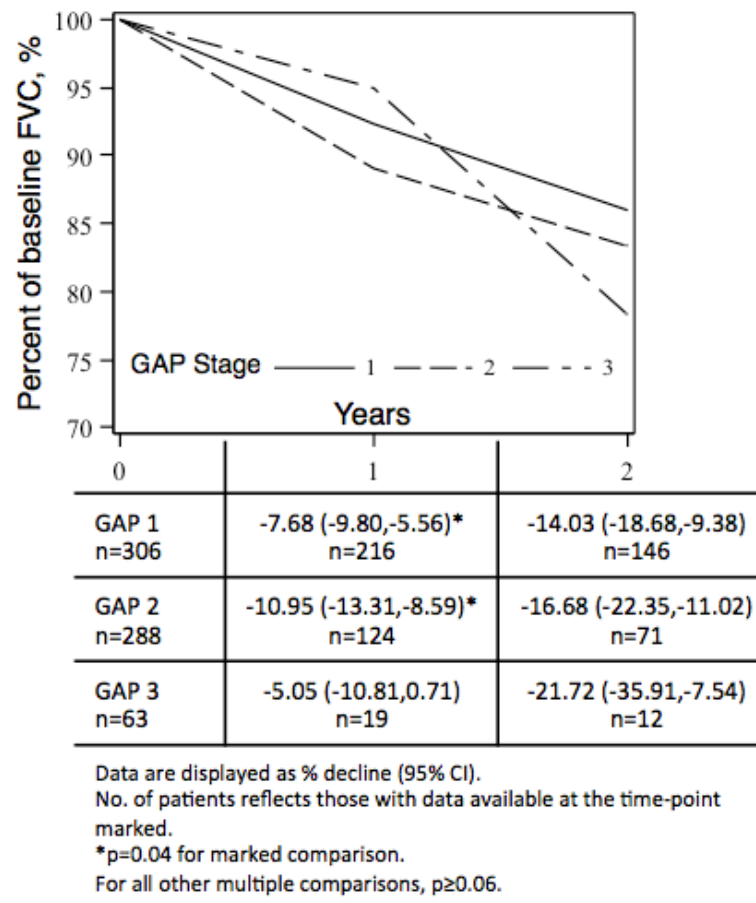
Predictor	FVC				DLCO			
	HR	CI 95%	p-value	No.	HR	CI 95%	p-value	No.
GAP Stage 1	<i>ref</i>			198	<i>ref</i>			195
GAP Stage 2	1.5	1.19-1.90	0.0006	193	1.58	1.25-2.00	0.0001	184
GAP Stage 3	2.71	1.83-4.00	<0.0001	35	2.25	1.71-3.82	<0.0001	33
10% PFT Decline	1.70	1.35-2.13	<0.0001	143	1.58	1.27-1.97	<0.0001	189

e-Figure 1. Absolute and relative FVC trajectory by GAP stage

1a. FVC over time



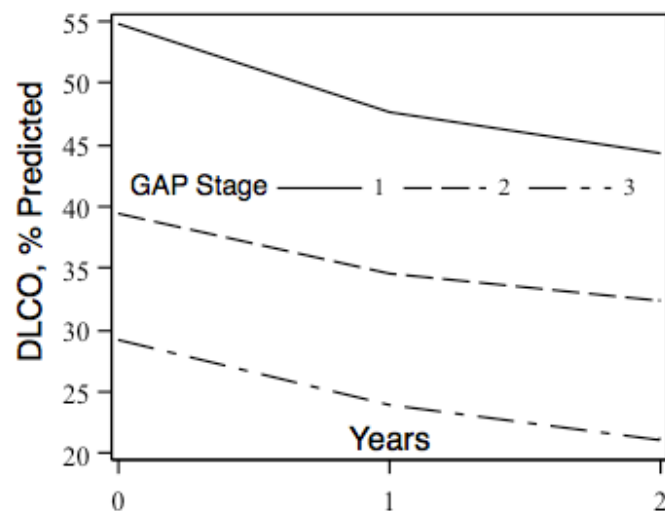
1b. Relative FVC decline from baseline



e-Figure 1: Shown is a side-by-side comparison of the absolute (S1a) and relative (S1b) FVC trajectories, with patients stratified by GAP stage. The associated tables show the absolute change in percent-predicted FVC between baseline and year 1 and between year 1 and year 2 for GAP stages 1, 2, and 3 (S1a), and the relative change from baseline at years 1 and 2 for GAP stages 1, 2, and 3 (S1b). For absolute yearly change in FVC, GAP 2 patients decline the most between baseline and year 1 at -6.06%, followed by GAP 1 at -5.48% and GAP 3 at -2.80% with GAP 2 declining significantly more than GAP 3 (p=0.05). Between year 1 and year 2, GAP 3 patients decline the most at -3.45% but this was not significant when compared to GAP 1 or 2. Gap 2 patients actually increase between year 1 and 2, making the difference between GAP 1 and 2 patients significantly different (p=0.01). Figure S1b shows that by year 2, there was no difference between groups in relative decline from baseline.

e-Figure 2. Absolute and Relative DLCO Trajectory by GAP stage

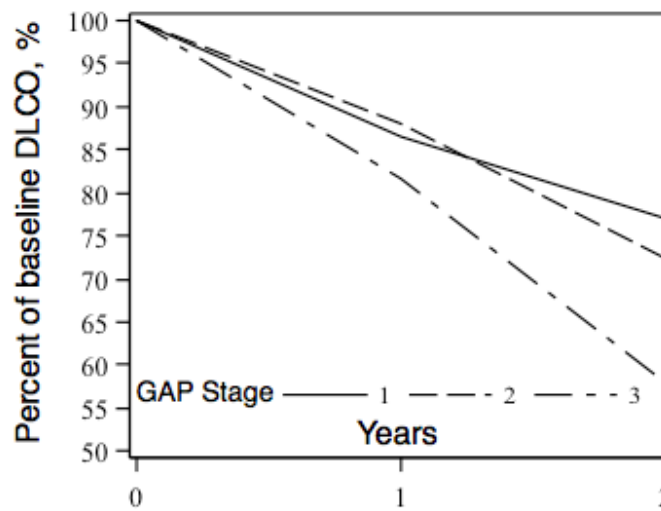
2a. DLCO over time



GAP 1	-7.16* (-8.32,-5.99) n=306	-3.34 (-4.72,-1.95) n=201
GAP 2	-4.87* (-6.20,-3.53) n=288	-2.21 (-4.11,-0.30) n=113
GAP 3	-5.27 (-8.55,-1.99) n=63	-2.86 (-7.59,1.87) n=19

Data displayed as % yearly change (95% CI) for given interval.
No. of patients reflects the start of the time interval.
*p=0.01 for marked comparison.
For all other multiple comparisons, p≥0.29.

2b. Relative DLCO decline by GAP stage

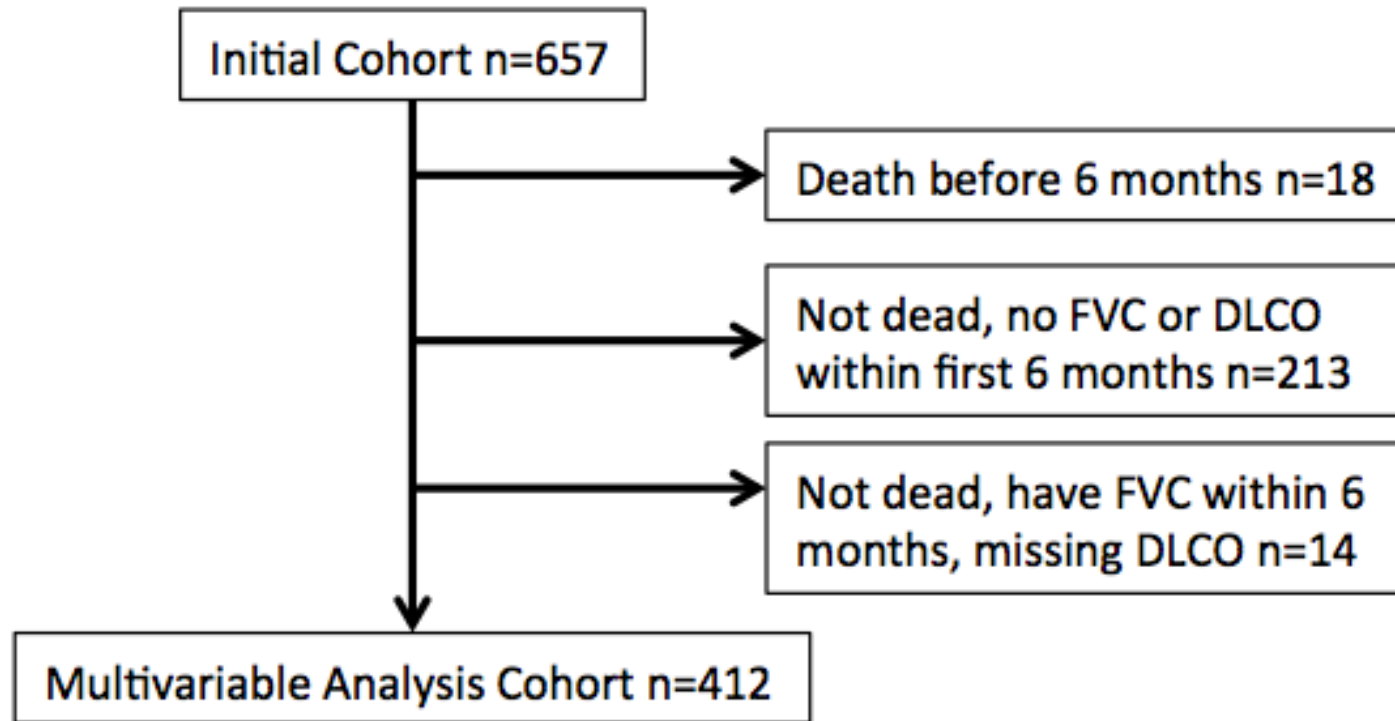


GAP 1 n=306	-13.48 (-16.83,-10.13) n=201	-22.98 (-29.57,-16.39) n=136
GAP 2 n=288	-11.98 (-15.76,-8.20) n=113	-27.62 (-35.51,-19.72) n=67
GAP 3 n=63	-18.35 (-27.48,-9.23) n=19	-42.06 (-61.26,-22.85) n=12

Data are displayed as % decline (95% CI).
No. of patients reflects those with data available at the time-point marked.
For all multiple comparisons, p≥0.07.

e-Figure 2: Shown is a side-by-side comparison of the absolute (S2a) and relative (S2b) DLCO trajectories, with patients stratified by GAP stage. The associated tables show the absolute change in percent-predicted DLCO between baseline and year 1 and between year 1 and year 2 for GAP stages 1, 2, and 3 (S2a), and the relative change from baseline at years 1 and 2 for GAP stages 1, 2, and 3 (S2b). For absolute yearly change in DLCO, GAP 1 patients declined the most between baseline and year 1 at -7.16%, followed by GAP 3 (-5.27%), and GAP 2 (-4.87%); the difference between GAP 1 and 2 groups reached statistical significance (p=0.01). There was no difference between groups between year 1 and year 2 for absolute change in DLCO. There was no difference between groups for relative change from baseline at year 1 or year 2.

e-Figure 3. Consort diagram for Cox analysis on 6-month PFT declines.



e-Figure 3: Consort diagram for Cox analysis on 6-month PFT declines. Shown is the number of patients in the original cohort (n=657), and reasons for exclusion from the Cox analysis. Of the 657 patients in the original cohort, 18 were dead by 6 months without follow-up PFT available, 213 were missing both FVC and DLCO data, and 14 were missing DLCO data (but had follow-up FVC available).