

Construct Validity and Minimal Important Difference of 6-Minute Walk Distance in Survivors of Acute Respiratory Failure

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e-Table 1. Construct Validity: Cross-sectional relationship of 6MWD (in % predicted) with mobility and physical function (Convergent Validity) and mental health measures (Discriminant Validity), across studies and data collection points

Time Point	Study	N	Convergent Validity Correlation with Measures of Physical Function (Pearson r)				Discriminant Validity Correlation with Measures of Mental Health (Pearson r)			
			4 Meter Walk	FPI	SF-36 PF domain (0-100)	EQ-5D Mobility [†]	SF-36 MH domain (0-100)	EQ-5D Anxiety [†]	HADS Anxiety Symptom s [†]	IES-R PTSD Symptoms [†]
Discharge	Denehy	97-98			0.32**		0.19			
3 month	Denehy	94-95			0.54**		0.34**			
3 month	ICAP	112-114			0.74**	-0.61**	0.18	-0.20*	-0.16	-0.05
6 month	Denehy	84-85			0.64**		0.50**			
6 month	ALTOS	153-155	0.52**	0.47**	0.51**	-0.44**	0.24**	-0.14	-0.15	-0.23**
6 month	ICAP	119			0.59**	-0.56**	0.21*	-0.16	-0.11	-0.08
12 month	Denehy	73-75			0.46**		0.35**			
12 month	ALTOS	143-149	0.63**	0.54**	0.64**	-0.51**	0.20*	-0.11	-0.19*	-0.28**
12 month	ICAP	114			0.65**	-0.58**	0.28**	-0.22*	-0.11	-0.20*

Abbreviations: 6MWD: six minute walk distance; FPI: Functional Performance Inventory; SF-36 PF: Medical Outcomes Short-Form 36 Physical Functioning domain; EQ-5D: Euro-QOL; SF-36 MH: Medical Outcomes Short-Form 36 Mental Health domain; HADS: Hospital Anxiety and Depression survey; IES-R PTSD: Impact of Event Scale-Revised Post-Traumatic Stress Disorder; * p<0.05; ** p<0.01; [†] For these scales, higher score indicate worse functioning and poorer mental health, resulting in negative correlation with the 6MWD for which greater distance walked indicate better functional capacity. Score ranges for patient-reported outcomes: SF-36 PF and MH (0-100); EQ-5D mobility and anxiety subscales (0-2); FPI total (0-3); HADS anxiety subscale (0-21); and IES-R (0-4).

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e-Table 2. Known Group Differences, t-tests of group differences in 6MWD (% predicted) by measures of muscle weakness and pulmonary function*

Time Point	Study	MMT < 48 n=5-26	MMT ≥ 48 n=93-248	p-value	FEV < 70% n=31-85	FEV ≥ 70% n=29-161	p-value
<i>Pooled Analysis</i>							
6 month	ALTOS & ICAP	0.31	0.63	<0.001	0.50	0.67	<0.001
12 month	ALTOS & ICAP	0.28	0.66	<0.001	0.52	0.71	<0.001
<i>Individual Study Analysis</i>							
3 month	ICAP	0.32	0.51	0.01	0.43	0.57	0.01
6 month	ALTOS	0.35	0.66	<0.001	0.57	0.69	0.004
6 month	ICAP	0.28	0.59	<0.001	0.40	0.61	<0.001
12 month	ALTOS	0.31	0.67	0.002	0.56	0.74	<0.001
12 month	ICAP	0.27	0.64	<0.001	0.48	0.68	<0.001

List of abbreviations: 6MWD: six minute walk distance; MMT: manual muscle testing; FEV: forced expiratory volume in 1 second

* N's for cells: ICAP at 3 Months: MMT<48 = 19; MMT>48 = 93; FEV<70% = 49; FEV>70%=51. ALTOS at 6 months: MMT<48 = 12; MMT>48 = 144; FEV<70% = 48; FEV>70%=99. ICAP at 6 months: MMT<48 = 14; MMT>48 = 104; FEV<70% = 31; FEV>70%=29. ALTOS at 12 months: MMT<48 = 5; MMT>48 = 139; FEV<70 = 46; FEV>70%=93. ICAP at 12 months: MMT<48 = 13; MMT>48 = 100; FEV<70% = 39; FEV>70%=68. Pooled at 6 months: MMT<48 = 26; MMT>48 = 248; FEV<70% =79 ; FEV>70%=128. Pooled at 12 months: MMT<48 = 18; MMT>48 = 239; FEV<70% =85 ; FEV>70%=161.

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e-Table 3. Predictive Validity of 6MWD (% predicted) for Post Discharge Outcomes: All-cause Mortality, Any Hospitalization, Alive at Home, and Return to Normal Activity, and Health Related Quality of Life

6MWD	Mortality ^a		Hospitalization ^a		Alive at home ^a		Return to Normal Activity ^a		SF-36 Physical Function	EQ5D Utility
	by 12m	Unadj. OR (95% CI)	between 6 and 12 m	Unadj. OR (95% CI)	at 12 m	Unadj. OR (95% CI)	at 12 m	Unadj. OR (95% CI)	at 12 m Beta (95% CI)	at 12 m Beta (95% CI)
Pooled Analysis										
3 month ICAP & Denehy	Total n = 210 Died, n=23	0.87** (0.80, 0.94)	Total n =183 Any hosp., n=39	0.89** (0.83, 0.95)	NA	NA	Total n =93 Normal, n=50	1.11* (1.02, 1.20)	2.9** (2.2, 3.6) Total n=159	NA
6 month ICAP & ALTOS	Total n = 273 Died, n=14	0.85** (0.77, 0.94)	Total n =237 Any hosp., n=60	0.87** (0.82, 0.94)	Total n =276 Home, n=244	1.17** (1.08, 1.26)	Total n =160 Normal, n=96	1.11** (1.03, 1.19)	3.6** (2.9, 4.3) Total n=249	1.6** (1.0, 2.2) Total n=250
6 months ICAP, ALTOS & Denehy	Total n = 338 Died, n=20	0.84** (0.77, 0.92)	Total n =322 Any hosp., n=74	0.89** (0.84, 0.94)	NA	NA	Total n =188 Normal, n=113	1.10** (1.02, 1.17)	3.4** (2.8, 3.9) Total n=317	NA
Individual Study Analysis										
Discharge Denehy	Total n = 111 Died, n=12	1.07 (0.93, 1.23)	Total n =111 Any hosp., n=42	0.96 (0.88, 1.06)	NA	NA	Total n =27 Normal, n=16	0.95 (0.75, 1.21)	1.6* (0.2, 3.0) Total n = 75	NA
3 month ICAP	Total n = 114 Died,	0.83** (0.74, 0.93)	Total n = 87 Any hosp.,	0.92 (0.83, 1.10)	Total n =111 Home,	1.26** (1.13, 1.39)	Total n =65 Normal,	1.12* (1.02, 1.24)	3.1** (2.1, 4.1)	1.4** (0.6, 2.3)

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	n=15		n=22		n=88		n=33		Total n=88	Total n=89
3 month Denehy	Total n = 96 Died, n=8	0.92 (0.80, 1.07)	Total n = 96 Any hosp., n=17	0.86** (0.77, 0.96)	NA	NA	Total n = 28 Normal, n=17	1.05 (0.87, 1.27)	2.6** (1.4, 3.7) Total n=71	NA
6 month ICAP	Total n = 119 Died, n=8	0.82** (0.71, 0.94)	Total n = 93 Any hosp., n=27	0.87** (0.78, 0.97)	Total n = 118 Home, n=102	1.28** (1.14, 1.44)	Total n = 66 Normal, n=38	1.07 (0.97, 1.19)	3.5** (2.5, 4.5) Total n=105	1.7** (0.9, 2.6) Total n=105
6 month Denehy	Total n = 85 Died, n=6	0.81* (0.69, 0.95)	Total n = 85 Any hosp., n=14	0.94 (0.85, 1.04)	NA	NA	Total n = 28 Normal, n=17	1.05 (0.87, 1.27)	2.6** (1.6, 3.7) Total n=68	NA
6 month ALTOS	Total n = 158 Died, n=6	0.90 (0.76, 1.06)	Total n = 144 Any hosp., n=33	0.89** (0.82, 0.97)	Total n = 158 Home, n=142	1.06 (0.95, 1.19)	Total n = 94 Normal, n=58	1.15* (1.03, 1.29)	3.8** (2.8, 4.8) Total n=144	1.6** (0.8, 2.5) Total n=145

$p \leq 0.05$, ** $p \leq 0.01$; Abbreviations: 6MWD: six minute walk distance; OR: odds ratio; Each analysis based on participants with an observation for both outcome and 6MWD at specified time point; Odds ratio for every 5% increase in % predicted value;^a Outcomes coding: Died=1, Alive=0; Any hospitalization during period=1, No hospitalization=0; Alive at home=1, not at home/died =0; Return to normal activity=1, did not return to normal activity=0; SF-36 PF (score range 0-100), EQ-5D Utility (0-100).^b Elliott data only has outcomes measured up to 6 month post discharge; All other studies have outcome data up to 12 month post discharge.

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e-Table 4. Responsiveness to Change in Recovery Trajectory: Mean change in 6MWD (% predicted) relative to patient reported change of >10 points on Normalized SF-36 Physical Functioning Score

Change Period	Study	Negative change >10 points SF-36 Physical Functioning Normalized Score (N = 1-17)	No Change (N = 21-226)	Positive change >10 points SF-36 Physical Functioning Normalized Score (N = 11-120)
<u>Pooled Analysis</u>				
3 to 6 month	ICAP/Denehy	-0.19** ^a	0.05 ^a	0.12* ^a
6 to 12 month	ICAP/ALTOS	-0.10** ^a	0.04	0.07 ^a
<u>Individual Study Analysis</u>				
Discharge to 3 month	Denehy	0.22* ^a	0.41	0.41 ^a
3 to 6 month	Denehy	-0.24** ^a	0.06	0.13** ^a
3 to 6 month	ICAP	0.04	0.05	0.12
6 to 12 month	ICAP	-0.13** ^a	0.02	0.06* ^a
6 to 12 month	ALTOS	-0.001	0.04	0.08

List of abbreviations: 6MWD: six minute walk distance; SF-36: Medical Outcomes Short-Form 36

* $p \leq 0.05$ and ** $p \leq 0.01$ for comparison between each of the change groups with the no change group; ^a $p \leq 0.05$ for comparison between the positive change group with the negative change group.

Additional Notes: ALTOS and ICAP scores normed to US general population; Denehy scores normed to Australian general population; Sample size by study and time point. Denehy discharge to 3m: positive change (29); no change (54); negative change (11). Denehy 3m to 6m: positive change (10); no change (61); negative change (8). ICAP 3m to 6m: positive change (15); no change (65); negative change (2). ICAP 6m to 12m: positive change (14); no change (71); negative change (8). ALTOS 6m to 12m: positive change (16); no change (106); negative change (2). Pooled 3m to 6m: positive change (25); no change(126); negative change(10). Pooled 6m to 12m: positive change (30); no change(177); negative change(10).

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e-Table 5. Minimal Clinically Important Difference for 6MWD (% predicted)

	ALTOS	ICAP	Denehy
<i>Anchor-Based</i>			
SF-36 PF domain*			
3 Month	--	0.03	0.03
6 Month	0.02	0.02	0.03
12 Month	0.03	0.03	0.03
EQ5-D Utility score**			
3 Month	--	0.05	--
6 Month	0.04	0.04	--
12 Month	0.03	0.04	--
<i>Distribution Based</i>			
Standard Error of Measurement			
3 month	--	0.06	0.05
6 month	0.05	0.06	0.06
Minimal Detectable Change₉₀			
3 month	--	0.14	0.13
6 month	0.12	0.13	0.14
0.5 SD (equivalent to moderate Cohen effect size)			
ICU discharge	--	--	0.09
Hospital discharge	--	--	0.11
3 month	--	0.14	0.12
6 month	0.11	0.12	0.14
12 month	0.13	0.12	0.13
0.2 SD (equivalent to small Cohen effect size)			
ICU discharge	--	--	0.03
Hospital discharge	--	--	0.04
3 month	--	0.06	0.05
6 month	0.04	0.05	0.05
12 month	0.05	0.05	0.05

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Abbreviations: 6MWD: six minute walk distance; SF-36 PF: Medical Outcomes Short-Form 36 physical functioning domain; EQ-5D: Euro-QOL; SD: standard deviation; * MID calculated by multiplying linear regression beta estimate with SF-36 MID of 5 points,¹ using the SF-36 0-100 non-normalized scale; ** MID calculated by multiplying linear regression beta estimate with MID of 7.4 for the EQ-5D Utility score.² EQ-5D Utility score and MID multiplied by 100 to facilitate comparison with SF-36 estimates; Cross-sectional correlation for 6MWD with the SF-36 PF score (0.36 - 0.76, $p < 0.01$) and with the EQ-5D utility score (0.43 - 0.65, $p < 0.01$).

REFERENCES

1. Hays RD, Morales LS. The RAND SF-36 measure of health-related quality of life. *Ann Med* 2001;33:350-357.
2. Walters SJ, Brazier J. Comparison of the minimally important difference for two health state utility measures: EQ-5D and SF-6D. *Qual Life Res* 2005;14:1523–1532.

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