CHEST

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

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OBJECTIVE: The 6-min walk distance (6MWD), a widely used test of functional capacity, has limited evidence of construct validity among patients surviving acute respiratory failure (ARF) and ARDS. The objective of this study was to examine construct validity and responsiveness and estimate minimal important difference (MID) for the 6MWD in patients surviving ARF/ARDS.

METHODS: For this secondary data analysis of four international studies of adult patients surviving ARF/ARDS (N = 641), convergent and discriminant validity, known group validity, predictive validity, and responsiveness were assessed. MID was examined using anchor- and distribution-based approaches. Analyses were performed within studies and at various time points after hospital discharge to examine generalizability of findings.

RESULTS: The 6MWD demonstrated good convergent and discriminant validity, with moderate to strong correlations with physical health measures ($|r| = 0.36$-0.76) and weaker correlations with mental health measures ($|r| = 0.03$-0.45). Known-groups validity was demonstrated by differences in 6MWD between groups with differing muscle strength and pulmonary function (all $P < .01$). Patients reporting improved function walked farther, supporting responsiveness. 6MWD also predicted multiple outcomes, including future mortality, hospitalization, and health-related quality of life. The 6MWD MID, a small but consistent patient-perceivable effect, was 20 to 30 m. Findings were similar for 6MWD % predicted, with an MID of 3% to 5%.

CONCLUSIONS: In patients surviving ARF/ARDS, the 6MWD is a valid and responsive measure of functional capacity. The MID will facilitate planning and interpretation of future group comparison studies in this population. CHEST 2015; 147(5):1316-1326

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ABBREVIATIONS: 6MWD = 6-min walk distance; ALTOS = ARDSNet Long Term Outcomes Study; ARF = acute respiratory failure; ED-5D = Euro-QOL; HRQL = health-related quality of life; ICAP = Improving Care of Acute Lung Injury Patients; MID = minimal important difference; PF = physical functioning; SF-36 = Medical Outcomes Survey 36-Item Short Form

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Patients who survive acute respiratory failure (ARF) and ARDS frequently experience important and long-lasting physical impairments.[1,2] The 6-min walk distance (6MWD) is a widely used measure of functional capacity in studies of patients surviving ARF/ARDS.[1] Robust literature on the validity of the 6MWD exists for geriatric, cardiac, neurologic, and COPD populations,[3-9] but a comprehensive validation of the 6MWD has not been done among patients surviving ARF/ARDS. These patients differ from chronically ill populations due to acute onset of physical impairments and younger age; therefore, determining the validity, responsiveness, and minimal important difference (MID), defined as the smallest difference perceivable by patients, for the 6MWD is important for planning and interpretation of future research studies.[10] The present study used data from four international longitudinal studies to examine the construct validity of the 6MWD in patients surviving ARF/ARDS.

Materials and Methods

Study Design

Secondary analyses were performed using data from two US-based studies (ARDSNet Long Term Outcomes Study [ALTOS] and Improving Care of Acute Lung Injury Patients [ICAP])[11,12] and two Australian-based studies.[13,14] Patients from these studies with at least one 6MWD assessment in the 12 months after critical illness were included. The ALTOS included patients surviving ARDS from 12 hospitals across five study sites, with 6- and 12-month follow-up occurring between 2008 and 2012.[11] ALTOS subjects were recruited based on participation in at least one of three co-enrolling National Heart, Lung, and Blood Institute ARDS Network randomized trials evaluating aerosolized albuterol vs placebo (Albuterol to Treat Acute Lung Injury [ALTA] trial),[15] early vs delayed enteral feeding (Early vs Delayed Enteral Feeding to Treat People With Acute Lung Injury or Acute Respiratory Distress Syndrome [EDEN] trial),[16] and omega-3 fatty acid and antioxidant supplement vs placebo (Omega-3 Fatty Acid/Antioxidant Supplementation for Treating People With Acute Lung Injury or Acute Respiratory Distress Syndrome [OMEGA] trial).[17] The ICAP study was a prospective cohort study in patients surviving ARDS recruited from four academic teaching hospitals in Baltimore, Maryland, with 3-, 6-, and 12-month follow-up occurring between 2005 and 2009.[12] The Denehy et al[13] study was a blinded randomized trial of intensive rehabilitation across ICU, hospital, and community settings vs usual physiotherapy care in patients with ARF in a single hospital in Melbourne, Victoria, Australia. Patient assessments at hospital discharge and 3-, 6-, and 12-month follow-up between 2008 and 2010 were included in this analysis. The Elliott et al[14] study was a blinded randomized trial of an 8-week home-based rehabilitation program conducted in patients with ARF recruited from 12 hospitals across three study sites in Australia. Patient evaluations conducted at 1, 8, and 26 weeks after hospital discharge (coded as hospital discharge, 3 and 6 month, for this analysis) between 2005 and 2009 were included in this analysis. In all studies, the randomized interventions did not have an effect on physical outcomes, so patients in both arms of each trial were pooled for this analysis.[11,13,14,18,19]

All studies obtained informed consent from participants and were approved by relevant institutional review boards (Johns Hopkins School of Medicine IRB-X #NA_00041630 [ICAP] and IRB-5 #NA_00013113 [ALTOS]; Austin Health Human Research Ethics Committee #H2006/02424 [Denehy]; and University of Technology at Sydney Human Research Ethics Committee #2004000062 [Elliott]). Consistent with the 2012 Berlin consensus meeting,[20] we use the term "ARDS" rather than "acute lung injury" throughout this article.

Study Measures

The primary study measure 6MWD was based on American Thoracic Society guidelines[21] in all studies with modest variations, including using a single 6MWD at each follow-up in the studies (as done in prior ARF/ARDS research[2]) and using the longest available distance (based on American Thoracic Society guidelines[21]) during home visits. The 6MWD was presented in meters and as % predicted (calculated using US[22] and Australian[23] normative values) for all studies except Elliott et al[14] in which % predicted values were not available.

Well-established performance-based and patient-reported measures reflecting important aspects of physical functioning (PF) were used to assess convergent and known-groups validity of the 6MWD. These include the 4-m timed walk speed (in meters per second),[24-26] manual muscle testing using the Medical Research Council sum score[27,28] (range, 0-60, with <48 indicating ICU-acquired weakness[29]), and spirometry[30] (reported as FEV_1 % predicted based on normative values[31]). Patient-reported measures included the Medical Outcomes Survey 36-Item Short Form (SF-36)[32] PF domain, the Functional Performance Inventory[33] overall score, and the Euro-QOL (EQ-5D)[34] mobility subscale. These measures often are used in studies of physical outcomes in patients surviving ARF/ARDS.[35-39]

Well-established patient-reported mental health measures were used to assess discriminant validity, including the SF-36 mental health domain, anxiety subscales of the Hospital Anxiety and Depression Scale[40] and EQ-5D, and the overall posttraumatic stress disorder symptom score of the Impact of Event Scale–Revised.[41] Prior reports of the correlation between physical and mental health measures have been weak (typically, $r<0.3$).[42-44]

Hospitalization, mortality, alive-at-home status (whether patients were living at home), return to normal activity (return to work, school, homemaking, or volunteering as was occurring prior to hospitalization), and health-related quality of life (HRQL) up to 12 months postdischarge were used to test predictive validity. Data were obtained through patient or proxy report, although medical records were also used in Denehy et al.[13] Hospitalizations occurring within 3 and 6 months can be self-reported with 98% and 96% accuracy, respectively.[45] Mortality data were not available in Elliott et al.[14]

The normed version of the SF-36 PF domain score, available in all studies, was used to assess responsiveness. Patient rating of global change in PF, administered at 6 and 12 months in the Denehy et al[13] trial, was also used in responsiveness analyses. This measure asked patients to rate improvement in their ability to perform daily PF activities using a visual analog scale with 0 indicating no improvement and 10 indicating maximum improvement.

Statistical Analysis

Construct Validity: Pearson correlations were used to examine convergent and discriminant validity. To establish convergent validity, we

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hypothesized that physical health outcomes would be at least moderately correlated ($r > 0.40$) with 6MWD. To establish discriminant validity, we hypothesized negligible to weak relationships ($r < 0.30$) between mental health outcomes and 6MWD. Furthermore, we expected the correlation of 6MWD with physical health outcomes to be consistently stronger than with mental health outcomes. For known-groups validity tests, the two-sample independent *t* test was used to determine whether mean 6MWD significantly differed in groups based on physical health. We hypothesized that patients with ICU-acquired weakness (manual muscle testing strength score < 48) and impaired pulmonary function (FEV_1 < 70% predicted) would perform significantly worse as determined by 6MWD than patients with greater muscle strength and pulmonary function.

Predictive Validity: We used logistic and linear regression to examine the association of a 30-m difference in the 6MWD, reflecting a meaningful difference for 6MWD in other populations.[46,47] 6MWD at discharge, 3 months, and 6 months were hypothesized to predict future mortality, rehospitalization, alive-at-home status, return to normal activity, and HRQL (SF-36 PF domain and EQ-5D utility) at or by 12 months.

Responsiveness: Linear regression was used to test whether change in 6MWD parallels substantial change observed in related physical outcomes in the same period. We examined responsiveness for three postdischarge periods: discharge to 3 months, 3 to 6 months, and 6 to 12 months. We categorized change in the normed SF-36 PF domain between two time points as negative if scores decreased by ≥ 10 points, no change if scores decreased or increased by < 10 points, and positive if scores increased by ≥ 10 points. The 10-point increment represented 1 SD for the normed SF-36 PF domain and has been identified as an important change by clinical experts.[48] A patient PF improvement rating of > 5 in Denehy et al[13] reflected substantial improvement. Survivors with a positive change or substantial improvement in PF were expected to walk substantially farther than survivors reporting no change, negative change, or nonsubstantial improvement. We further examined whether change in 6MWD could discriminate between patients reporting substantial improvement from those reporting less improvement by evaluating the area under the receiver operating characteristic curve.

Estimating MID: We used multiple anchor- and distribution-based methods to estimate the 6MWD MID.[49] Anchor-based methods used the SF-36 PF domain (scale, 0-100) and EQ-5D utility (original 0-1.0 multiplied by 100 for comparison with SF-36). These outcomes were chosen as anchors given their distinct, but important concepts of HRQL (EQ-5D utility includes physical and mental aspects), strong convergent validity with the 6MWD (SF-36 PF, $r = 0.36$-0.76; EQ-5D, $r = 0.43$-0.65; $P < .01$), and the availability of previously reported MIDs. To estimate an anchor-based MID, we used a linear regression model with 6MWD as the outcome and the anchor measure SF-36 PF or EQ-5D utility as the predictor. The β-coefficient from this model represents the number of meters from the 6MWD equivalent to one point in the anchor measure assessed at the same time point. The β-coefficient multiplied by the anchor's MID (five points for SF-36 PF and 7.4 for EQ-5D [which is the published MID for the utility score 0.074×100])[50,51] determines the 6MWD MID estimate.

For the distribution-based methods, SE of measurement, minimal detectable change at the 90% CI, and 0.50 SD, were calculated as in prior studies.[49,52,53] We also evaluated 0.20 SD of 6MWD to reflect a small effect size based on Cohen's[54] criteria.

We conducted analyses separately for each study and for various time points to examine whether findings were consistent despite differences in study design, patient characteristics, and time since discharge. The preceding analyses were also replicated using 6MWD % predicted (rather than 6MWD in meters), which accounts for differences in walk distances across patient age, sex, and physical differences.

TABLE 1] Participant Characteristics by Study

Variable	ICAP[12] (n = 162)	ALTOS[11] (n = 183)	Elliott et al[14] (n = 180)	Denehy et al[13] (n = 126)
Age, y	48 ± 14	48 ± 15	57 ± 16	59 ± 15
Male sex	93 (57)	90 (48)	109 (61)	76 (60)
BMI, kg/m²	28 ± 7	31 ± 8	…	28 ± 6
Race				
White	96 (59)	163 (89)	…	…
Black	63 (39)	15 (8)	…	…
Other	3 (2)	5 (3)	…	…
Education, y	13 ± 3	13 ± 3	…	…
Employed	68 (42)	96 (53)	…	…
Charlson Comorbidity Index	2.1 ± 2.5	1.1 ± 1.7	…	…
Functional Comorbidity Index	1.6 ± 1.4	1.9 ± 1.4	…	…
APACHE score	24 ± 8[a]	84 ± 25[b]	19 ± 10[a]	19 ± 6[a]
Ventilation duration, d	14 ± 15	11 ± 10	6 ± 6	5 ± 6
ICU length of stay, d	19 ± 17	14 ± 11	9 ± 8	10 ± 7
Hospital length of stay, d	30 ± 23	22 ± 15	24 ± 19	31 ± 27
6MWD at 6 mo, m	321 ± 149	368 ± 159	423 ± 143	383 ± 143
6MWD, % predicted[c]	0.55 ± 0.25	0.64 ± 0.23	…	0.71 ± 0.24

Data are presented as mean ± SD or No. (%). 6MWD = 6-min walk distance; ALTOS = ARDSNet Long Term Outcomes Study; APACHE = Acute Physiology and Chronic Health Evaluation; ICAP = Improving Care of Acute Lung Injury Patients.
[a]APACHE II.
[b]APACHE III.
[c]6MWD % predicted data were not available for the Elliott et al[14] trial.

TABLE 2] Construct Validity: Cross-sectional Relationship of 6MWD (in Meters) With Mobility and PF (Convergent Validity) and MH Measures (Discriminant Validity) Across Studies and Data Collection Time Points

			Convergent Validity Correlation With Measures of PF				Discriminant Validity Correlation With Measures of MH			
Time Point	Study	n	4-m Walk	FPI	SF-36 PF Domain	EQ-5D Mobility[a]	SF-36 MH Domain	EQ-5D Anxiety[a]	HADS Anxiety Symptoms[a]	IES-R PTSD Symptoms[a]
Discharge	Elliott et al[14]	174	…	…	0.72[b]	…	0.18[c]	…	…	…
Discharge	Denehy et al[13]	99	…	…	0.36[b]	…	0.20	…	…	…
3 mo	Elliott et al[14]	145	…	…	0.56[b]	…	0.16	…	…	…
3 mo	Denehy et al[13]	96	…	…	0.68[b]	…	0.31[b]	…	…	…
3 mo	ICAP[12]	112-114	…	…	0.76[b]	−0.61[b]	0.22[c]	−0.21[c]	−0.18	−0.03
6 mo	Elliott et al[14]	142	…	…	0.46[b]	…	0.12	…	…	…
6 mo	Denehy et al[13]	86	…	…	0.73[b]	…	0.45[b]	…	…	…
6 mo	ALTOS[11]	154-155	0.59[b]	0.52[b]	0.60[b]	−0.50[b]	0.23[b]	−0.17[c]	−0.10	−0.20[c]
6 mo	ICAP[12]	119	…	…	0.66[b]	−0.56[b]	0.16	−0.12	−0.04	−0.07
12 mo	Denehy et al[13]	76	…	…	0.53[b]	…	0.25[c]	…	…	…
12 mo	ALTOS[11]	143-149	0.67[b]	0.58[b]	0.68[b]	−0.56[b]	0.21[c]	−0.15	−0.18[c]	−0.25[b]
12 mo	ICAP[12]	115	…	…	0.70[b]	−0.59[b]	0.28[b]	−0.23[c]	−0.12	−0.19[c]

Data are presented as Pearson *r* unless otherwise indicated. ED-5D = Euro-QOL; FPI = Functional Performance Inventory; HADS = Hospital Anxiety and Depression Scale; IES-R = Impact of Event Scale–Revised; MH = mental health; PF = physical functioning; PTSD = posttraumatic stress disorder; SF-36 = Medical Outcomes Survey 36-Item Short Form. See Table 1 legend for expansion of other abbreviations.

[a]For these scales, higher score indicates worse PF and poorer MH, resulting in negative correlation with the 6MWD for which greater distance walked indicates better functional capacity. Score ranges for patient-reported outcomes are as follows: 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).

[b]$P < .01$.

[c]$P < .05$.

Results

Patient age, sex, and BMI were similar, with a range of mechanical ventilation durations and ICU lengths of stay represented across studies (Table 1). 6MWDs at 6 months were modestly higher in the two Australian trials vs the two US studies. Findings for 6MWD % predicted, which accounts for patient age, sex, and physical differences, were comparable to those for 6MWD in meters and are reported in e-Tables 1 to 5.

Construct Validity

Consistently across studies, countries, and follow-up time points, correlations of the 6MWD with other PF measures were moderately strong and were mostly weak to negligible with mental health measures, supporting construct validity (Table 2, e-Table 1). Known-groups validity tests further supported construct validity, with significantly shorter distance walked for survivors with ICU-acquired weakness and impaired pulmonary function compared with their higher-functioning counterparts (Table 3, e-Table 2).

Predictive Validity

Based on pooled analyses, 6MWD can significantly predict future mortality, rehospitalization, alive-at-home status, return to normal activity, and HRQL (Table 4, e-Table 3). Prediction of 12-month HRQL was particularly consistent across the studies and time points 6MWD was assessed. 6MWD was less consistently associated with the remaining outcomes in the individual studies possibly because of the rarity of these events in some studies.

Responsiveness

Survivors with positive SF-36 PF domain changes walked farther than those reporting no change or negative change (Table 5, e-Table 4). This finding was most apparent in the pooled analysis. Positive SF-36 PF domain changes between 3 and 6 months were associated with 6MWD increases of 65 (95% CI, 46-83) m compared with 26 (95% CI, 9-42) m for the no-change group and −29 (95% CI, −53 to −5) m for the negative-change group (Table 5). Similar results were observed between 6 and 12 months but not for the period from discharge to 3-month follow-up when all three change groups walked substantially longer distances. However, the latter finding appears to be largely due to one of the two trials examining this earlier period.

For the patient rating of global change, the group reporting substantial vs modest or no improvement had a larger mean increase in 6MWD between discharge and 6 months (239 [95% CI, 216-262] vs 113 [95% CI, 94-132] m, respectively; $P < .001$) and between 6 and 12 months (21 [95% CI, 10-38] vs −44 [95% CI, −59 to −30] m, respectively; $P = .003$). Similar to the SF-36 PF domain results for this study, mean 6MWD increased substantially in the immediate postdischarge period, even if survivors rated their functional improvement as modest or no improvement. Change in 6MWD discriminated between the substantial vs modest or no improvement groups at both 6 and 12 months, with areas under the receiver operating characteristic curve of 0.79 (95% CI, 0.67-0.90) and 0.79 (95% CI, 0.66-0.92), respectively.

TABLE 3] Known-Group Validity, *t* Tests of Group Differences in 6MWD (in Meters) by Measures of Muscle Weakness and Pulmonary Function[a]

Time Point	Study	MMT < 48 (n = 5-26)	MMT ≥ 48 (n = 93-248)	*P* Value	FEV_1 < 70% (n = 31-79)	FEV_1 ≥ 70% (n = 29-161)	*P* Value
Pooled analysis							
6 mo	ALTOS[11] and ICAP[12]	161	369	< .001	294	382	< .001
12 mo	ALTOS[11] and ICAP[12]	162	384	< .001	308	412	< .001
Individual study analysis							
3 mo	ICAP[12]	180	304	.003	249	339	.006
6 mo	ALTOS[11]	187	385	< .001	331	395	.006
6 mo	ICAP[12]	139	347	< .001	238	338	.003
12 mo	ALTOS[11]	161	394	.001	324	429	< .001
12 mo	ICAP[12]	162	370	< .001	290	390	.003

MMT = manual muscle testing. See Table 1 legend for expansion of other abbreviations.

[a]n for cells: ICAP at 3 mo: MMT < 48 = 19; MMT > 48 = 93; FEV_1 < 70% = 49; FEV_1 > 70% = 51. ALTOS at 6 mo: MMT < 48 = 12; MMT > 48 = 144; FEV_1 < 70% = 48; FEV_1 > 70% = 99. ICAP at 6 mo: MMT < 48 = 14; MMT > 48 = 104; FEV_1 < 70% = 31; FEV_1 > 70% = 29. ALTOS at 12 mo: MMT < 48 = 5; MMT > 48 = 139; FEV_1 < 70% = 46; FEV_1 > 70% = 93. ICAP at 12 mo: MMT < 48 = 13; MMT > 48 = 100; FEV_1 < 70% = 39; FEV_1 > 70% = 68. Pooled analysis at 6 mo: MMT < 48 = 26; MMT > 48 = 248; FEV_1 < 70% = 79; FEV_1 > 70% = 128. Pooled analysis at 12 mo: MMT < 48 = 18; MMT > 48 = 239; FEV_1 < 70% = 85; FEV_1 > 70% = 161.

TABLE 4] Predictive Validity of 6MWD (per 30 Meters) for Postdischarge Outcomes: All-Cause Mortality, Any Hospitalization, Alive-at-Home Status, Return to Normal Activity, and Health-Related Quality of Life

	Mortality[a]		Hospitalization[a]		Alive-at-Home Status[a]		Return to Normal Activity[a]			
6MWD Time Point Study	By 12 mo	Unadjusted OR (95% CI)	Between 6 and 12 mo	Unadjusted OR (95% CI)	At 12 mo	Unadjusted OR (95% CI)	At 12 mo	Unadjusted OR (95% CI)	SF-36 PF at 12 mo β (95% CI)	EQ-5D Utility at 12 mo β (95% CI)
Pooled analysis										
3 mo										
ICAP[12] and Denehy et al[13]	Total, N = 214 Died, n = 23	0.86[b] (0.80-0.94)	Total, N = 187 Any hosp., n = 39	0.91[b] (0.85-0.98)	NA	NA	Total, N = 93 Normal, n = 50	1.09[c] (1.01-1.18)	3.3[b] (2.6-4.0) Total, N = 162	NA
6 mo										
ICAP[12] and ALTOS[11]	Total, N = 273 Died, n = 14	0.84[b] (0.75-0.93)	Total, N = 237 Any hosp., n = 60	0.89[b] (0.83-0.95)	Total, N = 276 Home, n = 244	1.18[b] (1.09-1.27)	Total, N = 160 Normal, n = 96	1.11[b] (1.04-1.20)	4.1[b] (3.2-5.0) Total, N = 105	1.8[b] (1.2-2.3) Total, N = 250
ICAP,[12] ALTOS,[11] and Denehy et al[13]	Total, N = 362 Died, n = 20	0.84[b] (0.77-0.91)	Total, N = 326 Any hosp., n = 74	0.91[b] (0.86-0.96)	NA	NA	Total, N = 183 Normal, n = 111	1.12[b] (1.05-1.20)	3.9[b] (3.3-4.4) Total, N = 320	NA
Individual study analysis										
Discharge										
Elliott et al[14]	Total, N = 177 Died, n = 4 (by 6 mo)[d]	0.92 (0.72-1.16)	Total, N = 177 Any hosp., n = 35 (by 6 mo)[d]	1.02 (0.93-1.11)	Total, N = 177 Home, n = 156 (at 6 mo)[d]	1.10 (0.99-1.23)	NA	NA	2.7[b] (1.8-3.6) Total, N = 156 (at 6 mo)[a]	NA
Denehy et al[13]	Total, N = 117 Died, n = 13	1.03 (0.90-1.17)	Total, N = 117 Any hosp., n = 17	1.06 (0.94-1.19)	NA	NA	NA	NA	1.8[b] (0.6-3.1) Total, N = 78	NA
3 mo										
ICAP[12]	Total, N = 114 Died, n = 15	0.83[b] (0.74-0.93)	Total, N = 87 Any hosp., n = 22	0.92 (0.84-1.01)	Total, N = 112 Home, n = 88	1.25[b] (1.13-1.38)	Total, N = 74 Normal, n = 38	1.13[b] (1.03-1.24)	3.6[b] (2.6-4.5) Total, N = 88	1.6[b] (0.8-2.4) Total, N = 89

(Continued)

TABLE 4] *(continued)*

6MWD Time Point Study	Mortality[a]		Hospitalization[a]		Alive-at-Home Status[a]		Return to Normal Activity[a]		SF-36 PF at 12 mo β (95% CI)	EQ-5D Utility at 12 mo β (95% CI)
	By 12 mo	Unadjusted OR (95% CI)	Between 6 and 12 mo	Unadjusted OR (95% CI)	At 12 mo	Unadjusted OR (95% CI)	At 12 mo	Unadjusted OR (95% CI)		
Denehy et al[13]	Total, N = 100 Died, n = 8	0.92 (0.80-1.07)	Total, N = 100 Any hosp., n = 17	0.91 (0.82-1.01)	NA	NA	Total, N = 28 Normal, n = 17	1.00 (0.94-1.20)	2.7[b] (1.6-3.8) Total, N = 74	NA
6 mo										
ICAP[12]	Total, N = 119 Died, n = 8	0.79[b] (0.68-0.92)	Total, N = 93 Any hosp., n = 27	0.91 (0.82-1.01)	Total, N = 118 Home, n = 102	1.30[b] (1.15-1.47)	Total, N = 66 Normal, n = 38	1.05 (0.94-1.16)	4.1[b] (3.2-5.0) Total, N = 105	2.0[b] (1.2-2.8) Total, N = 105
Denehy et al[13]	Total, N = 89 Died, n = 6	0.83[c] (0.70-0.97)	Total, N = 89 Any hosp., n = 14	0.97 (0.88-1.09)	NA	NA	Total, N = 23 Normal, n = 15	1.38 (0.98-1.95)	2.9[b] (1.9-3.9) Total, N = 71	NA
ALTOS[11]	Total, N = 154 Died, n = 6	0.90 (0.76-1.06)	Total, N = 144 Any hosp., n = 33	0.88[b] (0.81-0.96)	Total, N = 158 Home, n = 142	1.08 (0.97-1.20)	Total, N = 94 Normal, n = 58	1.18[b] (1.06-1.31)	4.2[b] (3.3-5.8) Total, N = 144	1.7[b] (1.0-2.4) Total, N = 145

Each analysis was based on participants with an observation for both outcome and 6MWD at the specified time point. OR for a 30-m increase in 6MWD. hosp. = hospital; NA = not available. See Table 1 and 2 legends for expansion of other abbreviations.

[a]Outcomes coding: died = 1; alive = 0; any hospitalization during period = 1; no hospitalization = 0; alive-at-home status = 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 (score range, 0-100).

[b]$P \leq .01$.

[c]$P \leq .05$.

[d]Elliott data only have outcomes measured up to 6 mo postdischarge. All other studies have outcome data up to 12 mo postdischarge.

TABLE 5] Responsiveness to Change in Recovery Trajectory: Mean Change in 6MWD (in Meters) Relative to Patient-Reported Change of > 10 points on Normalized SF-36 PF Domain Score

Change Period	Study	Negative Change > 10 Points SF-36 PF Domain Normalized Score (n = 1-17)	No Change (n = 21-233)	Positive Change > 10 Points SF-36 PF Domain Normalized Score (n = 11-120)
Pooled analysis				
Discharge to 3 mo	Denehy et al,[13] Elliott et al[14]	94	147	143
3-6 mo	ICAP,[12] Denehy et al,[13] Elliott et al[14]	−29[a,b]	26	65[a,b]
6-12 mo	ICAP,[12] ALTOS[11]	−56[a,c]	16	35[a]
Individual study analysis				
Discharge to 2 mo	Elliott et al[14]	−62[a]	68	114[a,c]
Discharge to 3 mo	Denehy et al[13]	109[a,b]	226	225[a]
2-6 mo	Elliott et al[14]	39	23	70[c]
3-6 mo	Denehy et al[13]	−127[a,b]	29	65[a]
3-6 mo	ICAP[12]	23	28	58
6-12 mo	ICAP[12]	−69[a,c]	8	31[a]
6-12 mo	ALTOS[11]	−4	21	39

ALTOS and ICAP scores normalized to US general population with mean ± SD of 50 ± 10. Denehy and Elliott scores normalized to Australian general population. Sample size by study and time point: Elliott discharge to 2 mo: positive change (n = 89), no change (n = 56), negative change (n = 1). Denehy discharge to 3 mo: positive change (n = 31), no change (n = 55), negative change (n = 11). Elliott 2-6 mo: positive change (n = 20), no change (n = 104), negative change (n = 10). Denehy 3-6 mo: positive change (n = 11), no change (n = 64), negative change (n = 8). ICAP 3-6 mo: positive change (n = 15), no change (n = 65), negative change (n = 2). ICAP 6-12 mo: positive change (n = 14), no change (n = 71), negative change (n = 8). ALTOS 6-12 mo: positive change (n = 16), no change (n = 106), negative change (n = 2). Pooled discharge to 3 mo: positive change (n = 120), no change (n = 111), negative change (n = 12). Pooled 3-6 mo: positive change (n = 46), no change (n = 233), negative change (n = 20). Pooled 6-12 mo: positive change (n = 30), no change (n = 177), negative change (n = 10). See Table 1 and 2 legends for expansion of abbreviations.

[a] $P \leq .05$ for comparison between the positive change group vs the negative change group.

[b] $P \leq .01$ for comparison between each change group vs the no-change group.

[c] $P \leq .05$ for comparison between each change groups vs the no-change group.

Estimating MID

Using known MIDs for the SF-36 and the EQ-5D utility score, anchor-based MID estimates for the 6MWD ranged between 14 and 30 m (Table 6), which was consistent across time points, study, and country. Estimates using the EQ-5D MID were modestly larger than those using the SF-36 MID (Table 6, e-Table 5). Distribution-based MID estimates were generally larger than anchor-based estimates but were also consistent across time points, study, and country. Specifically, the range of estimates for each measure was as follows: SE of measurement, 31 to 38 m; minimal detectable change at the 90% CI, 67 to 88 m; 0.5 SD, 53 to 84 m; and 0.2 SD, 21 to 34 m (Table 6, e-Table 5).

Discussion

Overall, the 6MWD is a valid measure of functional capacity for patients surviving ARF/ARDS. Consistent evidence of concurrent construct validity was found at various time points postdischarge and across international studies with different patient samples and study designs. The 6MWD was also found to have predictive validity and was responsive to changes in PF.

Using recommended methods for estimating MID,[49] we determined that 20 to 30 m reflects the 6MWD MID. Anchor-based estimates, which were given greater weight,[49] were approximately 20 m and comparable with or only modestly smaller than prior reports for anchor-based MIDs in geriatric patients and patients with COPD.[46,55] The present distribution-based MID estimates were modestly larger than the anchor-based ones but were also consistent with prior studies with geriatric, COPD, and chronic pulmonary disease populations.[47,55-57] Identifying a single MID is difficult given the challenges in defining "minimum." However, the convergence of the present anchor-based estimates with the distribution-based SE of measurement and 0.2 SD[49,53,58] suggests that a narrow range of 20 to 30 m would be a reasonable MID for the 6MWD. Overall, anchor- and distribution-based MID estimates were surprisingly consistent across the studied patient populations, settings, and points along the recovery trajectory. Although anchor-based MID may be determined cross-sectionally or longitudinally,[59] the present anchor-based estimates are from cross-sectional, between-group analyses and

TABLE 6] Minimal Important Difference for 6MWD (in Meters)

Approach	ALTOS,[11] m	ICAP,[12] m	Denehy et al,[13] m	Elliott et al,[14] m
Anchor based				
SF-36 PF domain[a]				
3 mo	…	22	18	17
6 mo	14	16	19	14
12 mo	18	18	17	…
EQ-5D utility score[b]				
3 mo	…	30	…	…
6 mo	20	23	…	…
12 mo	24	22	…	…
Distribution based				
SE of measurement				
3 mo	…	38	32	31
6 mo	31	…	36	…
MDC-90				
3 mo	…	88	74	72
6 mo	72	78	84	…
0.5 SD[c]				
ICU discharge	…	…	53	…
Hospital discharge	…	…	65	64
3 mo	…	84	71	70
6 mo	69	75	80	72
12 mo	79	75	77	…
0.2 SD[d]				
ICU discharge	…	…	21	…
Hospital discharge	…	…	26	26
3 mo	…	34	29	28
6 mo	28	30	32	29
12 mo	32	30	31	…

MCD-90 = minimal detectable change at the 90% CI. See Table 1 and 2 legends for expansion of other abbreviations.
[a]MID calculated by multiplying linear regression β-estimate with SF-36 MID of 5 points,[40] using the SF-36 0-100 nonnormalized scale.
[b]MID calculated by multiplying linear regression β-estimate with MID of 7.4 for the EQ-5D utility score.[41] 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, $P < .01$) and with the EQ-5D utility score (0.43-0.65, $P < .01$).
[c]Equivalent to moderate Cohen effect size.
[d]Equivalent to small Cohen effect size.

are most appropriate for group comparisons than for within-subject change.

The findings on 6MWD % predicted largely paralleled those from the 6MWD in meters, with evidence of concurrent construct validity, predictive validity, and responsiveness across studies and time points. Similarly, although distribution-based MID estimates were larger than anchor-based MIDs, a narrow range of 3% to 5% predicted 6MWD was observed that likely represents a small but patient-perceivable difference. The similarity of findings for both 6MWD in meters and % predicted suggests that age, sex, and physical attributes (height, weight) do not substantially influence the validity of the 6MWD.

This study provides a comprehensive validation of 6MWD among patients surviving ARF/ARDS. However, potential limitations to this research exist. First, the selected variables (eg, patient rating of improvement in functioning) were not available in all studies, limiting our ability to replicate or pool data across studies for a small number of the analyses. Second, we relied on the SF-36 PF domain and EQ-5D as anchor measures. These measures assess functioning more broadly and do not

precisely match the construct assessed by the 6MWD that focuses more specifically on walking aspects of functional capacity. Third, analyses that require categorization can lead to small sample sizes within specific cells. The lack of statistical significance for some comparisons in the responsiveness and predictive validity analyses may be due to this issue; however, pooling data across studies generally addresses this problem. Finally, our MID analyses were focused on group-level comparisons, and the findings cannot be extended to intrapatient MIDs. Despite these limitations, an extensive set of similar variables across these four international studies has provided rigorous evaluation of the validity of the 6MWD. Furthermore, the consistency of the findings across diverse study populations, study designs, and time points and for 6MWD evaluated in both meters and as % predicted support generalizability.

Conclusions

The 6MWD is a commonly used evaluation of PF in both clinical and research settings. This test requires minimal equipment and can be undertaken by patients with various functional abilities. The study demonstrates that 6MWD is a valid measure for clinicians and researchers to assess functional capacity among patients surviving ARF/ARDS. The 6MWD MID, which is 20 to 30 m or 3% to 5% predicted, can help clinicians using the 6MWD to assess and interpret the efficacy of research interventions among patients with ARF/ARDS postdischarge.

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Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

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