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Evaluating Physical Outcomes in ARDS Survivors: Validity, Responsiveness & Minimal Important Difference of 4-Meter Gait Speed Test

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Abstract

Objective—To examine the reliability, validity, responsiveness, and minimal important difference of the 4-meter (4-m) gait speed test in acute respiratory distress syndrome (ARDS) survivors.

Design—Secondary analyses of data from two longitudinal follow-up studies of ARDS survivors. Test-retest and inter-rater reliability, construct validity (convergent, discriminant, known group), predictive validity, and responsiveness were examined. The minimal important difference was estimated using anchor- and distribution based approaches.

Setting—A national multicenter prospective study (ARDSNet Long-Term Outcome Study [ALTOS]) and a multi-site prospective study in Baltimore, MD (Improving Care of Acute Lung Injury Patients [ICAP]).

Patients—ARDS survivors with 4-m gait speed assessment up to 60 months after ARDS (ALTOS, N=184; ICAP, N=122).

Interventions—Not Applicable

Measurements and Main Results—4-m gait speed was assessed at 6 and 12 months follow-up (ALTOS) and 36, 48 and 60 months follow-up (ICAP). Excellent test-retest (ICC: 0.89–0.99 across studies and follow-up) and inter-rater (ICC: 0.97) reliability were found. Convergent validity was supported by moderate-to-strong correlations (69% of 32 >0.40) with other physical function measures. Discriminant validity was supported by weak correlations (86% of 28 <0.30) with mental health measures. Survivors with impaired vs. non-impaired measures of muscle strength and pulmonary function had significantly slower 4-m gait speed (all but one $p<0.05$). Moreover, 4-m gait speed significantly predicted future hospitalization and health-related quality of life. Gait speed changes were consistent with reported changes in function, supporting responsiveness. The estimated 4-m gait speed MID was 0.03–0.06 m/sec.

Conclusions—The 4-m gait speed is a reliable, valid, and responsive measure of physical function in ARDS survivors. The estimated minimal important difference will facilitate sample size calculations for clinical studies evaluating the 4-m gait speed test in ARDS survivors.

Keywords

gait speed; ARDS; reliability; validity; psychometrics; clinimetrics

INTRODUCTION

Patients who survive acute respiratory distress syndrome (ARDS) often have long-lasting impairments in physical functioning(1–3). Gait speed is an assessment of physical functioning frequently used in other populations that appears well suited for ARDS survivors since it is quick and simple to conduct, and requires minimal equipment and space.

Gait speed is reliable(4–8) and valid across many populations, including older adults, multiple sclerosis, stroke, hemodialysis, and chronic obstructive pulmonary disease (COPD) (6,9–13). Gait speed also predicts important outcomes, including mortality, hospitalization, functional decline, discharge location, falls, and need for services.(10,13–16)

Gait speed is one component of the Short Physical Performance Battery (SPPB), a well-established, validated set of performance assessments. However, gait speed alone, predicts incident disability nearly as well as the entire SPPB.(17) Furthermore, gait speed is recommended for routine assessment as the “sixth vital sign” (18) and for inclusion in interventional studies focused on sarcopenia and frail older adults.(19,20). Gait speed is also included in one definition of frailty(21).

Among gait speed tests, the 4-meter (4-m) gait speed test has been recommended to assess locomotion in the NIH Toolbox (www.nihttoolbox.org), an initiative to develop comprehensive standardized sets of functional measures(22). However, the 4-m gait speed test has not been psychometrically evaluated in ARDS survivors. Furthermore, the minimal important difference (MID), defined as the smallest difference perceivable by patients, has not been determined for this population. The MID is valuable for determining sample size and interpreting differences between treatment groups. Using data from two different multi-site studies of ARDS survivors (N=306), this study investigates the reliability, concurrent construct validity, predictive validity, responsiveness, and MID for the 4-m gait speed test at different time points during the first 5 years of recovery after ARDS.

MATERIALS and METHODS

Study Design

Secondary analyses were performed using data from two studies: ARDSNet Long-Term Outcome Study (ALTOS) and Improving Care of Acute Lung Injury Patients (ICAP) study. (3,23) ALTOS is a multi-center national study, the details of which have been published previously(23) and are briefly summarized herein. The data used in this analysis include ALTOS subjects recruited from 12 hospitals within 5 ARDSNet study centers, with 6 and 12 month follow-up occurring between 2008 and 2012.(23) ALTOS subjects were recruited based on participation in at least one of three co-enrolling ARDS Network randomized trials evaluating aerosolized albuterol versus placebo (ALTA trial)(24), early versus delayed enteral feeding (EDEN trial)(25), and omega-3 fatty acid and antioxidant supplement versus placebo (OMEGA trial)(26). The ICAP study is a prospective cohort study evaluating ARDS survivors from 4 teaching hospitals in Baltimore, MD. Data from the 36, 48 and 60 month follow-up, occurring between 2007 and 2012, were included in this analysis.(3)

Patients with at least one 4-m gait speed were included. All studies obtained informed consent from participants, and were approved by relevant institutional review boards.

Study Measures

4-m gait speed, in meters per second (m/sec), is the primary measure for this psychometric study. In ALTOS and ICAP, the test was performed twice at each assessment(27). As recommended, the fastest speed was used for these analyses,(28) except for test-retest reliability which used both tests from each assessment. Data for inter-rater reliability were drawn from on-going quality assurance (QA) reviews of research staff conducted in both studies. These reviews involved comparison of the research staff’s gait speed measurements versus an expert trainer’s measurements for the test. If multiple QA reviews were conducted

for a specific staff member, the most recent review was used to prevent intra-staff clustering across repeated measures.

Well-established measures reflecting important aspects of physical function were used to assess convergent validity and known group validity of the 4-m gait speed test. These measures included the following performance-based tests: the 6MWT(29,30), manual muscle testing (MMT) of strength using the Medical Research Council sum score(31–33) (range, 0 to 60, with <48 indicating “ICU-acquired weakness,”(34)) and spirometry(35) (reported as percent predicted value for forced expiratory volume in 1 second (FEV₁) using normative values(36)). Patient-reported measures included the physical function (PF) domain of the Medical Outcomes Study Short-Form 36 quality of life survey version 2 (SF-36)(37), the mobility subscale of the EQ-5D-3L quality of life survey(38), the number of dependencies using Katz’s activities of daily living (ADL) scale(39) and using Lawton’s instrumental activities of daily living (IADL)(40), and the overall score of the Functional Performance Inventory–Short Form (FPI-SF) survey(41).

Well-established patient-reported mental health measures were used to assess discriminant validity, including the mental health (MH) domain of the SF-36, anxiety subscales of the Hospital Anxiety and Depression Scale (HADS)(42) and the EQ-5D-3L, and post-traumatic stress disorder symptom score of the Impact of Event Scale–Revised (IES-R)(43). Prior reports of the correlation between physical and mental health measures have been weak (typically $r < 0.3$) making them appropriate for assessing discriminant validity.(44–46)

For evaluating predictive validity, the following outcomes were used: mortality, hospitalization, alive at home status (whether patients were living at home or not), return to normal activity (including work, school, homemaking or volunteering as was occurring prior to hospitalization for ARDS), SF-36 PF score, and EQ-5D utility score. Data were patient (or proxy where appropriate) reported.

To assess responsiveness, the SF-36 PF score was used.

Statistical Analysis

Reliability—Intraclass correlation (ICC) was used to evaluate test-retest and inter-rater reliability.

Construct Validity—Pearson and Spearman correlations were used to examine convergent and discriminant validity. As a measure of physical function, 4-m gait speed is expected to be at least moderately correlated ($r > 0.40$) with similar physical health outcomes (convergent validity), but to have weak correlations ($r < 0.30$) with non-physical health outcomes, such as mental health (discriminant validity). Furthermore, we expected that the 4-m gait speed’s correlation with physical health outcomes would be stronger than with mental health outcomes. For known group construct validity tests, the 2-sample, independent t-test was used to determine whether mean gait speed significantly differed between patient groupings determined based on evaluation for ICU-acquired weakness (MMT strength score <48/60) and impaired pulmonary function (FEV₁ <70% predicted). We hypothesized that gait speed

would be significantly lower in patients with muscle weakness and impaired pulmonary function.

Predictive Validity—To determine if 4-m gait speed predicts subsequent outcomes, logistic and linear regression models were used with the previously described outcome variables as dependent variables and the 4-m gait speed (per 0.11 m/sec(11)) from an immediately prior timepoint as the independent variable.

Responsiveness—Linear regression was used to test whether change in gait speed differed for participants who improved, declined or did not change on the SF-36 PF. Based on available data in the two studies, we examined responsiveness for three time periods: 6 to 12 months, 36 to 48 months and 48 to 60 months. We categorized change in the SF-36 PF as “decline” if scores decreased by 10 points, “no change” if score decreased or increased by <10 points, and “improvement” if score increased by 10 points. The 10-point increment represented 1 standard deviation for the SF-36 PF and has been identified as important change by clinical experts.(47)

Estimating Minimally Important Difference (MID)—As recommended(48), we used multiple anchor- and distribution-based methods to estimate the MID. Anchors include the SF-36 PF and EQ-5D utility (EQ-5D was multiplied by 100 for easier presentation). These outcomes were chosen as anchors as they represent distinct, but important, health-related quality of life concepts (EQ-5D utility includes physical and mental aspects), have strong convergent validity with 4-m gait speed, and have previously reported MIDs. To estimate an anchor-based MID, we fit a linear regression model at each timepoint with gait speed as the outcome and an anchor measure, either SF-36 PF or EQ-5D utility as the predictor. The beta coefficient from this model represents the difference in average gait speed that is equivalent to a 1 point difference in the anchor measure at the given follow-up. The beta coefficient multiplied by the anchor’s MID (5 points for SF-36 PF and 7.4 for EQ-5D utility (i.e., the MID of 0.074 multiplied by 100)(49,50) determines the 4-m gait speed MID estimate using that anchor.

For the distribution-based methods, standard error of measurement (SEM) and minimal detectable change at the 90% confidence interval (CI) for the 4-m gait speed were calculated as in prior studies(48,51,52). The 0.2 and 0.5 standard deviation (SD) of 4-m gait speed were calculated to reflect a small and moderate effect size, based on Cohen’s criteria.(53)

We conducted analyses separately for each study and for each follow-up to examine whether findings were consistent despite differences in patient characteristics and follow-up timepoint. For greater power and precision, we pooled analyses over follow-up assessments when feasible. For pooled analyses, repeated measures were accounted by computing robust standard errors for correlation coefficients. Standard errors for regression coefficients in pooled analyses were adjusted using mixed models to account for repeated measures per individual over time (54,55) For the distribution-based MIDs, pooled variance of the 4-m gait speed was computed by taking the weighted average of the variance estimates at each follow-up, based on the sample size of each follow-up divided by total observations. The square root of the pooled variance was used to estimate pooled SEM.

RESULTS

Patient characteristics were generally similar between the ALTOS and ICAP cohorts (Table 1). However, ICAP had a higher proportion of Black participants than ALTOS and had longer lengths of stay. Mean (standard deviation) walking speed at the time of the initial evaluation (6 months for ALTOS and 36 months for ICAP) was the same in both studies at 1.0 (0.3) meter/sec.

Reliability

The 4-m gait speed test demonstrated excellent reliability. ICCs for test-retest reliability were 0.89–0.99 across both studies and all five follow-ups. ICC for inter-rater reliability, based on 32 pairs of observations, was 0.97 when pooled across both studies.

Construct Validity

Across both studies and all five follow-ups, 69% of the cross-sectional correlations of the 4-m gait speed with other physical health measures were >0.40 (Table 2). Correlations with mental health measures were generally weak, with 86% of correlations, <0.30 (Table 2). These findings provide evidence of convergent and discriminant validity, respectively.

As hypothesized for the known groups analysis, patients with ICU-acquired weakness (MMT <48 vs. 48) and impaired pulmonary function ($FEV_1 <70\%$ vs. 70% predicted) had significantly slower gait speed, and results were generally consistent across studies and follow-ups through 60 months (Table 3).

Predictive Validity

Gait speed significantly predicted future hospitalization and health-related quality of life in both studies (Table 4). Moreover, among ICAP participants, gait speed significantly predicted mortality, alive at home status, and return to work or normal activity. The magnitude of the associations across both studies and for each ICAP follow-up timepoint (presented in supplemental Table E1) were comparable and in the expected direction, although not all were statistically significant.

Responsiveness

Statistically significant increases in gait speed were observed for patients with a >10 point increase in the SF-36 PF domain for ICAP participants in pooled analysis and for changes between 48 and 60 months (Table 5). Statistically significant declines in gait speed were also observed for patients with >10 point decrease for 48 and 60 months. Gait speed increased and declined consistent with improvement or worsening in SF-36 PF among ALTOS participants between 6 and 12 months, but these changes were not statistically significant.

Estimating Minimally Important Difference (MID)

Anchor-based MID estimates for the 4-m gait speed test were 0.02–0.04 m/sec in pooled analyses (Table 6). A broader range, 0.03–0.05 m/sec, was observed at specific follow-up (supplemental Table E2). Distribution-based MID estimates were generally larger than anchor-based MID estimates. In pooled analyses, SEM and 0.2 SD were each 0.06 m/sec for

both studies. Minimal detectable change₉₀ was 0.13–0.14 m/sec and 0.5 SD was 0.14–0.15 m/sec in the two studies.

DISCUSSION

These analyses of 2 multi-site studies of ARDS survivors demonstrate that the 4-m gait speed test is a reliable, valid and responsive performance-based measure of physical functioning over 6 to 60 month follow-up. Data analyses support test-retest and inter-rater reliability of the 4-m gait speed test, as well as its concurrent construct validity, with evidence of convergent and discriminant validity and known group validity, across 5 discrete follow-up time points in 2 different ARDS studies. In addition, the 4-m gait speed test demonstrated predictive validity for outcomes, including hospitalization and health related quality of life, and responsiveness consistent with changes in patient-reported physical functioning. Convergence of anchor-based estimates with SEM suggested that 0.03 to 0.06 meters/sec is a reasonable range for the MID of the 4-m gait speed among ARDS survivors.

The reliability and construct validity of the 4-m gait speed test in ARDS survivors were similar to reports in other populations. In studies of healthy older adults, patients receiving rehabilitation after stroke, and COPD patients(4,6,8), excellent reliability (ICCs=0.86–0.97) were reported for gait speed tests of different distances. Prior studies in diverse populations have also found evidence of concurrent construct validity(5,6,12,56). Faster gait speed was positively associated with better physical health for a range of measures and outcomes and healthy subjects had faster gait speed than subjects with health conditions. However, our study also contributed evidence of discriminant validity, finding the expected weaker correlations between gait speed and mental health measures, which were often not examined in prior validation studies of the 4-m gait speed test. Furthermore, concurrent validity findings were robust across a wide range of relevant follow-up time points (i.e. 6 to 60 month) and across two multi-site studies (including one national study), supporting generalizability of these findings to other ARDS survivors across different points in their recovery trajectory.

For the predictive validity analyses in both ARDS study populations, lower odds of mortality and re-hospitalization, higher odds of being alive at home, and better future health-related quality of life were all observed with faster gait speed, although these relationships were not always statistically significant. Furthermore, pooled and time-specific estimates were consistent in direction and magnitude of association, affirming predictive validity for 4-m gait speed overall and at different time points. Our findings are consistent with those from previous studies. In diverse populations of older adults and hemodialysis patients of all ages, slower walking speed was predictive of mortality, hospitalization, disability, and nursing home placement.(10,13–16) Differences in statistical significance between the studies and time points may be due to relatively small sample sizes or the potential influence of unmeasured contextual or patient characteristics affecting survivors' return to work or their home.

The significant associations with re-hospitalization and future quality of life outcomes suggest the value the 4-m gait speed test may have for clinical practice and research.

Comparable predictive associations reported in geriatric samples have prompted calls for gait speed tests, such as the 4-m gait speed, to be assessed as the “sixth vital sign” (18,21) in clinical encounters and used in risk prediction and developing patient-centered care plans (14,15,57). Similarly, our findings support further evaluation of ARDS survivors with slow gait speed to help identify those who may benefit from additional interventions and to assist in developing individualized care planning to reduce risks of re-hospitalization and poor health-related quality of life. The need to target the right population for evaluations of post-intensive care interventions for critical illness survivors have also been noted (58,59). The 4-m gait speed test could play a role in future research to help screen for an appropriate sample for clinical trials.

Prior studies have reported on the responsiveness of gait speed, including the 4-m gait speed test(11), to intervention and to longitudinal change^(60–63). In our study, changes in 4-m gait speed generally parallel changes in patient-reported physical function, supporting responsiveness, although the differences in gait speed across change categories were not all statistically significant. Small sample sizes within selected change categories may have contributed to the lack of consistency observed.

As recommended(48) for MID estimation, we used multiple anchor-based and distribution-based approaches and gave greater weight to anchor-based estimates, which were approximately 0.03 m/sec. The distribution-based MID estimates, which do not provide direct evidence for the MID and have a supporting role in MID determination(48), were generally larger. However, the SEM and 0.2 SD estimates, at approximately 0.06 m/sec, were relatively close to the anchor-based estimates, suggesting that 0.03 to 0.06 m/sec would be a reasonable MID range for the 4-m gait speed test. Interventional studies aiming to detect a change that is larger than the minimum important difference, such as a moderate sized change, may consider a value of approximately 0.15 m/sec which corresponds to both the 0.5 SD moderate effect size and the minimal detectable change estimates.

Studies in other populations, often using sample sizes substantially smaller than the 306 patients included in our study, have reported variable estimates for the MID of the 4-m gait speed test. However, most range between 0.04 and 0.11 m/sec, generally consistent with our estimates. Perera and colleagues⁽⁶¹⁾ reported a MID range of 0.04 to 0.06 m/sec using different anchors in a sample of 492 older adults with various health conditions and determined 0.05 m/sec to be a small meaningful change. Kon and colleagues(11) reported MID of 0.08 when anchored to self-reported improvement and 0.11 m/sec when anchored to the incremental shuttle test among 463 COPD patients. A study in 43 healthy older adults found standard error measurement of 0.006–0.008 m/sec and minimal detectable change 0.01–0.02 m/sec for the 4-m gait speed test(8), while a range of 0.04–0.10 meters/sec for habitual gait speed using an approximately 4-m walkway was reported in 92 patients after hip fracture⁽⁶⁴⁾. For gait speed more generally, distribution-based MID (based on standard error of measurement) was 0.07 m/sec for a 30-meter test in 49 stable COPD patients(5), 0.30 m/sec (based on minimal detectable change of a 5-meter test) for 35 post-stroke patients(4), although it was smaller at 0.07 m/sec for those requiring physical assistance(4).

Both the 6MWT and the 4-m gait speed test demonstrated concurrent construct validity, predictive validity, and responsiveness for ARDS survivors, based on our study and a prior bi-national evaluation of the 6MWT⁽⁶⁵⁾. However, the NIH toolbox(22) categorizes 4-m gait speed as a measure of locomotion and 6MWT as an endurance measure. Researchers specifically interested in locomotion or endurance should consider these distinctions and select their measure accordingly. However, for researchers interested in these tests as proxies for patient-reported function or health-related quality of life, or to predict important future outcomes, the 4-m gait speed may work as well as the 6MWT. Furthermore, the 4-m gait speed test is more feasible than the 6MWT, requiring markedly less space and time to administer (<2 minutes for two tests using a 4 meter track length versus 6MWT requiring up to 57 minutes (6 minutes for each of 2 tests plus rest periods) and track length of at least 15 meters⁽⁶⁶⁾).

Despite this study's novelty and its strengths associated with combining two different multi-site studies and evaluating patients over 6 to 60 month follow-up, this study has several limitations. First, the sample sizes, especially at specific follow-up, are relatively small and may have contributed to the lack of statistical significance for specific evaluation of predictive validity and responsiveness. Due to this concern, given the highly consistent results across time points, we provided pooled analyses whenever feasible, to increase power. Second, anchor-based MID may be determined cross-sectionally or longitudinally⁽⁶⁷⁾; our estimates are from cross-sectional, between-group analyses and thus, are more appropriate for group comparisons rather than evaluating within-patient change over time. Finally, our study specifically focused on the 4-m gait speed among ARDS survivors and these results may not generalize to gait speed assessments using different distances or to other groups of ICU survivors. Furthermore, our data came from ARDS survivors whose characteristics and care may be influenced by their participation in research studies. However, a recent study demonstrated that 5, 8, and 10-meter distances yielded consistent results for gait speed ⁽⁶⁸⁾. Future studies should evaluate this test in other samples of ARDS survivors and other populations of critical illness survivors.

CONCLUSIONS

The 4-m gait speed is a reliable, valid and responsive measure of physical functioning among ARDS survivors. The MID range of 0.03–0.06 m/sec will help to interpret the efficacy of research interventions in this population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Table 1

Participant characteristics by study

Variables	ALTOS (N=184)	ICAP (N=122)
Age, years, mean (sd)	48.0 (14.6)	46.0 (12.9)
Male, n (%)	91 (50)	66 (54)
BMI kg/m ² , mean (sd)	31.0 (8.0)	28.5 (7.0)
Race, n (%)		
White	165 (90)	69 (57)
Black	14 (8)	50 (41)
Other	5 (3)	2 (2)
Education, years, mean (sd)	13.4 (3.0)	12.7 (2.9)
Employed, n (%)	93 (51)	76 (62)
Charlson Comorbidity Index, mean (sd)	1.1 (1.7)	1.8 (2.3)
Functional Comorbidity Index, mean (sd)	1.9 (1.5)	1.4 (1.4)
APACHE II score, mean (sd)	25.3 (8.0)	23.6 (7.6)
Ventilation duration, days, mean (sd)	10.8 (9.5)	13.6 (14.8)
ICU length of stay, days, mean (sd)	14.3 (11.0)	18.2 (17.8)
Hospital length of stay, days, mean (sd)	21.4 (15.0)	29.2 (22.4)
4-meter gait speed at first assessment ^I , meters per second, mean (sd)	1.0 (0.3)	1.0 (0.3)

Abbreviations: sd: standard deviation; BMI: Body Mass Index; Acute Physiology and Chronic Health Evaluation; ICU: Intensive Care Unit.

^IFirst 4-meter gait speed assessment for ALTOS (6 month)and ICAP (36 month).

Construct Validity: Cross-sectional association¹ of 4-meter gait speed (m/sec) with mobility and physical function (convergent validity) and mental health measures (discriminant validity)

Table 2

Convergent Validity: Correlation with Measures of Physical Function								
Follow-up, in months	Study	N	6 minute walk test	FPI Survey	No. ADL dependencies	No. IADL dependencies	SF-36 PF domain ²	EQ-5D Mobility ³
Pooled [†]	ALTOS	296–310	0.62 (<0.001)	0.50 (<0.001)	--	--	0.58 (<0.001)	–0.44 (<0.001)
6 mo.	ALTOS	153–158	0.56 (<0.001) ⁴	0.49 (<0.001)			0.58 (<0.001)	–0.41 (<0.001)
12 mo.	ALTOS	143–152	0.67 (<0.001) ⁴	0.50 (<0.001)			0.58 (<0.001)	–0.45 (<0.001)
Pooled [†]	ICAP	293–313	0.37 (<0.001)	--	–0.27 (<0.001)	–0.43 (<0.001)	0.57 (<0.001)	–0.42 (<0.001)
36 mo.	ICAP	92–96	0.37 (<0.001)		–0.19 (0.059)	–0.35 (<0.001)	0.55 (<0.001)	–0.30 (0.003)
48 mo.	ICAP	98–107	0.47 (<0.001)		–0.30 (0.002)	–0.38 (<0.001)	0.54 (<0.001)	–0.43 (<0.001)
60 mo.	ICAP	103–110	0.28 (0.005)		–0.39 (<0.001)	–0.57 (<0.001)	0.64 (<0.001)	–0.51 (<0.001)

Discriminant Validity: Correlation with Measures of Mental Health						
Follow-up, in months	Study	N	HADS Anxiety Symptoms	IES-R PTSD Symptoms	SF-36 MH domain ²	EQ-5D Anxiety ³
Pooled [†]	ALTOS	309–310	–0.17 (0.003)	–0.23 (<0.001)	0.20 (<0.001)	–0.18 (0.002)
6 mo.	ALTOS	157–158	–0.18 (0.022)	–0.24 (0.003)	0.24 (0.002)	–0.22 (0.005)
12 mo.	ALTOS	150–152	–0.15 (0.060)	–0.22 (0.006)	0.15 (0.093)	–0.16 (0.053)
Pooled [†]	ICAP	311–313	–0.25 (<0.001)	–0.29 (<0.001)	0.26 (<0.001)	–0.19 (<0.001)
36 mo.	ICAP	95–96	–0.19 (0.066)	–0.27 (0.008)	0.20 (0.050)	–0.13 (0.201)
48 mo.	ICAP	107	–0.20 (0.044)	–0.22 (0.026)	0.25 (0.011)	–0.09 (0.371)
60 mo.	ICAP	109–110	–0.36 (<0.001)	–0.39 (<0.001)	0.34 (<0.001)	–0.34 (<0.001)

Abbreviations: FPI: Functional Performance Inventory; ADL: Activities of Daily Living; IADL: Instrumental Activities of Daily Living, SF-36: Short Form-36.

[†]Clustered robust standard errors were calculated for data pooled across time points to account for repeated measures.

¹Based on Pearson correlations except for EQ-5D subscales, which used Spearman correlations. Moderate-to-strong associations with physical health measures ($r > 0.40$) expected for convergent validity; weak associations with mental health measures ($r < 0.30$) expected for discriminant validity.

²SF-36 physical function (PF) and mental health (MH) subscales (transformed version, score range:0–100, higher = better functioning).

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³EQ-5D subscales (Likert rating scales of 0, 1, and 2, higher = worse health).
⁴Previously reported in Chan et al.(2015)²⁴

Table 3

Mean (standard deviation, SD) 4-meter gait speed (m/sec), by known groups of strength and pulmonary function

Follow-up months	Study	Strength – Manual Muscle Testing (MMT) ¹			Pulmonary Function – % Predicted for Forced Expiratory Volume in 1 Second (FEV ₁) ²		
		<48 Mean (SD)	48 Mean (SD)	p-value ³	<70% Mean (SD)	70% Mean (SD)	p-value ³
Pooled ⁴	ALTOS	0.61 (0.28) N = 19	1.01 (0.28) N = 290	<0.001	0.90 (0.31) N = 94	1.02 (0.29) N = 199	<0.001
6	ALTOS	0.60 (0.25) N = 11	0.99 (0.30) N = 150	<0.001	0.90 (0.36) N = 48	1.00 (0.30) N = 103	0.074
12	ALTOS	0.62 (0.34) N = 8	1.02 (0.30) N = 140	<0.001	0.90 (0.24) N = 46	1.06 (0.28) N = 96	0.001
Pooled ⁴	ICAP	0.61 (0.27) N = 13	0.98 (0.27) N = 298	<0.001	0.85 (0.25) N = 79	1.01 (0.27) N = 224	<0.001
36	ICAP	0.63 (0.31) N = 4	1.00 (0.29) N = 92	0.013	0.88 (0.30) N = 24	1.02 (0.28) N = 69	0.049
48	ICAP	0.66 (0.19) N = 5	0.97 (0.27) N = 102	0.010	0.83 (0.23) N = 25	1.00 (0.27) N = 78	0.007
60	ICAP	0.54 (0.38) N = 4	0.97 (0.24) N = 104	<0.001	0.85 (0.24) N = 30	1.01 (0.25) N = 77	0.003

¹MMT Medical Research Council(MRC) score range between 0–60;

²FEV₁ (and FVC) predicted values were calculated based on age, sex, height, and race as previously described.³⁸

³ p-value based on t-test comparing mean 4-m gait speed between groups. Findings were consistent with the expected differences in gait speed in each comparison which supports known group validity. For example, in pooled analysis, ALTOS participants with muscle weakness (MMT MRC score <48) walked slower at 0.61 m/sec compared with ALTOS participants without muscle weakness (MRC 48) who walked faster at 1.01 m/sec, consistent with expectations.

⁴Linear regression model including the known group indicators and main effect of time; robust standard errors were computed to account for multiple 4M gait speed values per patient in pooled analyses.

Table 4

Predictive validity of 4-meter gait speed (per 0.11 m/sec) for post-discharge outcomes: All-cause mortality, any hospitalization, alive at home, return to normal activity, and health-related quality of life

Outcome ¹	Study	4M gait speed Assessment	Follow-Up Period for Outcome	Odds Ratio or Beta ⁴ (95% CI)
Mortality	ALTOS	6 month	6 to 12 months	OR = 0.93 (0.70,1.24)
	ICAP	36 month	36 to 60 months ²	OR = 0.44 (0.26,0.75) **
Hospitalization	ALTOS	6 month	6 to 12 months	OR = 0.78 (0.65,0.92) **
	ICAP (pooled)	36 month, 48 month	36 to 48 months, 48 to 60 months	OR = 0.77 (0.65,0.90) **
Alive at home	ALTOS	6 month	at 12 months	OR = 1.07 (0.89,1.30)
	ICAP (pooled)	36 month, 48 month	at 48 month, at 60 month	OR = 1.94 (1.33,2.82) **
Return to Normal Activity	ALTOS	6 month	at 12 months	OR = 1.01 (0.85,1.20)
	ICAP (pooled)	36 month, 48 month	at 48 month, at 60 month	OR = 1.34 (1.08,1.66) **
SF-36 Physical Function ³	ALTOS	6 month	at 12 months	Beta = 5.70 (4.19,7.22) **
	ICAP (pooled)	36 month, 48 month	at 48 month, at 60 month	Beta = 7.05 (5.18,8.93) **
EQ-5D Utility Score	ALTOS	6 month	at 12 months	Beta = 2.65 (1.48,3.83) **
	ICAP (pooled)	36 month, 48 month	at 48 month, at 60 month	Beta = 3.19 (1.84,4.54) **

* p 0.05

** p 0.01;

¹ Distribution of each outcome, Mortality: death = 1, alive = 0 (ALTOS: by 12m, 150 alive, 7 deaths; ICAP: by 60m, 90 alive, 6 deaths); Hospitalization: any = 1, none = 0 (ALTOS: 6–12m, 113 none, 33 any; ICAP: 36–60m, 129 none, 74 any); Alive at home: yes = 1, no = 0 (ALTOS: 12m, 144 yes, 17 no; ICAP pooled 48m and 60m, 189 yes, 12 no); Return to normal activity: yes = 1, no = 0 (ALTOS: 12m, 59 yes, 23 no; ICAP: pooled 48m and 60m, 69 yes, 70 no).

² Mortality by 60 months predicted by 36-month 4M gait speed because patients who died between 36 and 60 months did not have 48-month 4M gait speed data.

³ The transformed version of the SF-36 PF subscale score was used in regression models (range 0–100).

⁴ Faster gait speed is expected to predict better future outcomes. For example, in the pooled ICAP analyses, survivors who walked 0.11 m/sec faster (e.g. individuals walking at 0.91 m/sec vs. 0.80 m/sec) would have 56% and 23% lower odds of future mortality and hospitalization, respectively, but 94% and 34% higher odds of being alive at home and returning to normal activity, respectively, 12 months later. In addition, survivors who walk 0.11 m/sec faster report 7.05 higher scores on the SF-36 PF and 3.19 on the EQ-5D utility measures 12 months later.

Responsiveness to change in recovery trajectory: Mean change in 4 meter gait speed (m/sec) relative to patient-reported change¹ in SF-36 PF Score²

Table 5

Change period	Study	(a) Improvement Mean Change in 4-m gait speed, m/sec	(b) No change Mean Change in 4-m gait speed, m/sec	(c) Decline Mean Change in 4-m gait speed, m/sec	p-value (a) vs. (b)	p-value (c) vs. (b)	p-value (a) vs. (c)
6 to 12 mo.	ALTOS	0.10 (n=21)	0.04 (n=138)	-0.02 (n=8)	0.354	0.693	0.476
Pooled ICAP-only	ICAP	0.12 (n=15)	-0.02 (n=173)	-0.09 (n=15)	0.014	0.204	0.006
36 to 48 mo.	ICAP	0.04 (n=3)	-0.04 (n=84)	0.14 (n=5)	0.521	0.141	0.347
48 to 60 mo.	ICAP	0.16 (n=12)	-0.006 (n=89)	-0.16 (n=10)	0.012	0.014	<0.001

¹ Patient reported improvement reflects SF-36 PF score increase of 10 points or more between specified time points; No change reflects SF-36 PF score change -10 to 10 between specified time points; Patient reported decline reflects SF-36 PF score decrease by 10 points or more between specified time points. Change in gait speed is expected to be consistent with change in physical function based on SF-36 PF scores; faster gait speed were expected among those who improved on the SF-36 PF and slower gait speed among those who declined. For example, in pooled ICAP analysis, survivors with improved SF-36 PF scores walked on average 0.12 m/sec faster, while survivors with no change had a negligible difference in gait speed (-0.02 m/sec) and survivors with declines in SF-36 scores walked slower by 0.09 m/sec.

² The normed version of the SF-36 PF subscale score was used in responsiveness analyses.

Table 6Minimal Important Difference for 4-Meter Gait Speed (Pooled¹ Across Time Points)

Approach used to Estimate Minimal Important Difference	STUDY	N	MID (m/sec)
SF-36 PF domain (per 5 points)²- Anchor-Based³			
Pooled time points (6 & 12 months)	ALTOS	309	0.03
Pooled time points (36, 48, & 60 months)	ICAP	313	0.02
EQ-5D Utility score (per 7.4 points)⁴- Anchor-Based³			
Pooled time points (6 & 12 months)	ALTOS	308	0.04
Pooled time points (36, 48, & 60 months)	ICAP	313	0.02
Standard Error of Measurement (SEM) - Distribution-Based			
Pooled time points (6 & 12 months)	ALTOS	313	0.06
Pooled time points (36, 48, & 60 months)	ICAP	313	0.06
Minimal Detectable Change_{90%} - Distribution-Based			
Pooled time points (6 & 12 months)	ALTOS	313	0.14
Pooled time points (36, 48, & 60 months)	ICAP	313	0.13
Moderate Effect Size (Cohen's) 0.5 Standard Deviation - Distribution-Based			
Pooled time points (6 & 12 months)	ALTOS	313	0.15
Pooled time points (36, 48, & 60 months)	ICAP	313	0.14
Small Effect Size (Cohen's) 0.2 Standard Deviation - Distribution-Based			
Pooled time points (6 & 12 months)	ALTOS	313	0.06
Pooled time points (36, 48, & 60 months)	ICAP	313	0.06

¹Generalized Estimating Equations were used to estimate anchor-based MIDs in pooled analyses to account for potential correlation due to repeated measurement. For the distribution-based MIDs, pooled variance of the 4M gait speed was computed by taking the weighted average of the variance estimates at each follow-up, based on sample size of each follow-up divided by total observations. The square root of the pooled variance was used to estimate the SEM.

²The transformed version of the SF-36 PF subscale score was used in MID estimation (range 0–100).

³Anchor measures all demonstrate correlation >0.30 with gait speed (SF-36 PF: $r = 0.58$ in ALTOS and 0.57 in ICAP; EQ-5D: $r = 0.40$ in ALTOS and 0.36 in ICAP, all $p < 0.01$).

⁴Original EQ-5D utility score (ranges between –0.11 and 1.0) was multiplied by 100 to facilitate comparison with SF-36 PF score range.