1) Title: Outcome Measures Report Different Aspects of Patient Function Three Months Following Critical Care

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Abstract (250 words)

Background: Previous investigation of the relationship between physical performance and patient self-report physical function measures in intensive care unit survivors have not been performed.

Objectives: To (1) analyze the extent to which other activity-based measures of physical performance may serve as proxies for the six minute walk test (6 MWT); (2) determine the extent to which the Short Form 36 domain of physical function and physical component summary score, reflect components of physical performance and (3) examine the relationship between demographic and ICU variables and the 6MWT.

Design: Cross sectional data from 2 clinical trials.

Setting: Two acute care hospitals (Melbourne, Australia and Denver, USA).

Patients: 177 survivors of ICU.

Measurements: Were evaluated at three months. Performance-based measures were: 6MWT, timed up and go test (TUG), the five times sit to stand test (5xSTS), the Berg balance scale (BBS) and two self-report measures: the Short Form 36 physical function (PF) domain and the physical component summary (PCS) score.

Main Results: 6MWT showed excellent correlation with the TUG ($\rho=-0.79$) and BBS ($\rho=0.80$); and good correlation with 5xSTS ($\rho=-0.69$) and SF36 PF scores ($\rho=0.69$). 6MWT explained 54% and 33% of variance in SF36 PF and PCS scores respectively. No variables were clinically important in predicting 6MWT.

Conclusions: The 6MWT and TUG may both be acceptable measures of physical function performance three months after ICU. Performance based tests measure different constructs than self-report measures and choice of outcome variables should be aligned with study aims to ensure the most appropriate measure is used.

Key words: physical function, performance based tests, patient reported outcomes, critical care.

Running title: Physical function outcome measures in critical care

Introduction (3454 words)

The long-term consequences of a critical illness have recently been defined using a model of impairment [1] and reduced physical function is one of the most common limitations for ICU survivors [2].

Performance based measurement of functional ability after ICU discharge has been undertaken using a variety of measures, including the six minute walk test (6MWT) [3, 4], shuttle walk test and timed up and go test (TUG) [3]. These tests tap into the domain of 'activities' as defined by the International Classification of Function and Disability and Health (ICF) [5]. Self-report measures (patient reported outcomes), measure patient perception of their functional ability or level, and include the Short Form (SF) 36 [6] and Katz activities of daily living [7]. These measures tap into the domain of 'participation' as defined by the ICF. Embedding assessment measures into the ICF framework may aid choice of the right measures for patients at the correct timing of recovery [5].

The aim of this paper was to compare outcomes of function using both performance and self-report measures in ICU survivors at three months post critical illness. The specific purposes of the study were to (1) analyze the extent to which other (more expedited) activity-based measures of physical performance may serve as proxies for the 6 MWT; (2) determine the extent to which the SF 36 domain of physical function and physical component summary score, measures of physical participation, reflect components of physical performance and (3) examine the relationship between demographic and ICU variables and the 6MWT at three months.

Materials and Methods

Design and Setting

The data in this cross sectional study are from two randomized controlled trials. One trial, conducted by Denehy and colleagues from Melbourne Australia is complete and published (2013)[3] and the other is ongoing in Denver Colorado, USA. The data presented are from 3 months post ICU discharge (Australia) and 3 months post ICU admission (USA). Data were censored in the US arm at the date of data download and all consecutive patient data were used until the time of censoring. Ethical approval was obtained for both trials from respective Ethical review boards at Austin Health, Melbourne Australia and Colorado Multiple Institutional Review Board at University of Colorado, Anschutz Medical Campus Denver, USA. Both trials were registered; Australian New Zealand Clinical Trials Registry (ACTRN): 12605000776606; US registration: Clinical trials.gov: NCT01058421

Since the US study is ongoing the participant numbers represent a smaller proportion than those in the Australian study. Not all measurements were collected in both studies, although 3 of 5 reported are the same (6MWT, TUG and SF 36). Consequently the sample size varies for reported variables.

Participants

For both patient populations, all participants were admitted to an intensive care unit (ICU), were >18 years, English speaking, and did not have a physical or cognitive impairment that would prevent exercise. The Australian trial recruited participants who were in the ICU for five days while the US trial is recruiting participants who were in the ICU *and mechanically ventilated* for at least four days. Demographic details at trial recruitment and functional and health related quality of life physical function domain values at 3 months post critical illness were extracted from the two trial data bases by data base managers at each site.

Performance based functional activity measures

Further details of the method of testing in each test are described in the e-supplement. The 6MWT test was used to measure functional exercise ability [8]. Developed for older adults, the TUG measures functional mobility and assesses the time (seconds) taken to stand from a chair, walk 3 meters and return to the sitting position [9]. The 5 times sit to stand test involves timing the participant to stand up and sit down again 5 times as quickly as possible with the arms folded across the chest [10]. This test and the following Berg Balance Scale (BBS) were measured only in the US cohort. The BBS [11] is a 14 item test of balance that was previously validated against the TUG and Barthel index. The maximum score is 56 where a score range of 41-56 = low fall risk; 21-40 = medium fall risk and 0 –20 = high fall risk.

Self report participation measures of function

The Short Form 36 version 2 (SF-36v2) is an 8 domain, generic health status questionnaire [12] that has been validated [13] and recommended for use in the ICU population [14]. The physical function domain and physical component scores are used in this study to compare with performance measures. The questions that make up the physical function domain are given the electronic supplement in Table E1. The SF36 was used in all participants and administered face to face in 100% and 98% of the US and Australian populations respectively at 3 months.

Factors associated with performance based physical function

Risk factors that may be associated with physical function performance at 3 months were identified from demographic details and ICU variables and included length of stay in ICU, time on mechanical ventilation (MV) and illness severity at ICU admission using the APACHE II score.

Data Analyses

A full description of data analyses is available in the E- Supplement

Demographics were calculated and are presented for the total sample as well as the Australian and US samples separately. To analyze correlations between the 6MWT (continuous variable) and the other functional tests (aim 1), the Spearman's rank correlation coefficient was used. To determine the extent to which other measures of physical performance serve as proxies for the 6 MWT (aim 2), a general linear model was used to examine how much of the variance in SF36 physical function (PF) domain (transformed percentage score) and SF36 physical component summary (PCS) scores (US normed t-scores) was explained by 6MWT distances and TUG times. Potential co-variables also included in analyses were: demographic (age, gender) and ICU based (APACHEII scores, MV days and ICU LOS) variables. A categorical TUG variable was created based on the frequency distribution (quartiles) of "completers" scores which also included a group for the subjects who scored 120 (could not complete) and used in regression analyses. The TUG categories were 1= 120; 2= 12.51 – 84; 3= 9.01 – 12.5; 4 = 7.01 – 9; 5 = 0-7 seconds. Finally, to examine the relationship between demographic and ICU variables and the performance based 6MWT at 3 months (aim 3), the 6MWT was (1) dichotomized to above or below 50% of predicted normal values [3],[15] and logistic regression was used and (2) continuous values of percent predicted 6MWT were used in a linear regression model.

Results

A total of 177 patients completed performance based and self-report measures at 3 months after critical illness. Demographics at ICU discharge for the total sample and USA and Australian samples separately are presented in Table 1. Median (IQR) ICU LOS (days)

was 16 (9.8-23.5) for the USA compared to 7 (6-11) for the Australian sample. Also, MV days was 11 (8-18) for the USA compared to 3.8 (1.1-6.9) in the Australian sample.

Results of the performance based physical function tests are presented in Table 2. The median (IQR) 6MWT was 394 (274-485) m (25 % of patients walked less than 274 meters and 25% walked more than 485m). At 3 months, 5 of 127 participants (4%) were unable to perform the 6MWT and 4 (3%) walked less than 100 meters. Two of these 5 participants were from the Australian sample and both were able to complete the TUG, however the 3 US participants were not able to complete the TUG and only 1 was able to complete the BBS and 5xSTS test.

The median (IQR) percentage change in 6MWT distance between walks 1 and 2 for the Australian sample was -1.82 (-4.22 - 3.70) meters. Floor effects for the 6MWT occurred in 3.9% of participants. The mean TUG time was 14.96 s; floor effects for the TUG test occurred in 2.3% of patients. The mean 6MWT was 55% of predicted values [15] and the mean TUG was 59% of predicted values [16]. Thirty-five % (45/127) of participant's 6MWT distance fell below 50% of predicted values.

Two other variables had substantial floor or ceiling effects for the ICU population at 3 months post ICU admission: The BBS demonstrated a ceiling effect with 12 out of 26 (46%) subjects scoring 56, the highest score possible. The 5xSTS demonstrated a floor effect with 9 out of 26 (35%) subjects unable to perform the test. Results of the self-report participation tests are also in Table 2. The median PF domain score of the SF36 was 70%, which was 83% of predicted and the median PCS norm based score was 41.7/50 (83%).

The 6MWT demonstrated excellent correlation with the BBS and TUG (see esupp Figure E1 6MWT and TUG scatterplot) and good correlation with the 5 x STS. Table 3 presents the correlations. Participants with higher 6MWT distances tended to score lower (better) on the TUG (esupp Figure E1). The 6MWT demonstrated good correlation with the SF36 PF and SF36 PCS. Participants with higher 6MWT distances tended to score higher on the SF36 PF domain (Figure 1). As mean time to complete the TUG decreased (higher level of function), there was a trend for increasing SF36 PF domain scores (aim2).

With SF36 PCS as the dependent variable (esupp Table E2), there was no significant association for: APACHE II, gender and age. ICU LOS was excluded due to colinearity with MV days ($r = 0.827$). With SF36 PF as the dependent variable, TUG and significant covariates were entered using a stepwise general linear model that included 6MWT. TUG was the only variable that retained a significant association ($p=0.007$) with SF36 PF. The final model is given in Table 4. This model explains **54.3%** of the variance on the SF 36 PF score. With SF36 PCS as the dependent variable. 6MWT explained 29.8% of variance in SF36 PCS summary scores in this model (Table 4), with the addition of TUG only increasing this to **33.3%** (aim 2).

Finally, we examined whether any of the ICU or demographic covariates above were able to predict 6MWT distance walked at 3 months (aim 3). Forty-five of 127 subjects (35%) scored less than 50% of predicted values. When each covariate was entered separately into a logistic regression model, the only variable that was significant in the model ($p = 0.038$) was ICU LOS (MV time was not significant on univariate analysis). However this covariate had an odds ratio (95% CI) of 1.047 (1.002 to 1.094) and sensitivity of only 13%. Similarly the linear regression demonstrated that the entered covariates explained 13.8% of predicted 6MWD ($p<0.001$). However, while ICULOS made a unique contribution to the percent predicted 6MWT ($\beta=0.24$) this did not reach significance ($p=0.117$).

Discussion

In a population of moderately unwell ICU survivors from a mixed medical/surgical ICU we found that the 6MWT and TUG were highly correlated, and 6MWT and SF36 physical function domain correlated moderately. Together, the 6MWT and TUG explained 54% of the variance in the physical function domain score and 33% of the physical component score of the SF 36 v 2. No variables tested were clinically significant in predicting the 6MWT distance at 3 months. We additionally report that physical function ability was reduced compared with normal values at 3 months after ICU admission/discharge on both performance based activity tests and patient self-report physical participation tests.

The 6MWT measures functional exercise capacity and is reported to most closely reflect activities of daily living [8]. Indeed, the 6MWT was reported as an indicator of overall physical performance and mobility in populations of older people [17]. The TUG was developed in the geriatric population to test functional ability since it includes the components of sit to stand (function) and turning (balance) in addition to walking yet we found a high correlation between these 2 performance based tests. This result is consistent with others where significant correlations between 6MWT distances and measures of mobility, including standing balance, chair stands, and gait speed, in 86 older adults are reported [17], although ours is the only work to date to measure both of these tests concurrently in ICU survivors. Additionally, it is noteworthy that the differences between 2 consecutive 6MWT in the Australian sample were very small. Although it is recommended that the 6MWT be performed twice [8, 18], it may be possible at subsequent follow up that only 1 test is required in ICU survivors as the practice effect at 3 months post ICU discharge was very small.

The TUG test requires only a small space to perform (10m) while the 6MWT requires a 30m corridor. On this basis, given the excellent correlation, it may be possible to use the TUG in place of the 6MWT when the goal is to measure activity limitations. Both tests have normative data published for comparison and both measure activity limitations which result from impairments in strength that likely occurred during the ICU stay [5]. Neither test had large floor or ceiling effects in our sample. TUG is also reported to predict discharge destination in geriatric and knee replacement populations [19]. For these reasons, the TUG shows promise as a measure of activity, however the responsiveness of the test to interventions needs to be established.

While there were good correlations between the 6MWT and both the BBS and 5xSTS tests, these tests exhibited large ceiling or floor effects respectively in our population. The reduction in the range of scores on the BBS resulting from half the participants achieving the highest score may have effected the high correlation obtained for this test [20]. The 5xSTS was too difficult for 35% of the population, as standing from sitting requires a whole body movement that includes integration of muscle activity, proprioceptive responses and cognitive function [21].

There was a moderate correlation between 6MWT and SF36, consistent with other findings in an ICU population [22]. Given the 6MWT is reported to be a sub maximal test which is closely related to activities of daily living, this level of association is not surprising. This premise is further supported in that cardiopulmonary exercise testing (CPET), a maximal intensity test, was not correlated with either SF36 PF or PCS in an ICU population [23, 24].

Iwashyna and Netzer (2013) suggest using a conceptual framework to guide choice of assessments and subsequent interventions after critical illness, anchored in the World Health Organization's (WHO) International Classification of Functioning, Disability and Health (ICF)[5]. Within the model there is recognition that body systems (including impairment), activity limitation, restriction in participation, and quality of life are distinct aspects of response to a given illness. These different aspects may require unique approaches to assessment and treatment. For example, more than one measure may be required to differentiate limitations and participation at different time points of recovery. In our study, the performance based tests (eg: TUG and 6MWT) assess activity limitations and the SF36 PF and PCS measure how these limitations lead to participation level at 3 months post critical illness. Several questions asked as part of the SF36 PF domain, such as (3c) carrying groceries and (3j) bathing dressing (esupp Table E1), are related to how physical health limits participation rather than restricting activity such as measured by the 6MWT. It is therefore not a surprise that the 6MWT and TUG do not explain more of the variance in the SF36 PF domain. Furthermore the PCS includes questions from 4 different domains of the SF36, for example question 4 asks about how physical health is related to work restrictions. Predictably then, the 6MWT and TUG explained less variance for the PCS [5, 25] than for the Physical function domain. It is therefore reasonable to hypothesize that the 2 measures assess somewhat different constructs. For example walking distance measures activity limitations that may cause activity restrictions in the patient's own environment, but the SF 36 measures the more global ability to participate [5, 25].

Although self- report measures capture recovery from the very important perspective of the patient, these are known to be affected by a phenomenon called response shift [26]. This shift refers to the individuals' recalibration or re-conceptualization of their expectations related to the underlying construct as a result of their individual

experience of ICU and recovery [26]. Furthermore, at 3 months, the support of family, caregivers, patient resilience and psychological impairments all may impact patient perception of activity and participation. This finding is perhaps demonstrated well by examining the findings of Elliott et al where there was improvement in 6MWT distance greater than the reported minimal important clinical difference (25-35m) [27, 28] at 6 months but the SF36 PF domain improved by only 1 point over the same time frame (5 points is the reported MCID) [29].

ICU LOS was found to be significant in the dichotomized model, albeit perhaps not clinically relevant, as a predictor of achieving lower or higher distances on the 6MWT at 3 months. This finding was not supported when the 6MWT was used as a continuous variable. Using the 50% value was decided upon apriori and based on findings that the mean percent predicted 6MWT in the Australian study [3] was 52% at 3 months. We felt that it provided a good cut point to examine factors that may impact which patients reached this (arguably low) mean % predicted 6MWT. This finding is interesting since the low sensitivity suggests that length of time in ICU which is reported to reduce muscle strength [30] only weakly or does not predict 6MWT values at 3 months. There may be several reasons for this finding; Firstly, the type and intensity of physical therapy in the ICU may be variables that affect 6MWT performance after hospital discharge but we did not measure these. Secondly and importantly, other lifestyle factors may intervene between ICU and hospital discharge and the follow-up at 3 months that may impact muscle strength and functional exercise capacity. We previously reported that the number of steps per day achieved in our Australian cohort at 2 months were low compared with expected values [31]. These findings reinforce that survivors are relatively inactive compared with population norms, which may in turn affect their performance based activity as measured using the 6MWT. Certainly that only 55% of

predicted values were reached by 3 months may be related to activity levels once the patients return home.

Limitations

While combining data from these 2 studies increases sample size and improves generalisability of findings, the inclusion criteria were slightly different between studies. Nearly half of the patients in the Australian trial were surgical, these individuals may have been more highly functioning premorbidly, this needs to be considered when generalizing results from this work. The data analyses performed for this manuscript involved pooling data from both studies across both arms of the trials. Given the US patient numbers were small and the Australian trial showed no differences between groups we felt that data pooling was acceptable. Additionally, it is not possible to extrapolate our findings to other points of the patient trajectory since the relationship between patient self-report participation in physical activity and performance based measures of activity may conceivably change over time during recovery., We acknowledge that for the tests only conducted in the USA, the sample sizes for outcomes are small.

Conclusion and Recommendations

TUG and 6MWT were highly correlated at 3 months after critical illness suggesting that either of these 2 performance measures may be used at this time point. The 6MWT and TUG explained only half or one third of self reported physical function measured using SF36 PF domain and PCS summary score respectively. While the 6MWT remains a useful measure of functional exercise capacity, , even for quite disabled ICU survivors, it does not provide comprehensive information on the impact of how activity limitation impacts participation. This is important information for individualizing patient treatments. We therefore conclude that performance based tests measure different constructs than the SF 36 and that both

type of measures may be needed at different time points of patient recovery to provide the most useful information at the right time to guide further patient management.

We recommend use of both performance based and self-report tests integrated in the ICF model, but they should not be used interchangeably, rather, the most appropriate test should be chosen depending on whether activity limitation or restriction of participation are of most interest to the assessor and patient. For example a study with a primary aim focused on physical performance (e.g., muscle and functional recovery) may use the 6MWT or TUG test as primary outcome measures whereas a study more focused on the patient's ability to re-integrate into their home, work and social environment may use the SF-36 as a primary outcome, rather than 6MWT.

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Figure legends

Variable	Combined	Combined	USA	Australia
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Figure 1. Correlation between six minute walk (m) and SF36 Physical Function domain score.

Figure E1. Correlation between six minute walk (m) and timed up and go (secs) tests.

Outliers removed from graph.

Table 1: Demographic information at ICU admission

	n	Median (IQR ^e)	n	Median (IQR)	n	Median (IQR)
Age**	177	60.0 (49.0-72.0)	27	53.0 (36.0 – 62.5)	150	62.0 (50.0 – 75.0)
Gender(%male)	177	64%	27	67%	150	63%
BMI* ^a	169	26.2 (23.1-30.8)	27	24.4 (22.6 – 26.6)	142	27.0 (23.3 – 31.0)
APACHE II ^b	177	19.0 (16.0-23.0)	27	18.0 (14.0 – 22.0)	150	19.0 (16.0 – 23.0)
ICU ^c LOS (days)***	176	8.0 (6.0-14.0)	26	16.0 (9.8 – 23.5)	149	7.00 (6.0 – 11.0)
MV ^d days***	177	5.00 (2.0-10.0)	27	11.0 (8.0 – 18.0)	150	3.8 (1.1 – 6.9)
Diagnosis: Med/Surg %***	177		27	89/11	150	55/45
ICU diagnosis %			27		150	
Pulmonary sepsis (Pneumonia/ALI/ARDS)				55.5		17
Cardiac				7.5		17
Surgery				11		38
Liver disease/transplant						10.5
Sepsis				18.5		8.5
Other				7.5		9

Footnotes: ^aBMI Body mass index; ^bAPACHE Acute Physiological and Chronic Health

Evaluation; ^cICU Intensive care unit; ^dMV Mechanical Ventilation; ^eIQR interquartile range.

Significant between group differences, *p=0.05, **p<0.01, ***p≤0.001

Functional test	n	Normal value	Median or Mean	IQR ^g
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Table 2: Descriptive results for physical function tests.

6MWT ^a (m)	127	662	394.0	274.0-485.0
		(626.7-699.16)		
6MWT mean (SD)			367.58	
			(167.61)	
SF36 PF ^b	127	84.64	70.0	40.0-90.0
		(21.86)(45)		
SF36 PCS ^c	126	50 (10)	41.7	33.6 – 48.5
TUG ^d (sec)	130	9.2	9.1	7.2-12.5
		(8.1-9.2)(29)		
mean (SD)			14.96	
			(19.28)	
Berg ^e (CO only)	26	54.5	52.0	40.8-56.0
		(0.93)(46)		
5xSTS ^f (sec) (CO only)	26	11.4	20.5	11.2-120.0
		(11.4-12.3)(47)		

Footnotes: ^a6MWT, six minute walk test; ^bSF36 PF, Short Form 36 physical function domain (percentage score); ^cSF36 PCSS, Short Form 36 physical component summary score (US normed t-score); ^dTUG, timed up and go test; ^eBerg, Berg balance score; ^f5xSTS, five times sit to stand test; ^gIQR, interquartile range

Table 3: Correlation between the six minute walk and timed up and go tests and other physical function measures. Values are for Spearman's rho (p)

Functional Test	TUG (secs) n=127	SF36 PF ^c	SF36 PCSS ^d	Steps per day n=47	Berg ^e n=26	5 X
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	rho	n	rho	n	rho	rho	rho	
6MWT ^a (m)	-0.793 (p<0.001)	123	0.690 (p<0.001)	122	0.503 (p<0.001)	0.457 (p=0.001)	0.800 (p<0.001)	(p<0.001)
TUG (secs)	-	126	-0.675 (p<0.001)	125	-0.539 (p<0.001)	-0.338 (p=0.020)	-.908 (p<0.001)	(p<0.001)

Footnotes: ^a6MWT, six minute walk test; ^bTUG, timed up and go test; ^cSF36 PF, short form 36 physical function domain (percentage score); ^dSF36 PCSS, short form 36 physical component summary score (US normed t-score), ^eBerg, Berg balance score; ^f5xSTS, five times sit to stand test

Table 4: Final general linear model for effect of variables on SF 36 physical function domain score

SF36 Physical Function Domain

Source	Mean Square	F test	p	Partial Eta Squared
Corrected Model	11220.166	27.773	<0.001	.543
Intercept	13202.990	32.682	<0.001	.218
6MWT	7450.639	18.443	<0.001	.136
TUG group	1496.117	3.703	0.007	.112
Error	403.988			

SF36 Physical Component Score

Corrected Model	3313.274	50.965	<0.001	.298
Intercept	18888.737	290.547	<0.001	.708

6MWT	3313.274	50.965	<0.001	.298
Error	65.011