An Exploratory Study of Long-term Outcome Measures in Critical Illness Survivors: Construct Validity of Physical Activity, Frailty and Health-Related Quality of Life Measures

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Abstract

Objective: Functional capacity is commonly impaired after critical illness. We sought to clarify the relationship between objective measures of physical activity, self-reported measures of health-related quality of life, and clinician reported global functioning capacity (frailty) in such patients, as well as the impact of prior chronic disease status on these functional outcomes.

Design: Prospective outcome study of critical illness survivors.

Setting: Community-based follow-up.

Patients: Participants of the Musculoskeletal Ultrasound Study in Critical Care: Longitudinal Evaluation Study (NCT01106300), invasively ventilated for >48 hours and on the intensive care unit >7days.

Measurements and Main Results: Physical activity levels (health-related quality of life [SF-36] and daily step counts [accelerometry]) were compared to norm-based or healthy control scores, respectively. Controls for frailty (Clinical Frailty Score) were non-morbid, age- and gender-matched to survivors.

Ninety-one patients were recruited on ICU admission: 41 were contacted for post-discharge assessment, and data collected from 30 [14 female; mean age 55.3 years (95%CI 48.3-62.3); mean post-discharge 576 days (95%CI 539-614)]. Patients' mean daily step count (5803, 95%CI 4792-6813) was lower than that in controls (11735, 95%CI 10928-12542; $p<0.001$), and lower in those with pre-existing chronic disease than without (2989 [95%CI 776-5201] vs. 7737 [95%CI 4907-10567]; $p=0.013$). Physical activity measures (accelerometry, health-related quality of life, and frailty) demonstrated good construct validity across all three tools. Step variability (from standard deviation), was highly correlated with daily steps ($r^2=0.67$, $p<0.01$) demonstrating a potential boundary constraint.

Conclusions: Subjective and objective measures of physical activity are all informative in ICU survivors. They are all reduced 18 months post-discharge in ICU survivors, and worse in those with pre-admission chronic disease states. Investigating interventions to improve functional capacity in ICU survivors will require stratification based on the presence of pre-morbidity.

Introduction

Of the estimated 27 million intensive care unit (ICU) survivors alive today, over 60% will have experienced sustained and significant impairment of physical function after hospital discharge (1). However, the relationship between functional impairment and the presence of chronic disease prior to ICU admission is not well understood.

Such survivor disability has been assessed using objective (2, 3) and subjective (4) tools, with subjective questionnaire-based self-reporting (2, 5, 6) being commonly used. Health-related quality of life (HRQL) questionnaires have generally been employed as the default for long-term physical, psychological and cognitive outcomes in survivors of critical illness. Although objective assessment with physical activity (PA) monitoring and compliance analysis (7) may define physical disability in greater detail, the validity of such objective measures, when compared to the subjective measures used in the post-critical care population, is poorly described.

Meanwhile, rehabilitation goals need to be individualized given the increasing variation in medical complexity exhibited by critical illness survivors (8). Indeed, the lack of benefit demonstrated by some randomized controlled trials of rehabilitation could partly reflect the failure to do so (9-12). The current assessment tools used to establish the effectiveness of rehabilitation strategies in ICU survivors may not offer sufficient granularity to detect the variability in functional outcome (2), requiring large numbers of patients to adequately power interventional clinical trials. Such interventions may be targeted at reducing post-ICU frailty (13, 14).

We thus aimed to explore the relationship between objective measures of PA, self-reported measures of physical HRQOL, and clinician-reported global functioning (frailty).

In addition, we investigated the relationship between chronic disease status prior to critical illness, and functional outcome.

Materials and Methods

We studied patients recruited to the Musculoskeletal Ultrasound Study in Critical Care: Longitudinal Evaluation (MUSCLE-UK) study (NCT01106300, www.clinicaltrials.gov: ethical approval: University College London Ethics Committee A), which assessed the early impact of critical illness on muscle mass (15). Enrolment and follow-up are shown in Figure S1 of the Supplement.

In brief, patients were recruited within 24 hours of admission to a university hospital and a community hospital (August 2009-April 2011). All were anticipated to (a) be invasively ventilated for ≥48 hours, (b) spend ≥7 days in the intensive care unit (ICU) and (c) survive ICU. Patients were subsequently excluded if these criteria were not met. Patients were also excluded if pregnant, a lower limb amputee, or suffering a primary neuromuscular pathology or active disseminated cancer. At enrolment, written assent was obtained from the next-of-kin, with retrospective patient consent obtained when possible. Chronic disease was defined by hospital and general practice coding for management of chronic disease, plus the Charlson Co-morbidity Index (16). A home visit 18 months post-ICU discharge was requested from patients, when HRQL and frailty were assessed and an accelerometer fitted. This time point was selected to maximize information about long-term outcomes within the constraints of limited available resources.

Measures of physical activity

Objective PA was recorded daily using a bi-axial accelerometer armband (SenseWear; BodyMedia, Pittsburgh, PA, USA), and measured over at least five days incorporating one weekend and four weekdays. A valid PA assessment was defined as 90% on-body time per day for ≥5 days (7), and data analyzed using SenseWear Professional software (version 6.1).

Daily step counts were adjusted for age and time post-discharge, and compared with previously published controls (7). Patients were blinded to daily step count, such data only being accessible on data download. Daily step variability was taken as the standard deviation of at least five days of step data.

Subjective HRQL was assessed using the SF-36 Questionnaire v 2.0 (UK version, licensed from QualityMetric Inc, Lincoln, USA)(17), which comprises eight domain scales (Physical Function; Role-Physical; Bodily Pain; General Health; Vitality; Social Function; Role-Emotional; Mental Health). Two component summary scores (Physical [PCS] and Mental [MCS]) are derived from the four physical health and mental health domains respectively. Inbuilt algorithms determine domain scores (from 0 [least healthy] to 100 [most healthy]), which were compared to scores from a large published UK control cohort (18). Domain scores and component summary scores were also compared with norm-based control scores (mean, 50; standard deviation, 10) provided by inbuilt algorithms (17). Comparison to population norms are standard for ICU follow-up studies using SF-36 scoring (2, 5, 6).

Clinical frailty was assessed during ICU survivor home visits using the Clinical Frailty Scale (CFS), a valid tool previously successfully applied in the critically ill (4, 19). This is a short frailty scale focusing on levels of energy, activity, and exercise; impact of symptoms of medical problems on activities; level of physical and cognitive dependency inside and outside the home; and ability to cope with a minor illness (19), which correlates with a longer 70-item assessment of frailty (20). Scores range from 1 (very fit) to 9 (terminally ill) (see Table S1, Supplement), and relate to other individuals within the same age range.

Study scores were adjusted for time post ICU-discharge. A group of non-morbid controls, age- and gender-matched to the ICU survivors were recruited from the community (n=30), and their CFS scores assessed from observations on mobility and general lifestyle,

using the same technique of passive participant observation and during a similar period (30 minutes) as for the ICU survivors.

Statistical Analysis

General: Data were assessed for normality using D'Agostino and Pearson omnibus normality tests. Mean values were compared using two-tailed unpaired t-tests. Correlations between different measures of PA were determined by Spearman's rank correlation coefficient analysis, in order to assess construct validity. A post-hoc power calculation (G*Power 3.1 9.2, Kiel, Germany) was performed to determine whether sample sizes were large enough to show differences between patients with and without chronic disease. Statistical analysis was performed using Statistical Package for Social Sciences, version 22 (SPSS Inc, NY, USA). Data are reported as mean (95% Confidence Interval), except where only mean (standard deviation) control values were available.

Effect Sizes/Sample Size Calculations: Projected PA parameters for ICU survivors, and sub-cohorts with and without chronic disease, were derived from values reported in the literature, enabling effect and sample sizes for these three patient groupings (all survivors, those with chronic disease and those without) to be calculated for future interventional rehabilitation trials using G*Power (3.1 9.2, Kiel, Germany):

i) **Steps**: Three levels of daily step count were selected as statistical targets for future rehabilitation studies: A "somewhat active" population mean (8750 steps/day) for the whole ICU population (21, 22); the control level of steps (10,000 steps/day) for ICU survivors without pre-morbid disease (21, 22); and a 'low-active' mean (6250 steps/day) for survivors with pre-existing chronic disease (21, 22) (Table S2, Supplement).

ii) **Physical Health-Related Quality of Life:** Calculations were performed for normalization of SF-36 PCS for patients without pre-morbid chronic disease and those from the whole survivor group (score of 50); and those in survivors with pre-morbid chronic disease for improvement to the mean level of PCS values in non-critically ill individuals with chronic disease (mild chronic obstructive pulmonary disease, COPD) (score of 42) (23). (Table S2, Supplement).

iii) **Frailty**: A CFS score of 3 indicates low physical activity in a non-frail population (projected level for those with pre-morbid chronic disease); a score of 2 indicates normal activity (projected level for those without pre-morbid chronic disease)(19) (Table S2, Supplement).

Results

Test population

Of 91 patients recruited into the original study (15), 31 became ineligible either due to death or early discharge from ICU and 4 withdrew, leaving 56 patients discharged from hospital. Eighteen months post-ICU discharge (mean 576 days [95%CI 539-614]), 8 more had died, 7 were lost to follow-up, 6 had withdrawn, 3 had significant morbidity, and 2 were non-responders. Thirty patients provided post-ICU discharge data (14 female; age 55.3 years [95%CI 48.3-62.3]) (see Figure S1, Supplement). Baseline details of those providing complete data (including accelerometry) (n=27), plus the cohorts with (n=11) and without (n=16) chronic disease are shown in Table 1, and for those lost to follow-up, Figure S3, Supplement.

Measures of physical activity and the impact of chronic disease

i) Biaxial accelerometer data

Activity data were not collected from two immobile patients, and one patient was non-compliant; no remaining patients used walking aids. The use of activity monitors in this group of ICU survivors is well-tolerated and resulting assessments are valid. ICU survivors demonstrated reduced daily step count compared with previously-reported healthy controls (7) (5803 [95%CI 4792-6813] vs. 11,735 [95%CI 10,928-12,542]; p<0.001). However, previously healthy ICU survivors had a mean daily step count significantly greater than that of those who suffered pre-admission co-morbidity (7737 [95%CI 4907-10567] vs. 2989 [95%CI 776-5201]; p=0.013), but less than that of controls (7737 [95%CI 4907-10567] vs 11,735 [95%CI 10,928 - 12,542]; p=0.014, Figure 1).

Step variability, assessed by standard deviation, was highly correlated with daily steps (r^2=0.67, p<0.01, Figure 2) demonstrating a potential boundary constraint.

ii) *Health-Related Quality of Life*

ICU survivors had significantly worse PCS and Physical Function (PF) compared to controls (mean±SD: 41±12 vs. 50±10, p<0.001; and 52±36 vs. 88±20, p<0.001, respectively). Significant differences were seen between previously healthy ICU survivors and those with chronic disease, in PCS (46.0 [95%CI 39.9-52.0] vs. 34.0 [95%CI 28.0-40.0]; p=0.007) and PF scores (68.4 [95%CI 50.1-86.8] vs. 29.1[95%CI 12.4-45.7]; p=0.003). Data on differences in HRQOL domain and component summary scores for the various patient groups are summarized in Figure 2, with detailed comparison available in the Supplement, Table S4.

iii) Clinical frailty

Median CFS score was higher in ICU survivors than sex- and age-matched controls (4.0 [interquartile range (IQR)=3.0;upper quartile (Q_3)=5.0; lower quartile (Q_1)=2.0] versus 2.0 [IQR=1.0; Q_3=2.0; Q_1 =1.0]) indicating greater frailty. Differences were also seen between previously healthy and chronic disease cohorts (2.0 [IQR=2.8; Q_3=4.8; Q_1 =2.0] vs. 5.0 [IQR 3.0; Q_3=7.0; Q_1 =4.0]), respectively; the latter sub-cohort had a higher median CFS score than the matched controls 2.0 [IQR 2.0;Q_3=3.0;Q_1 =1.0].

Construct validity across physical function measures.

Construct validity, the degree to which a test measures what it claims to measure, is indicated by the Coefficient of Determination (r-squared) from regression between experimental and previously validated parameters.

High correlations across PA measures were maintained when corrected for age and time-post discharge. (Abbreviated construct validity is shown in Table 2; full results in the Supplement, Table S5, Figures S2 and S3).

PA measures demonstrated good construct validity across all three tools. Bedside physiology parameters showed no relationships with these measures (Table 2).

Floor and ceiling effect

Ceiling and floor effects refer to levels either above or below which variables can no longer be differentiated. No floor or ceiling effects were seen with accelerometer use. In HRQL, a 0% floor was seen across cohorts and domains, though 11.1% of previously healthy patients rated PF at maximal scores. CFS scoring demonstrated a floor effect of 0.07%, i.e., 1 patient in each sub-cohort was either very severely frail or terminally ill; and a ceiling effect of 0.04%, i.e., one patient was very active for the age-group.

Statistical calculations for future trial design

Estimated effect and sample sizes varied considerably (Table 3), likely secondary to the boundary constraint effect seen in patients with lower step counts (those with pre-morbid chronic disease).

Discussion

In our study, three independent methods of assessment - patient-reported HRQL, clinician-reported frailty score, and objective accelerometry - demonstrate impaired PA in ICU survivors, in agreement with published data (2, 24-29). However, we have shown that this impairment is not uniform, being greatest in those with pre-morbid chronic disease.

Our data show that accelerometry-derived data (daily step count) correlate well with other measures of physical incapacity (physical aspects of HRQL and frailty score) and demonstrate no floor or ceiling effects, unlike the SF-36 and CFS scores, confirming the validity of its use (Table 2; Table S5, and Figures S2, S3 of the Supplement). In addition, new insights are apparent from considering variation in daily PA. Thus, *variation* in daily step count was greatest in those most active, consistent with a boundary constraint effect: those with high exercise capacity can choose activity up to their maximal limit, whilst those least able to exercise are constrained to a narrow range of activity levels. The use of activity monitors - which are well-tolerated and show good compliance in this patient group - may therefore add greater granularity to assessment of functional disability post-critical illness.

Frailty is associated with greater risk of institutionalization, lower survival, and significantly lower HRQL in ICU survivors 12 months post-ICU admission (4, 29). We identified frailty in 37% of ICU survivors, compared with the 32% prevalence on ICU admission recently reported (4). Our data suggest that frailty correlates strongly with PF SF-36 scores and lower daily step counts, and may be a useful alternative outcome measure, especially given the potential of translating multi-modal community interventions from the ageing literature (30, 31).

Implications for prospective interventional trials

ICU survivors with and without chronic disease appear to behave as separate cohorts: by 18 months, the latter have daily steps counts only 1/3 lower than those of healthy controls, with substantially greater HRQL and significantly less frailty than the cohort with pre-morbid disease, reflecting a trajectory of recovery. In conjunction with a recent secondary analysis of a previously published exercise intervention study (32), this finding strengthens the argument that successful long-term interventions in ICU survivors will require stratification based on the presence of pre-morbidity, i.e. a personalized rehabilitation approach.

All three tools show good construct validity across assessments with little evidence of floor/ceiling effects suggesting that the assessment method should be determined by the purpose of the intervention – e.g. daily step count for an exercise only-intervention, and HRQL or frailty scales for multimodal interventions. Importantly, combined use of these outcome measures may elucidate useful components of multimodal interventions, especially in the setting of negative or neutral trial results (9-12).

The effect size calculations reveal potential difficulties in trial design, e.g. achieving the effect size necessary for CFS use would likely require a major interdisciplinary intervention (14). When considering physical rehabilitation, stratification of cohorts by presence or absence of chronic disease can reduce numbers significantly. However if a mixed cohort is used, the presence of high numbers of pre-morbidly healthy patients may result in a high proportion of 'false negative' results. This potential skew is likely a result of the boundary constraint demonstrated in this study: significant variation in step count in survivors without pre-morbid disease necessitates larger sample sizes.

The shaded areas in Figure 4 provide a hypothetical representation of the potential for rehabilitation in these two cohorts of ICU survivors: it shows the 'rehabilitation gap' between their observed PA levels 18 months post-ICU admission, and what might be achieved with suitable intervention.

Post-ICU HRQL differs with the presence or absence of pre-admission chronic disease. The nature of rehabilitation efforts required, and the maximal gain which they might deliver, is thus likely to vary between such groups; ICU-acquired PA deficits may also contribute to heterogeneity in response to rehabilitation. This is not clear when only the average impact is considered. The differences in scores between survivors without pre-morbidity and the whole ICU survivor group suggest that scores from previously healthy survivors could introduce Type II errors, potentially contributing to the lack of positive reports from intervention trials (9-12). In addition, psycho-social deficits (including depression and post-traumatic stress disorder), which are known to negatively impact PA capabilities, have been reported in ICU survivors (33) and may contribute to their physical dysfunction.

Limitations

Primary prevention of muscle wasting (34) and pro-active rehabilitation (35) mandate enrolling patients at ICU admission for trials (9). However, high dropout rates are well described in the literature, primarily due to mortality, either in hospital or during the first few months in the community (9, 12, 36-39). From our data, an 18-month follow-up study on 100 survivors would require recruiting 303 patients on admission to ICU. The use of inner city tertiary care locations as study sites increases the risk of patients being lost to follow-up due to the widespread locations of patients, and the lack of a fixed address for a proportion of the target population. In this pilot study, there were insufficient resources for

follow-up beyond 100 miles, and this contributed to the numbers lost. Age-adjustment of results overcame any potential influence from mean age differences in those followed up versus not followed up. Approaches to enable all measurements from each participant to be used, regardless of time of drop-out (40), may be worth investigating for future studies.

The small sample size, preventing stratification by diagnostic category (15) and extrapolation to specific patient subgroups, may impact generalizability. That said, ICU-induced muscle loss and subsequent physical debility appear to relate to the state of critical illness *per se*, rather than being linked to a specific diagnosis (15). Twenty-seven survivors contributed full data, a similar sample size to other studies of PA in ICU survivors and individuals with chronic disease (7, 28, 41). Rates of attrition secondary to mortality and loss to follow-up were comparable to a high-quality published 1-year outcome study (28), highlighting the difficulty of research in this population. Further, a post-hoc power calculation (Table S6, Supplement) suggests that sufficient numbers of participants were studied to detect a between-groups difference using PA monitoring or the PCS of the SF-36 questionnaire. This is a further demonstration of the potentially powerful effect of stratification of outcome studies (32).

Accelerometers may overestimate step count compared with pedometer-based values (42), though the strong correlations observed between objective and subjective measures suggest that this is of minimal impact.

Conclusions

Activity monitoring appears well tolerated by ICU survivors, with a high level of compliance. Both subjective and objective measures suggest that PA levels are reduced 18 months post-discharge in ICU survivors, being worst in those with pre-admission chronic

disease states. This suggests that rehabilitation strategies and targets may need to differ for individuals with or without pre-morbid disease.

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Figure Legends

Figure 1: Daily Steps for the Cohort of Intensive Care Unit Survivors Providing Complete Data (including Accelerometry) (n=27) and Subgroups of the Previously Healthy (n=16) and those with Pre-existing Chronic Disease (n=11) versus Controls. *indicates $p<0.05$ for unpaired two tailed student's T-test. #indicates $p<0.05$ for Mann-Whitney U test as data was non-normally distributed.

Figure 2: Linear Regression between Mean Daily Steps and Standard Deviation (as a Measure of Step Variability) in the Cohort of Intensive Care Unit Survivors Providing Complete Data (including Accelerometry) (n=27).

Figure 3: Health-Related Quality of Life (from Medical Outcomes Study Short Form 36 Questionnaire Domain Scores) for Population Controls, Critical Illness Survivor Cohort Providing Complete Data (including Accelerometry) (n=27) and Sub-cohorts with (n=11) or without (n=16) Pre-morbid Chronic Disease. PF: Physical Function, RP: Role Physical, BP: Bodily Pain, GH: General Health, VT: vitality, SF: Social Functioning, RE: Role Emotional, MH: Mental Health. ICU: Intensive Care Unit; *UK population controls (n= 8889) (18)

Figure 4: Schematic Projecting Health-Related Quality of Life Surplus, Deficit and Possible Rehabilitation Target in Critical Illness Survivors (n=27) Stratified by Presence of Chronic Disease. PF: Physical Function, RP: Role Physical, BP: Bodily Pain, GH: General Health, VT: vitality, SF: Social Functioning, RE: Role Emotional, MH: Mental Health. ICU: Intensive Care Unit; * UK population controls (n= 8889) (18)

Digital Content Supplement Captions

Figures

Figure S1. STROBE Flowchart for Patients in Musculoskeletal Ultrasound Study in Critical Care: Longitudinal Evaluation Study [1] Follow-Up QOL: Quality of life; CFS: Clinical Frailty Scale; PA: Physical Activity; LTF: Lost to follow-up (no known address); NR: Non-responder (correct address); W/D: Withdrawn; n/a: Not available.

Figure S2: Relationships between Daily Step Count Parameters and Health-Related Quality of Life (from Medical Outcomes Study Short Form 36 Questionnaire Domain Scores) in Intensive Care Unit Survivors (n=27).

A: SF-36 Component Summary scores versus age-adjusted daily step count

B: SF-36 Physical Function domain score versus age-adjusted daily step count

C: SF-36 Physical Function domain score versus age-adjusted variation in daily step count

D: Age-adjusted daily step count versus age-adjusted variation in daily step count

Construct validity was assessed by determining values of r-squared between parameters of step count (derived from accelerometry), and norm-based scores from the SF-36 survey. SF-36: Medical Outcomes Study Short Form 36 questionnaire; PCS: SF-36 Physical Component Summary score; MCS: SF-36 Mental Component Summary score; Physical Function: SF-36 Physical Function domain score; steps/d: daily step count; r^2: Coefficient of determination.

Figure S3: Relationships Between Clinical Frailty Scale Score and Medical Outcomes Study Short Form 36 Questionnaire Physical Function Domain Score or Time Post-Discharge-Adjusted Daily Step Count in Intensive Care Unit Survivors (n=27).

A: SF-36 Physical Function domain score versus Clinical Frailty Scale score

B: Time post-discharge-adjusted daily step count versus Clinical Frailty Scale score

Construct validity was assessed by determining values of r-squared between time post-discharge-adjusted daily step count (derived from accelerometry), and Physical Function scores (from the SF-36 survey), versus Clinical Frailty Scale Score (without adjustment for age and time post-discharge). SF-36: Medical Outcomes Study Short Form 36 questionnaire; Physical Function: SF-36 Physical Function domain score; r^2: Coefficient of determination.

Tables

Table S1. Description of Clinical Frailty Scale Scores [4].

Table S2: Mean Projected Values for Exercise Parameters Post-intervention

CFS: Clinical Frailty Scale; PCS: Physical Component Summary Score from SF-36; ICU: Intensive Care Unit.

Table S3. Patient Characteristics: Followed up versus Non-followed up Patients From Full Cohort of Intensive Care Unit Survivors (n=30).

ICU: intensive care unit; LOS: Length of stay; APACHE II: Acute Physiology and Chronic Health Evaluation score; SAPS II: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment Score; CCI: Charlson Co Morbidity Index; RF_{CSA}: Rectus Femoris Cross Sectional Area; $\Delta RF_{CSA}d10\%$: Change in RF_{CSA} over 10 days expressed as a percentage; COPD: Chronic Obstructive Pulmonary Disease; CVA: Cerebro-vascular accident. Values are mean with (95% Confidence Intervals), except for [b] indicating median with range. Student's T-test was used except for [a](Chi-squared) and [b](Mann Whitney U test); [c] indicates $p<0.05$. [d]Including one patient with Non-Insulin Dependent Diabetes Mellitus taking metformin. [e]Including one patient with severe Crohn's disease (not scored by Charlson Co Morbidity Index [7]), hypothyroidism and hypertension.

Table S4. Health-Related Quality of Life (from Medical Outcomes Study Short Form 36 Questionnaire Domain Scores) for Population Controls, Critical Illness Survivors

Undergoing Activity Monitoring (n=27) and Sub-cohorts With (n=11) or Without (n=16) Pre-morbid Chronic Disease. Mean (Standard Deviation) *Score range 0-100; higher scores show greater quality of life. † Data from Jenkinson et al, 1999 [3]. ICU: Intensive Care Unit. PF: Physical Function, RP: Role Physical, BP: Bodily Pain, GH: General Health, VT: vitality, SF: Social Functioning, RE: Role Emotional, MH: Mental Health.

Table S5. Adjusted and Unadjusted Values of Clinical Frailty Scale Scores and Parameters of Daily Step Count versus Measures of Physical Activity and Bedside Physiology from Intensive Care Unit Survivors Undergoing Activity Monitoring (n=27): Full Construct Validity Analysis. CSF: Clinical Frailty Scale score; PCS: SF-36 Physical Component Summary score; MCS: SF-36 Mental Component Summary score; PF: SF-36 Physical Function score (norm-based); AA: Age Adjusted; TPDA: Time Post-Discharge Adjusted; d: day; APACHE II: Acute Physiology and Chronic Health Evaluation II score; SAPS II: Simplified Acute Physiology Score II; SOFA: Sequential Organ Failure Assessment; r^2: Coefficient of determination. NS indicates $p>0.05$.

Table S6: Post-hoc Power Calculations for Different Outcome Measures Studied to Detect a Difference Between Patients With and Without Chronic Disease States.

All power calculations were performed for alpha=0.05 beta=0.80 and two-tailed Students' T-test except for [a]=Mann-Whitney U test; SD: Standard Deviation; SF-36: Medical Outcomes Study Short Form 36 questionnaire; PCS: SF-36 Physical Component Summary score.

Figure
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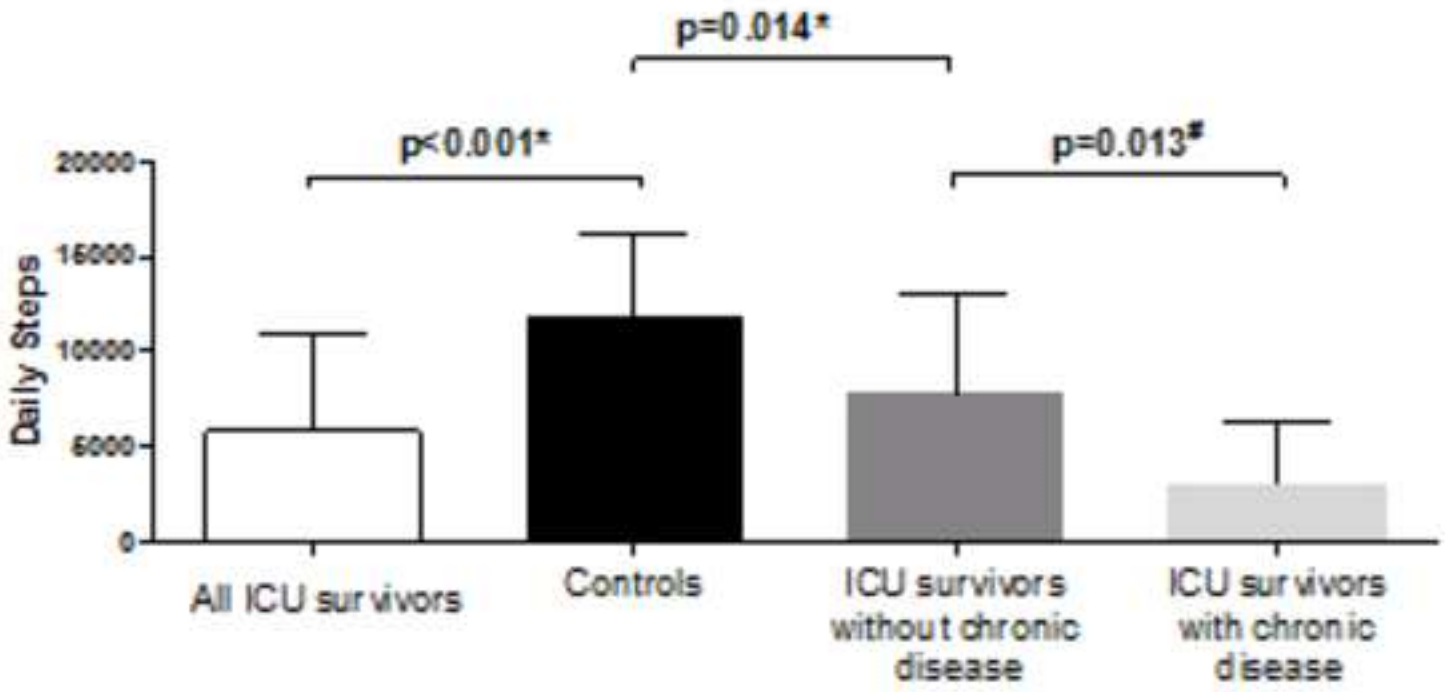

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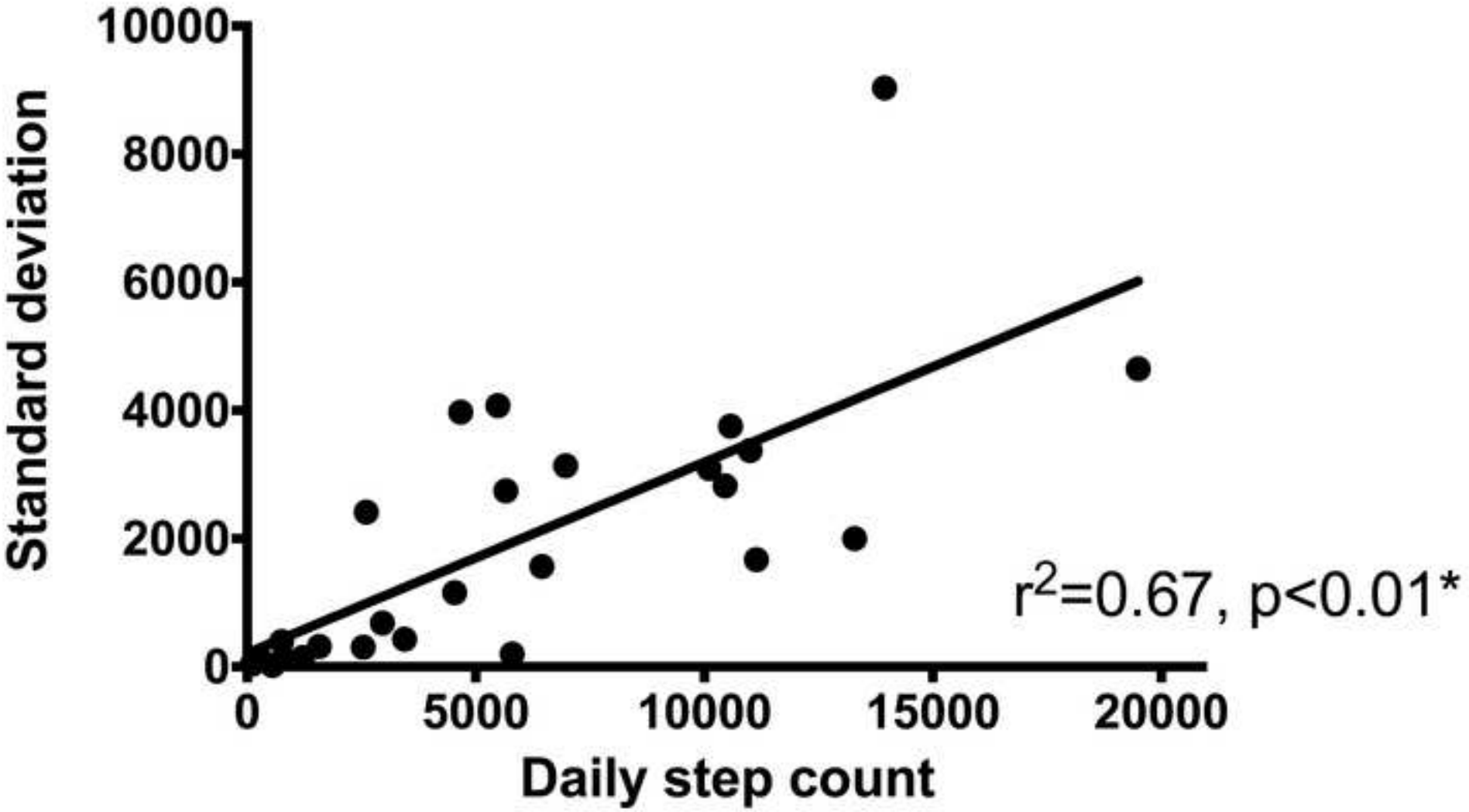

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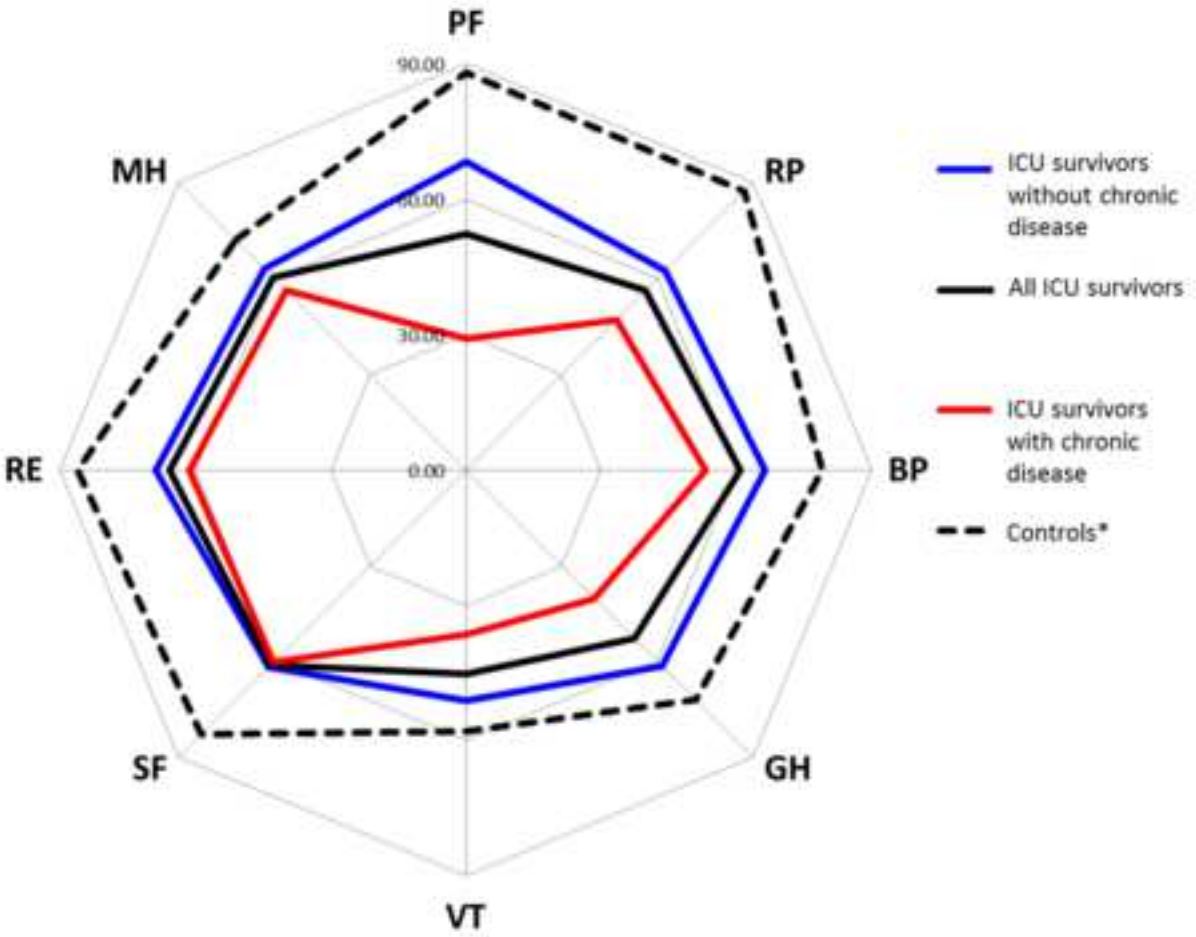

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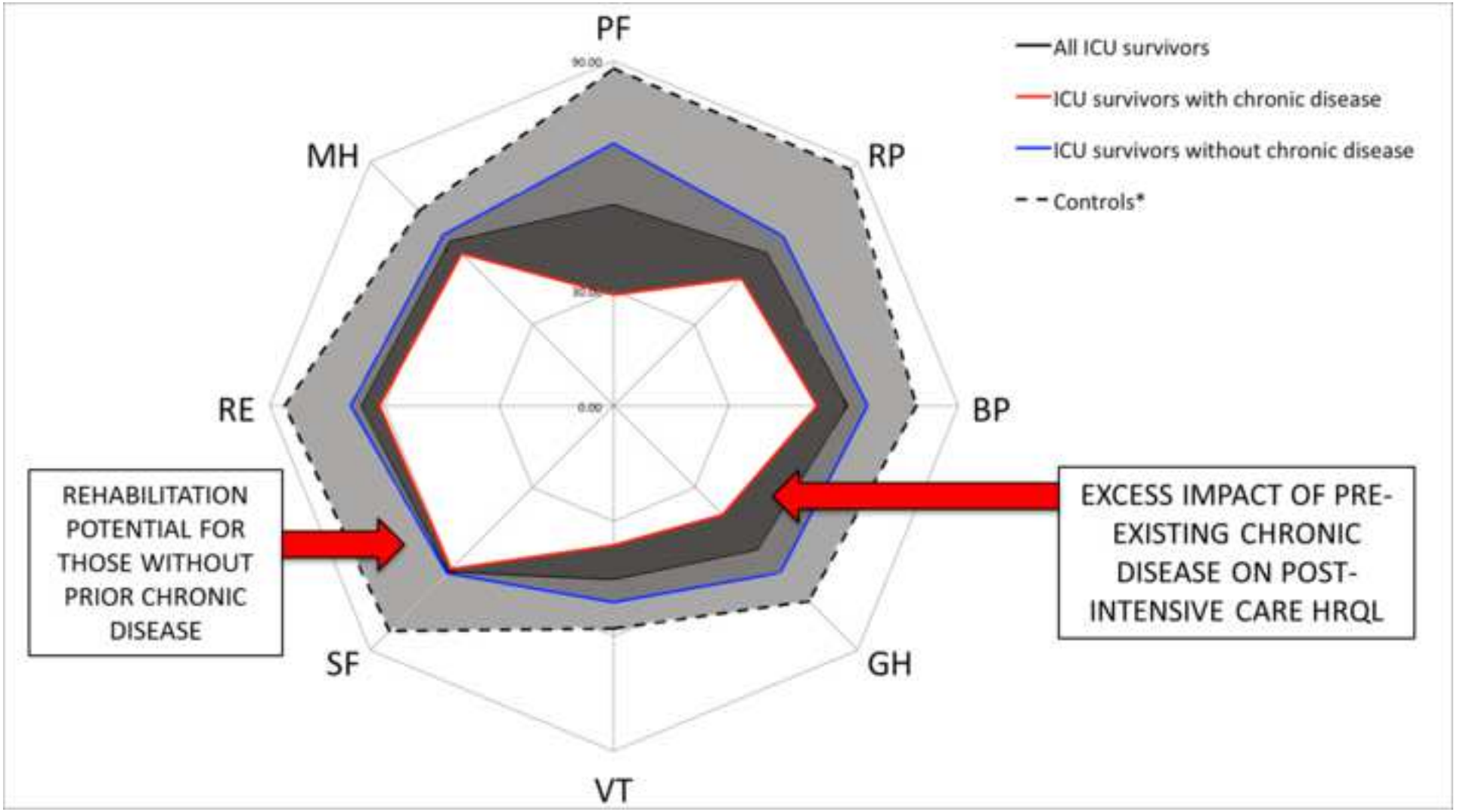

Table

Characteristic	Whole cohort	Without Chronic Disease	With Chronic Disease	P value
n	27	16	11	
Age (years)	54 (46.6-61.6)	44.4 (35.8-53)	68.2 (59.1-77.4)	**<0.001**[c]
Male sex n (%)[a]	13 (48.1)	6 (37.5)	7 (63.6)	0.181
Pre-ICU LOS (days)[b]	1 (1-4)	1 (1-4)	2 (1-3)	0.072
Ventilator days [b]	7 (2-24)	7 (2-16)	7 (4-24)	0.426
ICU LOS (days) [b]	16 (7-73)	13.5 (7-34)	16 (10-73)	0.142
Hospital LOS (days) [b]	33 (15-141)	28 (15-67)	38 (17-141)	0.488
APACHE II	23.5 (21.5-25.5)	23.0 (20.3-25.7)	24.3 (20.8-27.7)	0.529
SAPS II	44.8 (39.5-50.0)	46.1 (38.5-53.8)	42.8 (34.8-50.9)	0.601
Admission SOFA	8.8 (7.5-10.1)	9.1 (7.2-11.1)	8.3 (6.5-10.0)	0.515
CCI [b]	0 (0-5)	0 (0-1) [d]	3 (0-5) [e]	**<0.0001** [c]
Admission RF_{CSA} (mm^2)	430 (360-499)	450 (347-552)	400.7 (298-504)	0.631
$\Delta RF_{CSA}d10\%$	17.9 (13.4-22.4)	16 (10.0-22.1)	21.2 (13.1-29.4)	0.265
Discharge home (%)	18 (66.7)	9 (56.3)	9 (81.8)	0.227
Admission diagnosis, n (%)				
Sepsis				
Trauma	13 (48.1)	7 (43.8)	6 (54.5)	
Intracranial bleeding	6 (22.2)	6 (37.5)	0 (0.0)	
Cardiogenic shock	2 (7.4)	2 (12.5)	0 (0.0)	
	6 (22.2)	1 (6.3)	5 (45.5)	
Comorbidities, n (%)				
COPD		0 (0.0)	4 (36.3)	
Ischaemic heart disease		0 (0.0)	4 (36.3)	

Hypertension	2 (12.5)	4 (36.3)
Diabetes Mellitus	1 (0.1)	1 (9.1)
Haematological disease	0 (0.0)	1 (9.1)
Obesity	0 (0.0)	1 (9.1)
Chronic pancreatitis	0 (0.0)	1 (9.1)
Renal impairment	0 (0.0)	4 (36.3)
Crohn's disease	0 (0.0)	1 (9.1)
Thyroid disease	2 (12.5)	1 (9.1)
Parkinson's disease	0 (0.0)	1 (9.1)

Table 1. Patient Characteristics: Intensive Care Unit Survivors Providing Physical Activity Data (n=27) and sub-cohorts with (n-11) or without (n=16) chronic disease.

ICU: intensive care unit; LOS: Length of stay; APACHE II: Acute Physiology and Chronic Health Evaluation score; SAPS II: Simplified Acute Physiology Score; SOFA: Sequential Organ Failure Assessment Score; CCI: Charlson Co Morbidity Index; RF_{CSA}: Rectus Femoris Cross Sectional Area; $\Delta RF_{CSA}d10\%$: Change in RF_{CSA} over 10 days expressed as a percentage; COPD: Chronic Obstructive Pulmonary Disease. Values are mean with (95% Confidence Intervals), except for [b] indicating median with range. Student's T-test was used except for [a](Chi-squared) and [b](Mann Whitney U); [c] indicates $p<0.05$. [d] Including one patient with Non-Insulin Dependent Diabetes Mellitus taking metformin. [e]Including one patient with severe Crohn's disease (not scored by Charlson Comorbidity Index [16]), hypothyroidism and hypertension.

Table

Comparator	CFS		Daily step count		Variation in daily step count	
	r^2	p-value	r^2	p-value	r^2	p-value
SF-36 PCS	0.56	<0.01	0.25	<0.01	0.09	NS
SF-36 MCS	0.21	<0.05	0.03	NS	0.03	NS
SF-36 PF	0.67	<0.01	0.51	<0.01	0.24	<0.01
Daily step count	0.55	<0.01	-	-	0.67	<0.01
Variation in daily step count	0.32	<0.01	0.67	<0.01	-	-
APACHE II	0.04	NS	0.06	NS	0.07	NS
SAPS II	0.002	NS	0.02	NS	0.01	NS
SOFA	0.06	NS	0.01	NS	0.001	NS

Table 2: Values of Clinical Frailty Scale Scores and Parameters of Daily Step Count versus Measures of Physical Activity and Bedside Physiology: Abbreviated Construct Validity Data.

CSF: Clinical Frailty Scale score; PCS: SF-36 Physical Component Summary score; MCS: SF-36 Mental Component Summary score; PF: SF-36 Physical Function score (norm-based); d: day; APACHE II: Acute Physiology and Chronic Health Evaluation II score; SAPS II: Simplified Acute Physiology Score II; SOFA: Sequential Organ Failure Assessment; r^2: Coefficient of determination. NS indicates $p>0.05$.

Table

Physical Activity Parameter	Effect or Sample Size	Whole Cohort	Without Chronic Disease	With Chronic Disease
Daily step count	Effect Size	0.29	0.22	0.5
	n	62	103	24
PCS	Effect Size	0.37	0.18	0.31
	n	38	162	54
CSF	Effect Size	0.42	0.29	0.43
	n	30	60	30

Table 3: Estimated Effect (ES) and Sample (n) Sizes for Future Interventional Clinical Trials in Intensive Care Unit (ICU) Survivors: whole Intensive Care Unit survivor cohort, those with and without chronic disease. CSF: Clinical Frailty Scale score; PCS: SF-36 Physical Component Summary score; n: sample size.

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