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Fatigue Symptoms during the First Year after ARDS

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Abbreviation List

ARDS: acute respiratory distress syndrome

ALTOS: ARDSNet Long-term Outcomes Study

CI: confidence interval

FACIT-F: Functional Assessment of Chronic Illness Therapy–Fatigue Scale

SD: standard deviation

Abstract

Background: Fatigue is commonly reported by acute respiratory distress syndrome (ARDS) survivors, but empirical data are scarce.

Research Question: We evaluated fatigue prevalence and associated variables in a prospective study of ARDS survivors.

Study Design and Methods: This analysis is part of the ARDSNet Long-term Outcomes Study (ALTOS), conducted at 38 U.S. hospitals. Using age- and sex-adjusted, time-averaged random effects regression models, we evaluated associations between the validated Functional Assessment of Chronic Illness Therapy–Fatigue Scale (FACIT-F) with patient and critical illness variables, and with physical, cognitive and mental health status at 6- and 12-months post-ARDS.

Results: Among ARDS survivors, 501 of 711 (70%) and 436 of 659 (66%) reported clinically significant symptoms of fatigue at 6 and 12 months, respectively, with 41% and 28% reporting clinically important improvement and worsening, respectively (n=638). At 6 months, the prevalence of fatigue (70%) was greater than impaired physical functioning (50%), anxiety (42%) or depression (36%); 33% reported both impaired physical function and fatigue, and 27% reported co-existing anxiety, depression and fatigue. Fatigue was less severe in men and in those employed before ARDS. Critical illness variables (e.g., illness severity, length of stay) had little association with fatigue symptoms. Worse physical, cognitive and mental health symptoms were associated with greater fatigue at both 6- and 12-month follow-up.

Interpretation: During the first year after ARDS, over two-thirds of survivors report clinically significant fatigue symptoms. Due to frequent co-occurrence, clinicians should evaluate and manage survivors' physical, cognitive and mental health status when fatigue is endorsed.

Advances in critical care medicine have translated into decreased mortality due to Acute Respiratory Distress Syndrome (ARDS), but survivors often experience significant long-lasting impairments in physical, cognitive and mental health.[1–8] Accompanying this constellation of morbidities, survivors frequently endorse fatigue in the months following hospital discharge.[9,10] While ICU-acquired weakness and negative psychological symptoms are recognized as important and common sequelae of ARDS,[11] there are little empirical data on the course of fatigue, and associations with these other morbidities. This omission was identified in the *Intensive Care Medicine* Research Agenda on Intensive Care Unit-Acquired Weakness, in which authors recommend that future studies should "evaluate the prevalence and severity of fatigue in ICU survivors and define its association with psychiatric disorders, pain, cognitive impairment, and axonal loss".[12]

Our objective was to evaluate the prevalence of self-reported fatigue and its association with physical, cognitive and mental health status over 6- and 12-month follow up in a national cohort of patients surviving ARDS.

Methods

Participants

Data used in this analysis are part of the ARDS Network Long-Term Outcomes Study (ALTOS), a national multi-centered prospective study of ARDS survivors [13,14] recruited from 38 hospitals in the United States.[15–18] In ALTOS, telephone-based follow-up assessments, conducted at 6 and 12 months after ARDS, occurred from 2008 to 2014.[13,14,19] Committee IRB-5 of the Institutional Review Board of Johns Hopkins University School of Medicine and all participating institutions approved these studies, and patients or their surrogates provided informed consent (Approval: NA_00013113).

Fatigue Measure

The fatigue subscale of the Functional Assessment of Chronic Illness Therapy (FACIT-F) instrument is a valid and reliable self-reported measure of fatigue, evaluated in patients from diverse populations, including anemia,[20] rheumatoid arthritis,[21] critical illness,[22] and cancer.[23] The 13-item FACIT-F evaluates fatigue symptoms experienced over the past 7 days with scoring via a 5-point Likert scale ranging from "not at all" to "very much". The raw total score ranges from 0 (severe fatigue) to 52 (negligible fatigue). Raw scores are converted to a transformed scale (range: 0 to 100), with a score ≤68 representing a clinically significant threshold for fatigue compared to the general population.[23]

Physical, Cognitive and Mental Health Measures

Other patient-reported outcome measures obtained by ALTOS at 6- and 12-month follow-up assessments included: 1) the Short Form-36 Version 2 Physical Component Summary and Mental Component Summary scales[24] (standardized score; range = 0-100, mean = 50; standard deviation (SD) = 10; higher score = better function); 2) Functional Performance Inventory-Short Form or FPI-SF [25] (range = 0-3; higher scores = better physical function; score ≤2 = physical dysfunction) [26]; 3) Mini-Mental State Examination[27] (range = 0-30; higher scores = better cognitive function; score ≤24 = cognitive impairment)[28]; 4) Impact of Events Scale-Revised or IES-R for Post Traumatic Distress Syndrome symptoms,[29] (range: 0-4; higher score = more symptoms; score ≥1.6 = clinically significant symptoms) [29]; Hospital Anxiety and Depression Scale or HADS anxiety and depression subscales[30] (range: 0-21; higher score = more symptoms; score ≥8 = clinically significant symptoms).[31] The Physical Component Summary (SF-36v2) and the FPI-SF were used to measure physical health outcomes; MMSE for cognitive outcomes; Mental Component Summary (SF-36v2), IES-R, and HADS for mental health

outcomes. All patient outcome measures were purchased or used with appropriate permission from copyright holders.

Study Procedures

Trained research staff administered the FACIT-F and other measures (see above) at 6- and 12-month telephone-based follow-up assessments. Each research staff underwent initial training, consisting of didactic sessions, observation of survey administration, and then supervised practice in administering the survey. Thereafter, there were initial quality assurance reviews with simulated and then real participants, and then ongoing interval quality assurance reviews throughout the study.

Statistical Analysis

We used STATA version 15 for statistical analyses.[32] Exploratory analyses included inspection of histograms and spaghetti plots of patient outcomes over time and included change in raw FACIT-F scores between 6- and 12-month follow-up. We constructed Venn diagrams that included the overlap of patients reporting clinically significant fatigue (transformed FACIT-F $\leq$68) with clinically significant physical dysfunction (Functional Performance Inventory-Short Form score $\leq$ 2), cognitive dysfunction (Mini-Mental State Examination score $\leq$24), and anxiety and depressive symptoms (Hospital Anxiety and Depression Scale subscale scores $\geq$8) at 6-month follow-up.

Covariates for regression models were chosen *a priori* based on hypothesized clinical relationships with fatigue. We fit random intercept linear mixed effects models, after confirming that FACIT-F scores were normally distributed. This approach allowed the use of all data points from each individual, with a random intercept to capture patient heterogeneity at baseline. In exploratory data analysis, we plotted histograms and scatterplots of the proposed covariates versus fatigue at each time point. These exploratory analyses demonstrated no difference in associations over time. Hence, the regression models did not include a term for

time. As such, coefficients could be interpreted as the average relationship across time points ("time-averaged"). This model, adjusted for age and sex, was used to test individual associations of each covariate with fatigue (as measured using the transformed FACIT-F scores). This same regression model was used to evaluate a single post-hoc analysis evaluating baseline ARDS severity and fatigue. We fit separate, age- and sex-adjusted random effects regression models to evaluate the associations between physical, cognitive and mental health status at 6 and 12 months with fatigue at the same time point. We also modeled the lagged associations of physical, cognitive and mental health status variables at 6 months with fatigue at 12 months with a random intercept.

We chose one-half of a standard deviation (0.5 SD) as a standardized measure of change in physical, cognitive and mental health variables. A 0.5 SD is often used as an estimate of a distribution-based minimally important difference.[33, 34] For the outcome variable (FACIT-F), based on prior literature, we considered 3-4 points as a clinically important difference.[21]

Results

A total of 732 ARDS survivors were included in this evaluation, with 52% female, 82% white and mean (SD) age of 49 (15) years (Table 1). Prior to admission to the ICU, 91% of the patients were living independently and 49% had either full-time or part-time employment. Patients had mean (SD) APACHE III scores of 86 (26). Mean (SD) duration of mechanical ventilation was 11 (10) days, and ICU and hospital lengths of stay were 14 (11) and 22 (15) days, respectively. Pneumonia was identified as the primary risk factor for ARDS in the majority of patients (n = 447; 61%). Shock at baseline occurred in 41% of the sample. Mean (SD) mechanical ventilation-related parameters were positive end-expiratory pressure: 9 (4) mm Hg; inspiratory plateau pressure: 24 (6) mm Hg; and PaO_2:FiO_2 ratio: 166 (70). According to the Berlin definition of ARDS severity,[35] 29% (n=206) were mild, 53% (n=382) were moderate and

18% (n=129) were severe. (PaO_2:FiO_2 ratio missing for 15 patients.) Overall, 732 patients completed FACIT-F at either 6- or 12-month follow-up, with 711 and 659 participants completing the FACIT-F at 6- and 12-months, respectively, representing 94% and 95% response among eligible participants.

The mean transformed FACIT-F score (SD) at 6- and 12-month follow-up was 60 (17) and 62 (18), respectively. Clinically important fatigue (transformed FACIT-F ≤68) was reported by 70% (n=501) and 66% (n=436) at 6- and 12-months, respectively. Clinically important changes (defined as ≥3 points using raw FACIT-F scores [36]) between 6- and 12-month follow-up were observed, with 41% of all patients reporting a clinically important decrease, 28% increase, and 31% no change (Figure 1).

Figure 2 displays the overlap and frequency of clinically important fatigue (transformed FACIT-F score ≤68) along with clinically important impairment in physical, cognitive and mental health status at 6-month follow-up. The 70% prevalence of clinically important fatigue was greater than impaired physical function (50%), impaired cognition (24%), anxiety (42%) or depression (36%). One-third (33%) of the cohort reported both impaired physical function and fatigue, and 27% reported co-occurrence of clinically significant symptoms of anxiety, depression and fatigue.

For each baseline and critical illness variable, Table 2 reports associations with fatigue at 6- and 12-month follow-up. Adjusting for age, men (vs women) reported less fatigue, with a mean difference (95% confidence interval (CI)) of 7.4 (5.1, 9.8; p <0.001) points on the transformed FACIT-F fatigue scale. Moreover, after adjusting for age and sex, patients employed on a full-time or part-time basis prior to ARDS reported less fatigue, with a mean difference (95% CI) of 6.0 (3.6, 8.5; p <0.001) points. The APACHE III score had no clinically important association with fatigue, with a difference of 10 points in APACHE III being associated with a mean difference (95% CI) of only 0.5 (0.03- 1.0; p = 0.04) points on the transformed FACIT-F

fatigue scale. Other medical and treatment variables, such as ICU length of stay, presence of diabetes, or types of medications administered during the ICU admission were not significantly associated with fatigue symptoms at follow-up. A post-hoc analysis of the association of ARDS severity with fatigue demonstrated no statistically significant association (severe vs. mild ARDS $p = 0.41$, and moderate vs. mild $p = 0.71$).

Table 3 reports associations of physical, cognitive and mental health status scores with fatigue symptoms at both 6- and 12-month follow-up. Every model demonstrated a statistically significant and clinically important association between each measure of health status and fatigue symptoms. For example, a 0.5 standard deviation increase in physical functioning status, evaluated via the Short Form-36 Version 2 Physical Component Summary, and Functional Performance Inventory-Short Form, was associated with less fatigue, with a mean difference (95% CI) of 5.0 (4.6, 5.4; $p < 0.001$) and 4.7 (4.3, 5.1; $p < 0.001$) points, respectively. Similarly, a 0.5 standard deviation increase in anxiety and depressive symptoms was associated with greater fatigue, with a mean difference (95% CI) of -4.9 (-5.2, -4.5; $p <0.001$) and -5.9 (-6.2, -5.6; $p <0.001$), respectively.

Table 4 reports on associations of physical, cognitive and mental health status at 6 months with subsequent fatigue symptoms at 12 months. Although all models demonstrated a statistically significant association, the magnitude of these associations was not clinically important.

Discussion

Over the first 12 months after ARDS, clinically important fatigue symptoms were very common in survivors, with 70% prevalence at 6-month follow-up, 31% reporting no clinically important change and 28% reporting worsening symptoms by 12-month follow-up. The prevalence of fatigue symptoms is greater than impairment in physical function, cognition, or

clinically important symptoms of anxiety or depression in the year following ARDS; fatigue symptoms frequently co-occur and are strongly associated with all of these other impairments. Men and patients employed prior to ARDS reported lower levels of fatigue during follow-up, but critical illness variables during admission for ARDS had little association with fatigue symptoms.

To our knowledge, this is the first large-scale longitudinal evaluation of fatigue symptoms over the first year after critical illness due to ARDS. A prior study, specifically validating the FACIT-F in ICU patients, evaluated 130 1-year survivors from a single mixed ICU (64% surgical) in Italy.[22] This study reported a mean (SD) FACIT-F transformed score of 66 (12), similar in magnitude to our score of 62 (18). By way of comparison, the mean FACIT-F scores from our ARDS study and the prior ICU study (see above) are worse than the mean (SD) score of 68 (15) reported in non-anemic patients with solid and hematological tumors prior to chemo- or radiation therapy, and of 75 (15) reported by the normal population, but better than scores of 50 (14) reported by oncology patients with anemia.[23]

Another ICU study evaluated fatigue symptoms using a different instrument, the Multidimensional Fatigue Inventory in 195 sepsis survivors admitted to a single German ICU at 6 months after discharge.[37] This study reported a 45% prevalence of clinically relevant fatigue symptoms and significant associations with a diagnosis of major depressive disorder or post traumatic stress disorder at 6-month follow-up.[37] Due to use of differing fatigue instruments, we cannot directly compare these scores. However, this single-site German sepsis study supports our national US-based ARDS study findings by reinforcing that clinically important fatigue symptoms are very common in critical illness survivors and co-occur with other post-ICU morbidities.

A recent study of 1,290 patients with chronic obstructive pulmonary disease reported that three-quarters had fatigue, evaluated using the Checklist Individual Strength-Fatigue

instrument.[38] While fatigue was significantly associated with lung function (e.g., FEV_1), 70% of the variance in fatigue scores could not be explained by demographics, clinical features and chronic obstructive pulmonary disease severity. This is similar to our study and emphasizes that, in addition to physical status, fatigue symptoms are also associated with cognitive and mental health status. This observation suggests that a comprehensive evaluation of patient status is indicated when evaluating symptoms of fatigue.

Despite robust associations at the same follow-up time points, we found that physical, cognitive and mental health status at 6-months was not strongly associated with subsequent fatigue symptoms at 12 months. This finding may be due to heterogeneity of fatigue symptom trajectories from 6 to 12-month follow-up, along with dynamic changes in physical, cognitive and mental health status also occurring during this stage of recovery. These findings emphasize the importance of broadly evaluating patient status at each follow-up assessment.

Understanding the many correlates with fatigue symptoms is important when considering treatment options. Evidence in other medical populations suggests that a comprehensive, multi-component treatment may be most effective. For example, fatigue management in patients recovering from cancer,[39–43] traumatic brain injury,[44–46] human immunodeficiency virus,[47,48] and multiple sclerosis [49–51] include development of an exercise program, proper nutrition/hydration, mood management, activity pacing, medication review and sleep hygiene – each representing issues that are frequently disrupted during critical illness recovery.

The strengths of this study include the large number of patients recruited from many study sites across the USA, along with very low loss to follow-up and high completion rates of multiple well-validated outcome measures, despite high levels of participant fatigue. Compared to our follow-up of 94% and 95% at 6 and 12 months, respectively, previous ICU studies had 47% and 43% follow-up, respectively. [37, 22]

This study has potential limitations. First, although the FACIT-F was previously validated in ICU survivors,[22] most data used to interpret FACIT-F scores are extrapolated from other populations.[20, 21, 23] However, our fatigue findings in ARDS survivors are consistent with these other populations. Second, the evolution of health status during post-ARDS recovery could directly impact the functional measures and/or reports of fatigue. We suggest that future work include more detailed evaluations of such hypotheses. Third, the use of validated surveys in this study provided patient-reported perspectives on fatigue along with physical, cognitive and mental health status. Future research should consider performance-based physical testing (e.g., electromyography/nerve conduction testing, muscle strength testing, 6-minute walk test), detailed cognitive testing, and psychiatric diagnosis (e.g., semi-structured interview by a trained clinician). Research including such performance-based tests may be helpful in delineating potential interventions that might target physical, cognitive and mental health status, as well as fatigue symptoms in survivors in the year following ARDS.

Interpretation

In the first year after ARDS, more than two-thirds of survivors report clinically significant and persistent fatigue symptoms. Such symptoms should prompt clinicians to broadly evaluate physical, cognitive and mental health status among survivors due to frequent co-occurrence of impairments in health status with fatigue and should prompt researchers to design and evaluate multi-component interventions to address this common problem in an effort to improve the outcomes of ARDS survivors.

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Table 1. Characteristics of Patient Cohort N=732

	Patient Cohort[a,b]
Baseline Status Prior to ICU Admission	
Age (years), mean (SD)	49 (15)
Male	352 (48)
White race	584 (82)
Residence - living independently	666 (91)
Employment - full or part-time	344 (49)
Body mass index (kg/m^2), mean (SD)	31 (8)
Diabetes co-morbidity	166 (23)
Prior stroke with sequelae	11 (2)
End stage renal disease requiring dialysis	14 (2)
Critical Illness Status	
Medical ICU admission	409 (56)
APACHE III score, mean (SD)	86 (26)
Primary lung injury risk factor:	
Pneumonia	447 (61)
Sepsis	129 (18)
Aspiration	76 (10)
Trauma	32 (4)
Transfusion	14 (2)
Other	39 (5)
Treatment in ICU with:	
Opioid	471 (95)
Vasopressor	390 (53)
Corticosteroid[c]	197 (32)
Neuromuscular blocker	91 (18)
Mechanical ventilation duration (days), mean (SD)	11 (10)
ICU length of stay (days), mean (SD)	14 (11)
Hospital length of stay (days), mean (SD)	22 (15)

Abbreviations: APACHE III = Acute Physiology And Chronic Health Evaluation III severity of illness score; ICU = intensive care unit; SD = Standard deviation;

a – Data are presented as number (%), unless otherwise indicated. Proportions might not add to 100% due to rounding.

b – Missing data: race-22, employment-36, body mass index-2, APACHE III score-21, duration of mechanical ventilation-1, ICU length of stay-3, hospital length of stay-5. Not all of the parent studies collected data for opioid, corticosteroid, or neuromuscular blocker use. For opioid and neuromuscular blocker, N=495, no missing data; for corticosteroid, N=634, missing data-22;

c –Defined as receiving >20mg of methylprednisolone-equivalents on one or more days in ICU.

Table 2. Age and Sex-adjusted Associations of Individual Baseline and Critical Illness Variables with Fatigue Symptoms over 6 and 12 Month Follow-up[a] (N = 732)

Variable	**Mean Difference (95% CI) in Fatigue**[a] [positive value = less fatigue]	***P value***
Baseline Status Prior to ICU Admission		
Age (per 10 years)	-0.7 (-1.5, 0.1)	0.10
Male	7.4 (5.1, 9.8)	<0.001
White race	-2.7 (-5.8, 0.5)	0.09
Employment (full or part-time vs. unemployed)	6.0 (3.6, 8.5)	<0.001
Diabetes comorbidity	-0.3 (-3.1, 2.6)	0.85
Critical Illness Status		
Medical ICU	0.2 (-2.2, 2.6)	0.88
APACHE III score (per 10 points)	0.5 (0.03, 1.0)	0.04
Treatment in ICU stay with:		
Vasopressor	-1.9 (-4.5, 0.6)	0.38
Corticosteroid[b]	-2.1 (-5.1, 1.0)	0.18
Neuromuscular blocker	1.4 (-2.4, 5.2)	0.43
ICU length of stay (per 5 days)	-0.5 (-1.1, 0.1)	0.07

Abbreviations: ICU = intensive care unit; SD = standard deviation; APACHE III = Acute Physiology and Chronic Health Evaluation III

a – Each row is a separate regression model evaluating the age and sex-adjusted association of the variable named in each row with fatigue, using a longitudinal time-averaged random effects regression model. For the variables of age and male sex, the regression model only adjusted for sex and age, respectively. Fatigue was measured using the transformed score from the validated FACIT-Fatigue scale (range: 0 to 100), with higher scores representing less fatigue.

b – Defined as receiving >20mg of methylprednisolone-equivalents on one or more days in ICU.

c- Missing data: race-22, employment-36, APACHE III score-21, ICU length of stay-3, Not all of the parent studies collected data for opioid, corticosteroid, or neuromuscular blocker use. For opioid and neuromuscular blocker, N=495 with no missing data; and for corticosteroid, N=634 with missing data-22.

Table 3. Age and Sex-adjusted Associations of Individual Physical, Cognitive, and Mental Health Status Variables with Fatigue Symptoms at 6- and 12-Month Follow-up (N =732)

Variable [scaled by 0.5 Standard Deviation]	**Mean Difference (95% Confidence Interval) in Fatigue**[a] [positive value = less fatigue]	***P***
Physical Component Summary (SF-36v2) [~6 points][b]	5.0 (4.6, 5.4)	<0.001
Physical Functioning (FPI –SF) [~0.5 point]	4.7 (4.3, 5.1)	<0.001
Cognition (MMSE) [~1 point]	0.9 (0.6, 1.3)	<0.001
Mental Component Summary (SF-36v2) [~7 points]	5.1 (4.7, 5.5)	<0.001
PTSD symptoms (IES-R) [~0.5 points]	-4.3 (-4.7, -3.9)	<0.001
Anxiety symptoms (HADS - Anxiety Subscale) [~2.5 points]	-4.9 (-5.2, -4.5)	<0.001
Depression symptoms (HADS - Depression Subscale) [2.5 points]	-5.9 (-6.2, -5.6)	<0.001

Abbreviations: SF-36: Short Form-36; FPI-SF: Functional Performance Inventory – Short Form; MMSE: Mini-mental State Exam; IES-R: Impact of Events Scale-Revised; HADS: Hospital Anxiety and Depression Scale;
For SF-36, FPI-SF and MMSE higher scores = better function; for IES-R and HADS higher scores = greater symptoms.

a - Each row reports the results of a **separate** regression model that evaluates the age- and sex-adjusted association of fatigue symptoms with the variable named in that row. All analyses evaluate fatigue symptoms and the variable named in the row at the **same** follow-up time point. Analyses were conducted using a longitudinal time-averaged random effects regression model. Fatigue symptoms were measured using the transformed score from the validated FACIT-Fatigue scale (range: 0 to 100), with higher scores representing **less** fatigue. Values presented represent the estimated mean difference in fatigue score for a 0.5 standard deviation difference in the variable named in the row, over both 6- and 12-month follow-up time points.

b - Interpretation of this first row is as follows: "**If Patient A had a Physical Component Summary score that was 0.5 standard deviations higher than Patient B, then Patient A's expected fatigue score would be 5.0 points higher than Patient B**."

Table 4. Age and Sex-adjusted Longitudinal Associations of Individual Physical, Cognitive, and Mental Health Status Variables at **6 Months** with Fatigue Symptoms at **12-Month** Follow-up[a] (N=732)

Variable at 6 months follow-up [scaled by 0.5 Standard Deviation]	**Mean Difference (95% Confidence Interval) in Fatigue at 12 Months[a] [positive value = less fatigue]**	***P***
Physical Component Summary (SF-36v2) [~6 points][b]	1.0 (0.3, 1.5)	0.002
Physical Functioning (FPI –SF) [~0.5 point]	1.2 (0.6, 1.7)	<0.001
Cognition (MMSE) [~1 point]	0.6 (0.2, 1.1)	0.006
Mental Component Summary (SF-36v2) [~7 points]	1.0 (0.4, 1.6)	<0.001
PSTD symptoms (IES-R) [~0.5 points]	-1.1 (-1.6, -0.5)	<0.001
Anxiety symptoms (HADS - Anxiety Subscale) [~2.5 points]	-1.0 (-1.6, -0.4)	<0.001
Depression symptoms (HADS - Depression Subscale) [2.5 points]	-1.7 (-2.3, -1.0)	<0.001

Abbreviations: SF-36: Short Form-36; FPI-SF: Functional Performance Inventory – Short Form; MMSE: Mini-mental State Exam; IES-R: Impact of Events Scale-Revised; HADS: Hospital Anxiety and Depression Scale;
For SF-36, FPI-SF and MMSE higher scores = better function; for IES-R and HADS higher scores = greater symptoms.

a. Each row reports the results of a separate regression model that evaluate the age- and sex-adjusted association of the variable named in the row at 6 months, with fatigue symptoms at 12 months. Analyses were conducted using a longitudinal random effects regression model. Fatigue symptoms were measured using the transformed score from the validated FACIT-Fatigue scale (range: 0 to 100), with higher scores representing less fatigue (range: 0 to 100). Values presented represent the estimated mean difference in 12-month fatigue score for a 0.5 standard deviation difference in the variable named in the row at 6 months.

b. The interpretation of first row is as follows: *"If Patient A had a Physical Component Summary score that was 0.5 standard deviations higher than Patient B at 6 month follow-up, then Patient A's expected fatigue score would be 1.0 point higher than Patient B's at 12 month follow-up."*

Figure Legends:

Figure 1: Histogram of Change in Raw Fatigue Scores Between 6- and 12-month Follow-up (n=638)

Legend: FACIT-F - The raw scores from the validated FACIT-Fatigue scale (range: 0 to 100), with higher scores representing less fatigue; Minimally clinically important difference (MCID) = 3 point change in raw score; 181 of 638 (28%) patients had a decrease in score ≥3 points (representing increased fatigue); 259 of 638 (41%) patients had an increase in score ≥3 points (representing decreased fatigue) from 6- to 12-month follow-up. Missing: 94 FACIT-fatigue scores at 6 and/or 12 months.

Figure 2: Venn Diagrams of Fatigue Symptoms with Impaired Physical Function and Cognition, and with Depression and Anxiety Symptoms, at 6-Month Follow-up

Legend:

a = 10 (1%), b = 4 (1%), c = 9 (1%)

Fatigue - FACIT-F: transformed fatigue score (percent of cohort with score ≤68); Impaired Physical Function: Functional Performance Inventory – Short Form (percent of cohort with score ≤ 2); Impaired cognition: Mini-Mental State Exam (percent of cohort with score ≤ 24); Anxiety and Depression: Hospital Anxiety and Depression Scale (Percent of cohort with subscale scores ≥8); missing data among of 732 patients, Fatigue-11, Anxiety-27, Depression-27, Functional Performance Inventory-26, MMSE-31.

Figure 1:

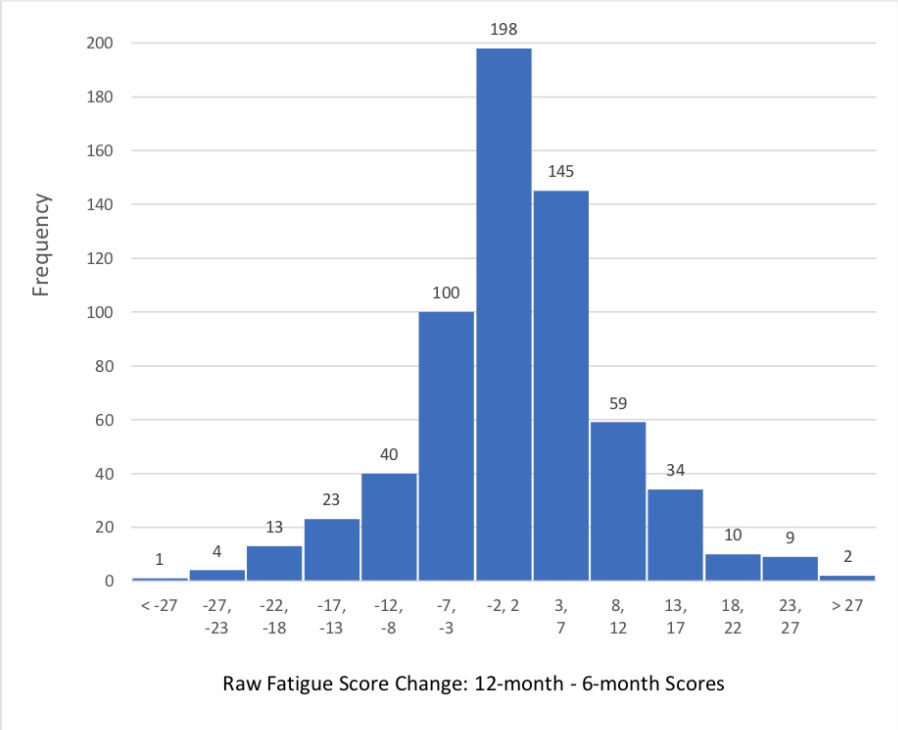
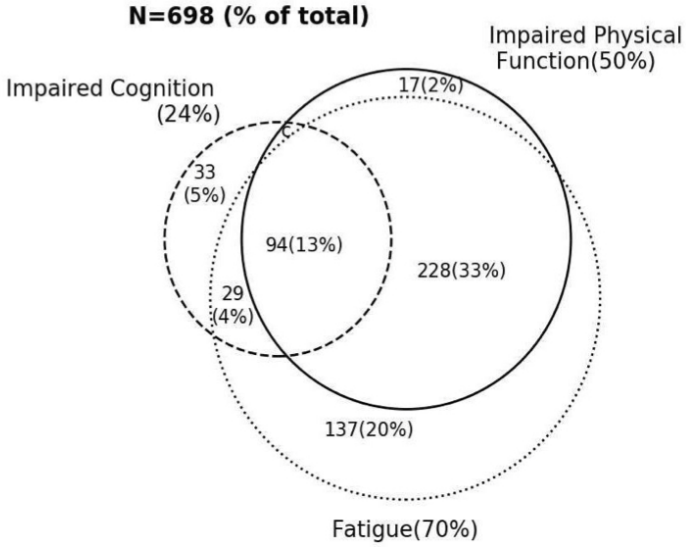
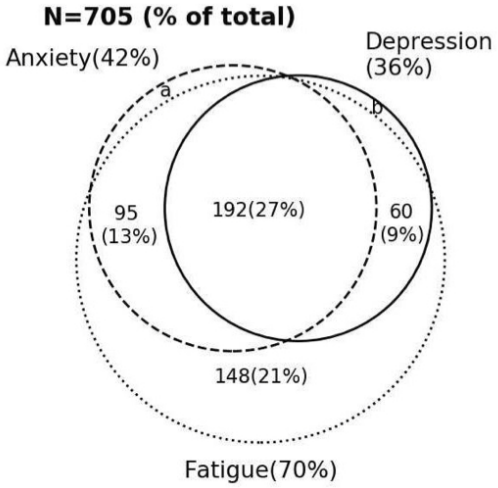

Frequency
200
180
160
140
120
100
80
60
40
20
0
1
4
13
23
40
100
198
145
59
34
10
9
2
< -27
-27, -23
-22, -18
-17, -13
-12, -8
-7, -3
-2, 2
3, 7
8, 12
13, 17
18, 22
23, 27
> 27
Raw Fatigue Score Change: 12-month - 6-month Scores

Figure 2:


N=698 (% of total)
Impaired Physical Function(50%)
Impaired Cognition (24%)
17(2%)
c
33 (5%)
94(13%)
228(33%)
29 (4%)
137(20%)
Fatigue(70%)


N=705 (% of total)
Anxiety(42%)
Depression (36%)
a
b
95 (13%)
192(27%)
60 (9%)
148(21%)
Fatigue(70%)