Online Data Supplement for

Understanding Patient Outcomes after Acute Respiratory Distress Syndrome: Identifying Subtypes of Physical, Cognitive, and Mental Health Outcomes

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APPENDIX 1: Description of Statistical Methods

Extended Description of Subtyping Approach

We used weighted network analysis (WNA), a technique developed for genetic analysis,(1) in order to identify ARDS outcome subtypes. Weighted network analysis is frequently used to deal with situations where a large number of predictors (usually genetic variations, such as single nucleotide polymorphisms) are associated with phenotypic variation. In simplest terms, a hierarchical clustering of predictor (genotype) variables is generated and then shaped/pruned on the basis of patterns of data in a heat map in the outcome (phenotype) data. We explain this process at length in the following paragraphs.

Because hierarchical clustering of the entire array of hospital admission predictors was expected to lead to unstable clustering, following an *a priori* specification, we used an initial step to limit the number of predictor variables. As we have reported elsewhere,(2) we used penalized

regression of the 6-month EQ-5D health utility to identify a limited subset of the 144 candidate predictors that were predictive of 6-month health utility. This initial step identified nine variables available at hospital admission: age, sex, Latino ethnicity, current smoking, body mass index, nadir respiratory rate (on the day of enrollment), pulmonary comorbidity, AIDS comorbidity, and baseline independence (i.e., whether the patient resided at home with no help, at home with informal help, or required either professional help at home or resided in a healthcare facility).

While the EQ-5D incorporates ratings of function, pain, and mental health, the utility score represents the overall state of health. We thus felt that it was a useful entry into variable reduction. While there was expected to be at least modest correlation between the EQ-5D and the various outcomes investigated in this research, the specific patterns of distribution of the constituents was the primary focus of the research reported here.

We then used those nine variables to begin WNA. We illustrate this process schematically in eFigure 1. In the first phase of WNA, we constructed the Euclidean distance matrix corresponding to a weighted network (as opposed to an unweighted network, in which distance between predictors are represented as 0 vs. 1, in a weighted network, predictors are associated by their distance). In this case the weighted network was formed from the 9 predictors defined in our first step. Next, we used average linkage hierarchical clustering with agglomerative partitioning to cluster patients according to their distance from other patients. This approach uses distance metrics and successively merges similar pairs of subjects.(3) The result is a *dendrogram* or cluster tree (see eFigure 1) where patients were grouped into clusters with near patients in the distance matrix across the 9 predictors. The terminal “leaves” of a dendrogram are individual patients.

We then plotted individual outcome variables below the dendrogram using a heatmap (eFigure 1) to visually compare the outcomes against the patients clustered according to predictor variables. As is typical with WNA, we then “pruned” the dendrogram in a semi-supervised manner that incorporated clinical insights as well as correlation patterns in the outcome variables, while preserving overall network topology. Pruning determines which level of the dendrogram defines the level at

which clusters should be defined. For ease of interpretation, we also generated a correlation matrix for individual outcomes. While this correlation matrix was not used in the analysis, it allowed for easy visualization of relevant associations. Such techniques are typically deployed in performing WNA.

The process of WNA thus yielded a cluster specification, in which patients with similar predictor and outcome profiles were grouped together. The number of clusters was determined to be the solution that best matched network structure while maintaining clinically relevant parsimony. We then performed cluster diagnostics and developed a classification algorithm, as outlined below.

Validation of Clusters Identified

We initially evaluated the adequacy of subtyping using the network module metrics of Langfelder(4) and inspecting for differences on the basis of expected sources of variance (e.g., age, degree of independence before admission) as well as distribution of standardized outcomes among the various clusters. The network module metrics of Langfelder are included within the R WGCNA library in the `modulePreservation()` function. The function helps identify non-reproducible clusters using a permutation-based approach. If the Z statistic from the permutation test is >10, we concluded that the cluster was valid and reproducible.

Development of Prediction Rule

We developed a prediction model for subtype membership, using recursive partitioning and regression trees (RPART).(5) RPART, a statistical learning technique designed to develop classification rules based on recursive partitioning of predictors, generates a final set of predictor variables and cutoff values within those predictors.(6-11) An advantage of this technique is that it develops an actual prediction rule that can be easily used to classify patients into respective clusters.

Prediction and secondary validation of identified subtypes

We reserved a subset of data (n=215) for validation. First, we obtained predicted cluster membership from both the RPART and WNA and compared their agreement using exact agreement and kappa.

To obtain the predicted cluster membership from the RPART, we applied the classification rule to the test data set.

To obtain the predicted cluster membership from the WNA, we used the steps outlined below:

1. First we extracted the module eigengene (ME) for each of our clusters. This is the 1st principal component of a given cluster and can be thought of as a summary profile of each cluster.
    a. The matrix of MEs has dimension q x k, where q is the number of predictors and k is the number of clusters.
2. Next, we obtain the correlation between each patient's predictors and the ME for each cluster. This provides a measure of how similar each patient is to the ME (i.e. general cluster profile). This is referred to as "module membership."(4, 12)
    a. Given a dataset with y patients and the q predictors, we have this dimensionality:
        i. Correlation (data, ME) = Correlation([y x q], [q x k]) = [y x k] (i.e. a row per patient, a column per cluster, and the correlation as each entry)

Each patient is assigned to the cluster associated with maximum, absolute correlation. If the maximum, absolute correlation was <0.3, we left the cluster unassigned, as there was no strong evidence for any cluster. This led to 10 (4.7%) observations being unclassified in the validation dataset.

Sample Size and Power Calculation

Two considerations affected sample size estimates, heuristics based on general experience, and formal estimates of power. Empirically, WNA has worked well with patient numbers as low as 20-

100 (1, 13-15) and predictor sets as small as 26.(14) By convention, sample sizes of 100-200 are adequate for clustering analyses; hence, the derivation set (N=430) had adequate power. Heuristics for RPART recommend 10-20 observations per classification variable.(16) We anticipated 5-7 predictor variables, requiring at most 140 patients. The derivation set therefore had adequate power. For classification rule performance in the validation dataset (n=215), our kappa estimate would have reasonable precision, with 95% confidence interval widths of 0.132 and 0.094 for correlations of 0.7 and 0.8, respectively. We had 80% power to detect an increase in the kappa from 0.7 (null hypothesis) to 0.785.(17) Assuming that 4 categories are predicted by RPART, across these 4 subtypes, we had ≥80% power to detect: (1) proportions that range evenly from 0.25 to 0.5 for dichotomous or categorical variables(18) (vs. a null hypothesis of no difference in proportions), and (2) a difference of ≥0.16 for continuous variables (vs. a null hypothesis correlation of 0.30). All power calculations were for $\alpha=0.05$ and were performed in PASS v. 11.(19)

Additional measurements made in the subgroup of participants with additional detailed outcome assessment

In the patients who were enrolled at certain centers within ALTOS, follow-up included an in-person visit at 6 months. In this sub-group, several additional assessments were made. Relevant to this study, we measured (a) baseline EQ-5D, (b) baseline SF-36, (c) current cognitive function using an instrument battery that included (i) Logical Memory I & II (immediate and delayed memory) from the Wechsler Memory Scale III,(20, 21) Digit Span (attention and working memory) from the Wechsler Adult Intelligence Scale III(20, 21), Similarities (verbal reasoning and concept formation) from the Wechsler Adult Intelligence Scale III(20, 21), Hayling Sentence Completion (executive function) from the Hayling and Brixton tests(22), and Verbal Fluency Test (language)(23). Baseline measurements for EQ-5D and SF-36 were anchored as a request to describe “your health immediately BEFORE the onset of the illness that caused you to be admitted to hospital.” Participants were also asked to report their total number of years of education.

Within this cohort we explored the association among cognitive and non-cognitive outcomes in two related ways. First, we explored Pearson correlation among all outcomes, both cognitive and non-cognitive. We considered Pearson correlation coefficient > 0.5 to indicate substantial correlation. We also employed principal components analysis of all outcomes to evaluate the inter-relationships of multiple outcomes. In order to visualize the associations, we used a biplot of the results of principal components analysis, which depicts the loadings of each underlying outcome on a grid of the first two principal components.

Exploration of ethnicity

Given that ethnicity was an important predictor of subtype membership, additional exploratory analyses were conducted to understand baseline differences in Latino vs. non-Latino patients, using available data, as described herein. First, we evaluated for differences, by ethnicity, in median income in the participant's home zip code. Second, we evaluated occupational status, by ethnicity, via separately analyzing: (1) employment status (i.e., employed, unemployed, disabled, retired) at the time of hospitalization and (2) the distribution of occupations among those who were employed. Occupation, defined according to the US Bureau of Labor Statistics 2010 Standard Occupational Classification (SOC), was coded as a binary variable (physically demanding vs. non-physically demanding employment). The following SOC occupations were categorized as physically demanding employment: Protective Service; Food Preparation and Serving Related; Building and Grounds Cleaning and Maintenance; Farming, Fishing, and Forestry; Construction and Extraction; Production; Installation, Maintenance, and Repair; and Transportation and Material Moving. Third, in the subgroup with additional detailed outcome assessment, we evaluated educational attainment by ethnicity. For all of these analyses, comparison of proportions was performed using Fisher's exact test and comparison of continuous variables using a t-test.

Exploration of relevance of severity of illness

In a *post hoc* exploratory analysis attempting to further evaluate the association of acute severity of illness with outcomes, we compared admission APACHE III score to the decrement in health status after ARDS. This analysis was performed among those patients among whom baseline health status was available. The results of this exploratory analysis are included below, in supplemental results.

APPENDIX 2: Supplemental Results

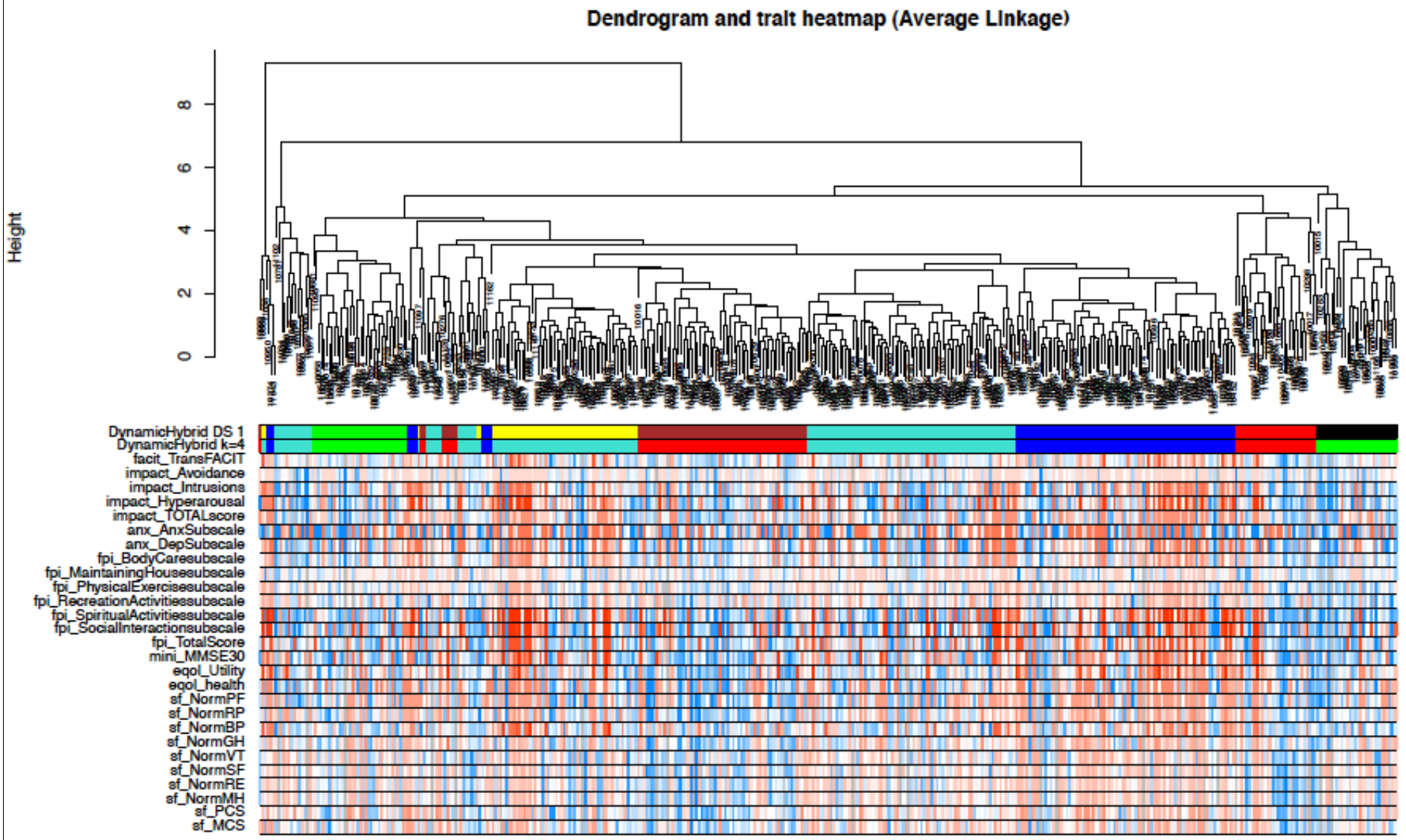
Weighted Network Analysis cluster identification

We used average linkage for the hierarchical clustering because it is the recommended linkage method (by Langfelder and Horvath) for weighted network analysis and yielded the best clustering results in our data set when evaluated against other various linkage methods (i.e., single, complete, or Ward's).(1)

We used the dynamic hybrid method for dendrogram cutting with deepSplit=1, where the deepSplit parameter controls the sensitivity to cluster splitting. We chose a minimum cluster size of 20 and used the Partitioning Around Medoids technique after the clusters stabilized, which allowed complete classification of observations and better matched the distribution of outcomes within the heat map of outcome instruments.(24) With merging of similar subtypes, this yielded the 4-cluster solution we validated.

eFigure 1 presents the actual results of WNA in our cohort, including the cluster break down before and after dynamic pruning of the dendrogram from hierarchical clustering.

eFigure 1. Results of Weighted Network Analysis in derivation cohort



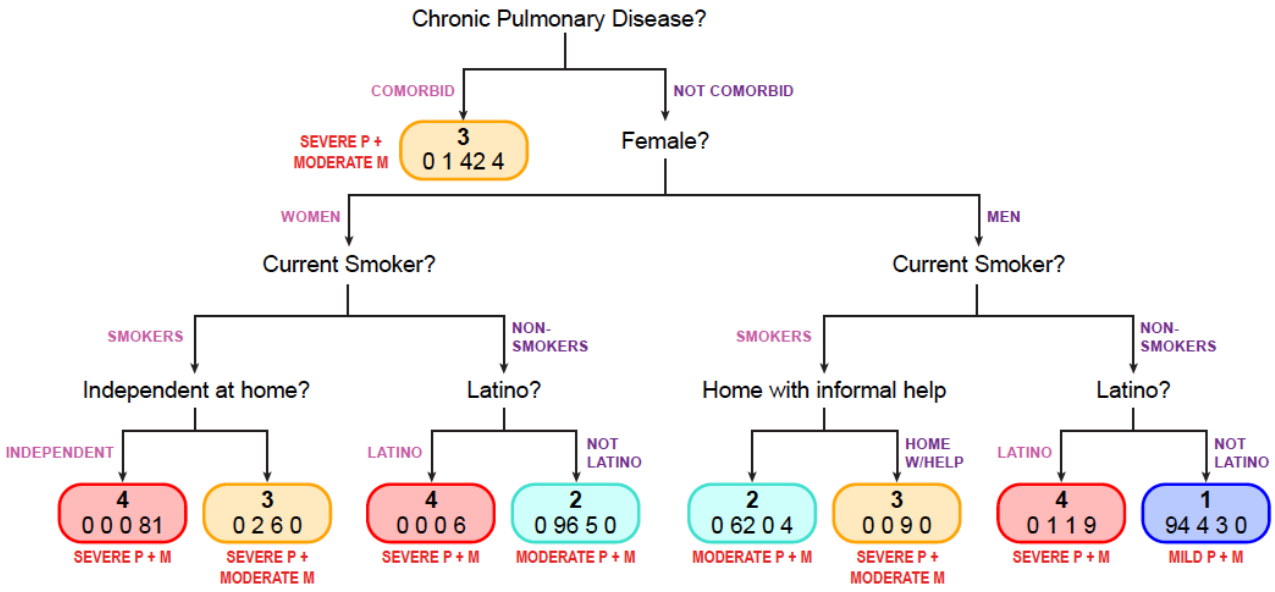
DynamicHybrid DS 1: initial cluster identification; DynamicHybrid k=4: final cluster; facit_TransFACIT: Functional Assessment of Chronic Illness Therapy-Fatigue; impact_Avoidance: Impact of Event Scale, Revised—Avoidance scale; impact_Intrusions: Impact of Event Scale, Revised—Intrusiveness scale; impact_Hyperarousal: Impact of Event Scale, Revised—Hyperarousal scale; impact_TOTALscore: Impact of Event Scale, Revised—overall score; anx_AnxSubscale: Hospital Anxiety and Depression Score – Anxiety scale; anx_DepSubscale: Hospital Anxiety and Depression Score – Depression scale; fpi_BodyCaresubscale: ; fpi_MaintainingHousesubscale: ; fpi_PhysicalExercisesubscale: ; fpi_RecreationActivitiessubscale: ; fpi_SpiritualActivitiessubscale: ;

fpi_SocialInteractionssubscale: ; fpi_TotalScore: ; mini_MMSE30: Mini Mental State Exam; eqol_Utility: Euro-QOL-5 Dimensions health utility index; eqol_health: Euro-QOL-5 Dimensions visual analogue scale; sf_NormPF: SF36v2 physical functioning scale; sf_NormRP: SF36v2 physical role functioning scale; sf_NormBP: SF36v2 bodily pain scale; sf_NormGH: SF36v2 general health perceptions scale; sf_NormVT: SF36v2 vitality scale; sf_NormSF: SF36v2 social role functioning; sf_NormRE: SF36v2 emotional role functioning scale; sf_NormMH: mental health scale; sf_PCS: SF36v2 Physical Component Score; sf_MCS: SF36v2 Mental Component Score.

The dendrogram is based on the nine predictor variables: age, sex, Latino ethnicity, current smoking at the time of hospital admission, body mass index, pulmonary comorbidity, AIDS comorbidity, nadir respiratory rate on the day of study enrollment, and residential independence at time of hospital admission. The colored bands immediately below the dendrogram represent the initial results, while the lower band is the cluster solution after the pruning procedure.

eFigure 2 displays the results of the RPART in the derivation dataset. The classifications showed good separation into distinct subtypes.

eFigure 2. RPART classification tree for subtype measurement



At each decision point, if the condition is true, go left. In each bubble (terminal node), the top number indicates the classified subtype number, while the second row of numbers indicates the number of patients in each subtype within the given node. Thus, in the rightmost bubble, the dominant subtype is Subtype 1. In that terminal node, 94 patients were in subtype 1, 4 in Subtype 2, 3 in Subtype 3, and none in Subtype 4.

Mild P + M (Subtype 1): mildly impaired physical and mental health status; Moderate P + M (Subtype 2): moderately impaired physical and mental health status; Severe P + Moderate M (Subtype 3): severely impaired physical and moderately impaired mental health status; Severe P + M (Subtype 4): severely impaired physical and mental health status.

Cluster validation

Using the module preservation metrics of Langfelder, the four clusters had Z statistics from the permutation test that ranged from 12.9 (Severely impaired physical and mental health status) to 22.6

(Moderately impaired physical and mental health status). All exceeded the pre-specified threshold for validity of a Z statistic greater than 10, as displayed in eTable 1.(4)

eTable 1. Module preservation metrics

Subtype	Subtype Size	Z-Statistic
1. Mildly impaired physical and mental health status	94	15.1
2. Moderately impaired physical and mental health status	166	22.6
3. Severely impaired physical health status	66	12.9
4. Severely impaired physical and mental health status	104	13.4

eTable 2. Cross-tabulation of WNA clusters vs. RPART classification in the derivation dataset (N=430). Kappa = 0.92, 95% CI: 0.89-0.95.

		RPART Prediction			
		Subtype 1	**Subtype 2**	**Subtype 3**	**Subtype 4**
WNA Class	**Subtype 1**	94	0	0	0
	Subtype 2	4	158	3	1
	Subtype 3	3	5	57	1
	Subtype 4	0	4	4	96

RPART: recursive partitioning and regression trees; WNA: weighted network analysis; Subtype 1: mildly impaired physical and mental health status; Subtype 2: moderately impaired physical and mental health status; Subtype 3: severely impaired physical health status; Subtype 4: severely impaired physical and mental health status.

eTable 3. Cross-tabulation of WNA clusters vs. RPART classification in the validation dataset (N=215). kappa=0.89, 95% CI: 0.83-0.94

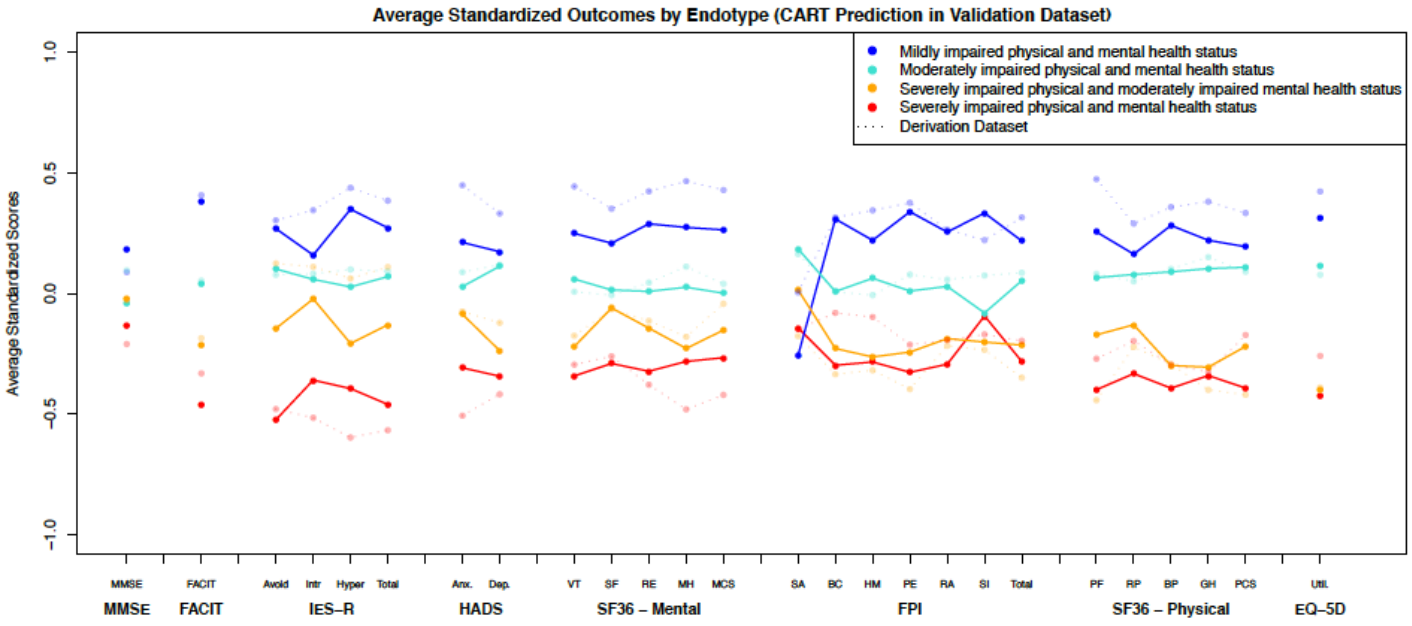
		RPART Prediction			
		Subtype 1	**Subtype 2**	**Subtype 3**	**Subtype 4**
WNA Class	**Subtype 1**	47	1	0	8
	Subtype 2	0	90	0	2
	Subtype 3	0	3	27	0
	Subtype 4	1	0	1	25

Ten patients (4.7%) were not able to be assigned to a WNA class, so this table reports 210 of 215 total patients in the validation dataset.
RPART: recursive partitioning and regression trees; WNA: weighted network analysis; Subtype 1: mildly impaired physical and mental health status; Subtype 2: moderately impaired physical and mental health status; Subtype 3: severely impaired physical health status; Subtype 4: severely impaired physical and mental health status.

Distribution of outcomes in the validation dataset

The pattern of distribution of outcomes overall and by subtype in the validation dataset closely mirrored those observed in the derivation dataset. These results are depicted graphically in eFigure 3.

eFigure 3. Standardized outcomes by subtype in validation dataset (N=215)



MMSE: Mini Mental State Exam; FACIT: Functional Assessment of Chronic Illness Therapy-Fatigue; IES-R: Impact of Event Scale, Revised [Avoid: Avoidance subscale; Intr: Intrusiveness subscale; Hyper: Hyperarousal subscale; Total: overall score]; HADS: Hospital Anxiety and Depression Score [Anx: Anxiety Scale; Dep: Depression Scale]; SF-36 v2: Medical Outcomes Study Short Form Health Survey [VT: vitality scale; SF: social functioning scale; RE: role emotional scale; MH: mental health scale; MCS: Mental Component Score; PF: physical functioning scale; RP: role physical scale; BP: bodily pain scale; GH: general health scale; PCS: Physical Component Score;]; FPI: Functional Performance Inventory [SA: Spiritual Activities scale; BC: Body Care scale; HM: Household Maintenance scale; PE: Physical Exercise scale; RA: Recreational Activities scale; SI: Social Interaction scale; Total: overall score]; EQ-5D: Euro-QOL-5 Dimensions [Util: health utility index].

Distribution of cognitive outcomes

Within the subgroup with additional detailed outcome assessment, we evaluated the distribution of cognitive outcomes by subtype. In this case, we combined patients from both the derivation and validation datasets by applying the RPART assignments. The only difference observed between the subtypes was that performance on the Similarities test, which evaluates abstract verbal

reasoning, was worse among the 26 patients with severely impaired physical and mental health status than among patients in the other three subtypes.

eTable 4. Distribution of cognitive impairment by subtype (mean [SD])

Instrument (cognitive domain)	Overall (n=181)	Mildly impaired physical and mental health status (n=49)	Moderately impaired physical and mental health status (n=78)	Severely impaired physical and moderately impaired mental health status (n=28)	Severely impaired physical and mental health status (n=26)	p-value
Logical Memory 1 (immediate memory)	-0.38 (1.03)	-0.54 (0.95)	-0.38 (1.04)	-0.43 (1.05)	-0.05 (1.12)	0.28
Logical Memory 2 (delayed memory)	-0.55 (0.96)	-0.64 (0.88)	-0.57 (0.97)	-0.48 (0.98)	-0.37 (1.05)	0.68
Digit Span (attention and working memory)	-0.04 (0.98)	0.02 (0.96)	-0.07 (1.03)	0.12 (0.86)	-0.27 (0.97)	0.49
Similarities (verbal reasoning and concept formation)	-0.17 (1.21)	0.04 (1.17)	-0.10 (1.21)	-0.18 (1.28)	-0.78 (1.08)	**0.04**
Hayling (executive function)	-0.58 (0.93)	-0.64 (0.87)	-0.49 (0.92)	-0.69 (1.07)	-0.62 (0.93)	0.74
Verbal Fluency Test (language)	-0.94 (1.08)	-0.91 (0.89)	-0.92 (1.08)	-0.80 (1.28)	-1.18 (1.16)	0.59

Numbers are expressed in terms of the number of standard deviations above (positive numbers) or below (negative numbers) the population norm.

Results of Correlation Analysis

We display, in eTable 5, the Pearson correlation of scores from each instrument across all patients (N=645). Substantial correlation was present for most instruments, with the exception of the MMSE, which did not correlate with other instruments. (In this group, detailed cognitive outcomes beyond the MMSE were not available.) FACIT, FPI, and EQ-5D were most strongly correlated with the other instruments. HADS-D was correlated with EQ-5D and the SF-36 PCS, while HADS-A and IES-R had weaker correlation with physical outcomes.

For the cognitive outcomes, notably MMSE was not substantially correlated with any of the cognitive instruments. Nor were any of the cognitive instruments correlated with any of the other outcome instruments (eTable 6). The lack of correlation of the MMSE and other cognitive tests may be due to the poor sensitivity of the MMSE in critically ill populations.(25)

eTable 5. Correlation matrix of primary outcome instruments employed (N=645)

	MMSE	FACIT	IES-R	HADS-A	HADS-D	SF-36 MCS	FPI	SF-36 PCS	EQ-5D utility
MMSE	1	0.15	-0.12	-0.10	-0.22	0.14	0.21	0.16	0.20
FACIT	0.15	1	-0.60	-0.67	-0.77	0.70	0.63	0.66	0.65
IES-R	-0.12	-0.60	1	0.69	0.62	-0.65	-0.40	-0.34	-0.46
HADS-A	-0.10	-0.67	0.69	1	0.69	-0.76	-0.41	-0.34	-0.52
HADS-D	-0.22	-0.77	0.62	0.69	1	-0.77	-0.61	-0.51	-0.61
SF-36 MCS	0.14	0.70	-0.65	-0.76	-0.77	1	0.45	0.26	0.56
FPI	0.21	0.63	-0.40	-0.41	-0.61	0.45	1	0.68	0.67
SF-36 PCS	0.16	0.66	-0.34	-0.34	-0.51	0.26	0.68	1	0.65
EQ-5D utility	0.20	0.65	-0.46	-0.52	-0.61	0.56	0.67	0.65	1

|Pearson correlation| > 0.5 is indicated by orange cells for ease of reference.
FACIT: Functional Assessment of Chronic Illness Therapy-Fatigue; IES-R: Impact of Event Scale, Revised; HADS-A: Hospital Anxiety and Depression Score - Anxiety; HADS-D: Hospital Anxiety and Depression Score - Depression; FPI: Functional Performance Inventory; MMSE: Mini Mental State Exam; EQ-5D: Euro-QOL-5 Dimensions; VAS: Visual Analog Scale; SF-36: Medical Outcomes Study Short Form Health Survey; PCS: Physical Component Score; MCS: Mental Component Score.

eTable 6. Correlation among cognitive outcomes and non-cognitive outcomes (N=181)

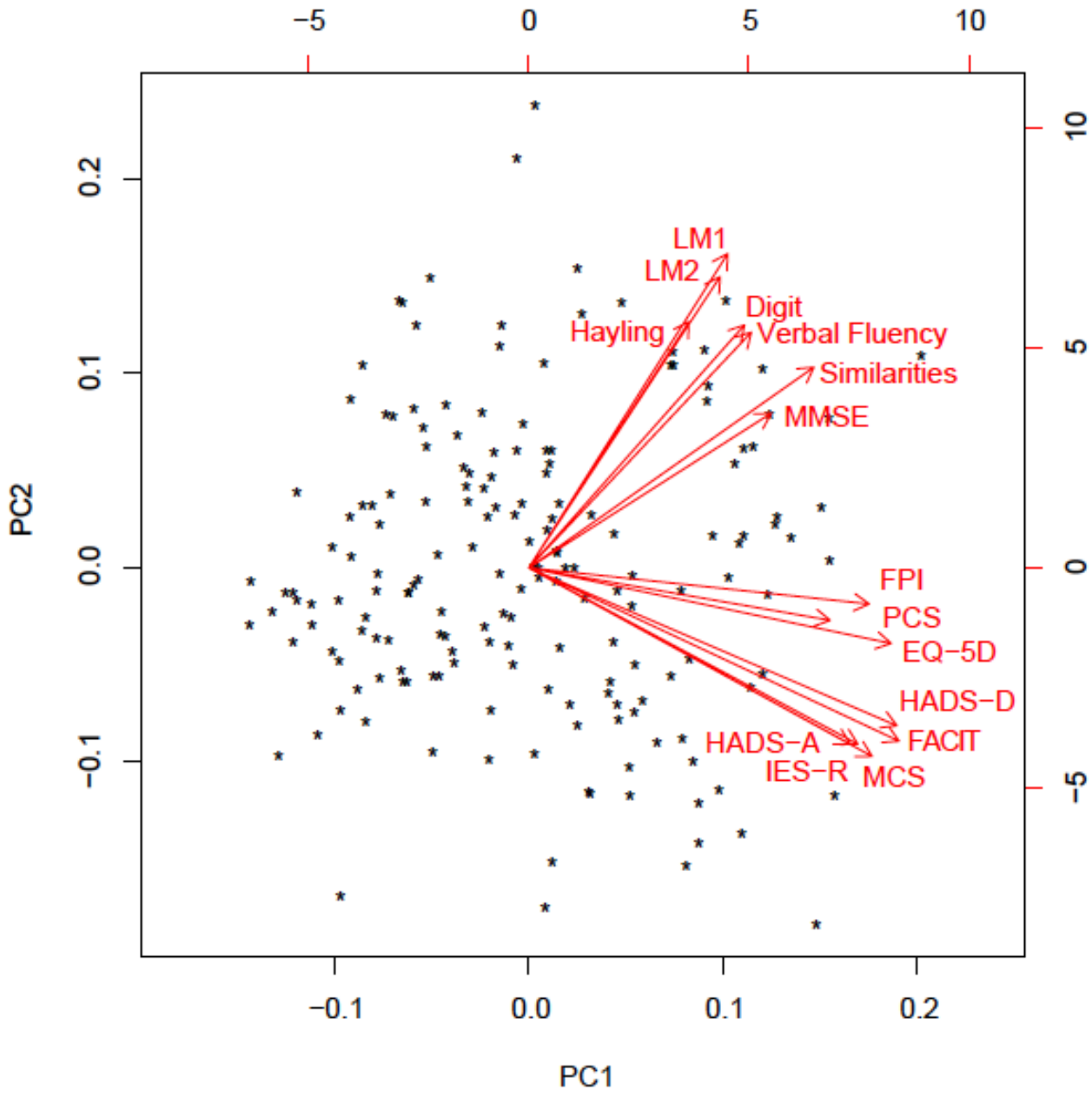
	LM 1	LM 2	Digits	Similarities	Hayling	Verbal Fluency Test
MMSE	0.35	0.29	0.40	0.35	0.36	0.29
FACIT	0.12	0.11	0.17	0.26	0.08	0.17
IES-R	-0.10	-0.15	-0.05	-0.30	-0.04	-0.18
HADS-A	-0.12	-0.13	-0.16	-0.36	0.03	-0.13
HADS-D	-0.11	-0.12	-0.18	-0.31	-0.12	-0.23
SF-36 v2 MCS	0.07	0.09	0.11	0.30	0.05	0.20
FPI	0.24	0.18	0.28	0.33	0.23	0.27
SF-36 v2 PCS	0.18	0.13	0.26	0.23	0.16	0.17
EQ-5D utility	0.21	0.19	0.25	0.36	0.18	0.27

FACIT: Functional Assessment of Chronic Illness Therapy-Fatigue; IES-R: Impact of Event Scale, Revised; HADS-A: Hospital Anxiety and Depression Score - Anxiety; HADS-D: Hospital Anxiety and Depression Score - Depression; FPI: Functional Performance Inventory; MMSE: Mini Mental State Exam; EQ-5D: Euro-QOL-5 Dimensions; SF-36: Medical Outcomes Study Short Form Health Survey; PCS: Physical Component Score; MCS: Mental Component Score; LM 1: Logical Memory 1; LM 2: Logical Memory 2.

As an exploratory analysis to visually depict the covariance of outcome instruments, principal components analysis was used, demonstrating that the cognitive outcomes were largely orthogonal to

the other outcomes. We depict this in the associated biplot in eFigure 4. Adjacency on the biplot suggests that instruments are well correlated with each other. While the cognitive outcomes were located near each other on the biplot, they were located far from the physical functional, QOL, and mental health outcomes. (The first two principal components accounted for 57% of the overall variance.)

eFigure 4. Biplot of principal components analysis



Cognitive outcomes cluster in the right upper quadrant of the biplot, while the other outcomes cluster in the right lower quadrant of the biplot.
PC1: first principal component; PC2: second principal component; FACIT: Functional Assessment of Chronic Illness Therapy-Fatigue; IES-R: Impact of Event Scale, Revised; HADS-A: Hospital Anxiety and Depression Score - Anxiety; HADS-D: Hospital Anxiety and

Depression Score - Depression; FPI: Functional Performance Inventory; MMSE: Mini Mental State Exam; EQ-5D: Euro-QOL-5 Dimensions; PCS: Physical Component Score of the SF-36 v2 (Medical Outcomes Study Short Form Health Survey); MCS: Mental Component Score of the SF-36 v2 (Medical Outcomes Study Short Form Health Survey); LM 1: Logical Memory 1; LM 2: Logical Memory 2; Verbal Fluency: Verbal Fluency Test;

Distribution of retrospectively measured baseline health status

In the subgroup with additional detailed outcome assessment, we evaluated patients' baseline (i.e. pre-ARDS) EQ-5D and SF-36 results, reported retrospectively by the patient. These results demonstrated that baseline EQ-5D and SF-36 differed by subtype, However, all four subtypes experienced a similar mean decrement in health status between this baseline measure and 6-month follow-up.

eTable 7. Distribution of baseline quality of life by subtype (mean [SD] or N [%])

Instrument	Overall	Mildly impaired physical and mental health status	Moderately impaired physical and mental health status	Severely impaired physical and moderately impaired mental health status	Severely impaired physical and mental health status	p-value
EQ-5D	**N=197**	**N=50**	**N=87**	**N=30**	**N=30**	
Baseline	0.78 (0.23)	0.85 (0.19)	0.79 (0.21)	0.71 (0.28)	0.70 (0.25)	**0.005**
Difference*	-0.08 (0.22)	-0.07 (0.19)	-0.06 (0.21)	-0.14 (0.24)	-0.09 (0.26)	0.33
Difference ≤ -0.07 (1 MID)	90 (46%)	22 (44%)	33 (38%)	19 (66%)	16 (53%)	0.07
Difference ≤ -0.166 (1 SD)	64 (33%)	15 (30%)	24 (28%)	13 (45%)	12 (40%)	0.29
SF-36 PCS	**N=189**	**N=48**	**N=86**	**N=29**	**N=26**	
Baseline	44 (13)	48 (11)	43 (13)	39 (12)	43 (13)	**0.01**
Difference*	-6 (12)	-8 (12)	-5 (12)	-7 (12)	-10 (12)	0.19
Difference ≤ -4 (1 MID)	100 (53%)	25 (52%)	43 (51%)	13 (45%)	19 (73%)	0.16
Difference ≤ -10 (1 SD)	68 (36%)	16 (33%)	27 (32%)	11 (38%)	14 (54%)	0.22
SF-36 MCS	**N=189**	**N=48**	**N=86**	**N=29**	**N=26**	
Baseline	48 (15)	54 (11)	47 (15)	44 (17)	46 (19)	**0.02**
Difference*	-2 (14)	-2 (10)	-1 (15)	-2 (13)	-8 (15)	0.11
Delta ≤ -4 (1 MID)	68 (36%)	15 (31%)	28 (33%)	13 (45%)	12 (46%)	0.40
Difference ≤ -10 (1 SD)	40 (21%)	7 (15%)	18 (21%)	6 (21%)	9 (35%)	0.26

*****6-month value minus baseline value
EQ-5D Difference was missing for 2 patients.
SF-36 Differences were missing for 1 patient.
The percentages reported in the table exclude missing patients from the denominator.

Distribution of residential status

At baseline, 91% of patients were residing at home independently. At 6 months, only 45% were residing at home independently (by 12 months that result had improved to 69% living at home independently). In eTable 8, we display residential status for the entire cohort, in this case using the RPART classification rule to identify subtype. Baseline differences in degree of independence drove all significant differences.

eTable 8. Residential status by RPART-predicted Subtype (N [%], All patients)

Residential status	Overall (n=645)	Mildly impaired physical and mental health status (n=154)	Moderately impaired physical and mental health status (n=264)	Severely impaired physical and moderately impaired mental health status (n=93)	Severely impaired physical and mental health status (n=134)	p-value
Residence at baseline						**<0.001**
Home independently	589 (91%)	145 (94%)	247 (94%)	65 (70%)	132 (99%)	
Home with informal help	36 (6%)	3 (2%)	8 (3%)	24 (26%)	1 (1%)	
Home with professional help	1 (<1%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)	
Intermediate care (rehab)	6 (1%)	2 (1%)	1 (<1%)	2 (2%)	1 (1%)	
Nursing home	9 (1%)	2 (1%)	6 (2%)	1 (1%)	0 (0%)	
Acute hospital	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	
Other	4 (1%)	1 (1%)	2 (1%)	1 (1%)	0 (0%)	
Residence at 6 months						0.49
Home independently	288 (45%)	76 (49%)	108 (41%)	40 (43%)	64 (48%)	
Home with informal help	129 (20%)	31 (20%)	48 (18%)	17 (18%)	33 (25%)	
Home with professional help	194 (30%)	41 (27%)	90 (34%)	30 (32%)	33 (25%)	
Intermediate care (rehab)	6 (1%)	0 (0%)	5 (2%)	0 (0%)	1 (1%)	
Nursing home	20 (3%)	4 (3%)	9 (3%)	5 (5%)	2 (1%)	
Acute hospital	6 (1%)	2 (1%)	2 (1%)	1 (1%)	1 (1%)	
Other	2 (<1%)	0 (0%)	2 (1%)	0 (0%)	0 (0%)	
Residence at 12 months						0.14
Home independently	445 (69%)	117 (76%)	174 (66%)	62 (67%)	92 (69%)	

Home with informal help	61 (9%)	10 (6%)	27 (10%)	6 (6%)	18 (13%)	
Home with professional help	72 (11%)	16 (10%)	30 (11%)	13 (14%)	13 (10%)	
Intermediate care (rehab)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	
Nursing home	17 (3%)	1 (1%)	11 (4%)	4 (4%)	1 (1%)	
Acute hospital	2 (<1%)	0 (0%)	1 (<1%)	1 (1%)	0 (0%)	
Other	3 (<1%)	0 (0%)	3 (1%)	0 (0%)	0 (0%)	
Missing	44 (7%)	10 (6%)	17 (6%)	7 (8%)	10 (7%)	
Change at 6 months						**<0.001**
Maintained home independently	271 (42%)	74 (48%)	106 (40%)	29 (31%)	62 (46%)	
Requiring help to home independently	17 (3%)	2 (1%)	2 (1%)	11 (12%)	2 (1%)	
Maintained requirement of help	39 (6%)	7 (5%)	15 (6%)	17 (18%)	0 (0%)	
Home independently to requiring help	318 (49%)	71 (46%)	141 (53%)	36 (39%)	70 (52%)	
Change at 12 months						**<0.001**
Maintained home independently	419 (65%)	114 (74%)	169 (64%)	45 (48%)	91 (68%)	
Requiring help to home independently	26 (4%)	3 (2%)	5 (2%)	17 (18%)	1 (1%)	
Maintained requirement of help	24 (4%)	4 (3%)	11 (4%)	8 (9%)	1 (1%)	
Home independently to requiring help	132 (20%)	23 (15%)	62 (23%)	16 (17%)	31 (23%)	
Missing	44 (7%)	10 (6%)	17 (6%)	7 (8%)	10 (7%)	

Exploration of ethnicity

eTable 9. Median (IQR) of median income for home zip code by ethnicity

Overall (n=645)	Not Latino (n=589)	Latino (n=56)	p value*
$47,400 ($37,700, $60,900)	$47,500 ($38,200, $61,200)	$43,850 ($33,150, $55,350)	0.090

*From Wilcoxon rank sum test
IQR=inter-quartile range

eTable 10. Distribution of employment and occupational characteristics by ethnicity

Variable	Overall (n=631)	Not Latino (n=578)	Latino (n=53)	p value
Baseline employment status				
Employed	307 (49%)	278 (48%)	29 (55%)	0.07
Unemployed	100 (16%)	93 (16%)	7 (13%)	
Disabled	134 (21%)	119 (21%)	15 (28%)	
Retired	88 (14%)	86 (15%)	2 (4%)	
	Overall (n=307)	Not Latino (n=278)	Latino (n=29)	
Physically demanding employment	109 (36%)	93 (33%)	16 (55%)	0.02

eTable 11. Distribution of educational attainment by ethnicity

Variable	Overall	Not Latino	Latino	p value
Peak educational attainment (years)	13.3 +/- 3.0	13.5 +/- 2.8	9.4 +/- 3.9	0.01

Correlation between acute illness severity and decrement in health status

Among the n=197 patients with baseline EQ-5D measured, the APACHE III score was not significantly different for those who experienced a minimally important decrease (change ≤ -0.07) vs. those who did not (80 vs. 86, p=0.10). This was also true for patients who experienced a decrease larger than one standard deviation (change ≤ -0.166) vs. those who did not (84 vs. 83, p=0.89). The correlation between APACHE III and change in EQ5D utility was minimal (-0.01).

Similar analyses were conducted for the n=189 patients with baseline SF-36 PCS and MCS.

PCS
MID (change ≤ -4): 82 vs. 85, p=0.42
1 SD (change ≤ -10): 83 vs. 84, p=0.69
Correlation between APACHE III and change in SF36 PCS was 0.05.

MCS
MID (change ≤ -4): 79 vs. 86, p=0.05
1 SD (change ≤ -10): 79 vs. 85, p=0.09
Correlation between APACHE III and change in SF36 MCS was 0.02

APPENDIX 3: Eligibility criteria for EDEN, OMEGA, ALTA, and ALTOS

Eligibility criteria for EDEN and OMEGA

EDEN and OMEGA Inclusion Criteria

Patients were eligible for inclusion if they met all of the below criteria. Criteria 1-3 must have been present within a 24-hour time period:

Acute onset (defined below) of:

1. PaO_2/FiO_2 ≤300 or equivalent adjusted for altitude

2. Bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph. The infiltrates could be patchy, diffuse, homogeneous, or asymmetric.

3. Requirement for positive pressure ventilation via endotracheal tube, and

4. No clinical evidence of left-sided cardiac failure to account for bilateral pulmonary infiltrates,

and

5. Intention of primary medical team to provide enteral nutrition to the patient

The 48-hour enrollment time window began when criteria 1-3 were met. If a patient met the first three inclusion criteria but had a PAOP (Pulmonary Arterial Wedge Pressure) >18 mmHg, then the first four criteria had to persist for >12 hours after the PAOP had declined to ≤18 mmHg, and still be within the 48-hour enrollment window.

“Acute onset” was defined as the duration of the hypoxemia criterion (#1) and the chest radiograph criterion (#2) must have been present for ≤ 28 days at the time of randomization. Opacities considered “consistent with pulmonary edema” included any opacities not fully explained by mass, atelectasis, or effusion or opacities known to be chronic (greater than 28 days). Vascular redistribution, indistinct vessels, and indistinct heart borders alone were not considered “consistent with pulmonary edema” and thus did not count as qualifying opacities for this study.

EDEN and OMEGA Exclusion Criteria

1. Age <13 years

2. Greater than 48 hours since all inclusion criteria met

3. Neuromuscular disease that impairs ability to ventilate without assistance, such as:

    a. cervical spinal cord injury at level C5 or higher

    b. amyotrophic lateral sclerosis

    c. Guillain-Barré Syndrome

    d. myasthenia gravis

    e. kyphoscoliosis or chest wall deformity resulting in severe exercise restriction, secondary polycythemia, or respirator dependence

4. Pregnant or breast-feeding

5. Severe chronic respiratory disease, demonstrated by any of:

    a. FEV1 <20 ml/kg PBW

    b. FEV1/FVC <50% predicted

    c. Chronic hypercapnea with $PaCO_2$ >45 mm Hg

    d. Chronic hypoxemia with PaO_2 <55 mm Hg on FiO_2 = 0.21

    e. Radiographic x-ray evidence of any chronic over-inflation or chronic interstitial infiltration

    f. Hospitalization within the past 6 months for respiratory failure

    g. Chronic restrictive, obstructive, neuromuscular, chest wall, or pulmonary vascular disease resulting in severe exercise restriction, secondary polycythemia, severe pulmonary hypertension with mean PAP >40 mm Hg, or respirator dependency

6. Burns greater than 40% total body surface area

7. Malignancy or other irreversible disease or condition for which 6-month mortality is estimated to be greater than 50%:

    a. Poorly controlled neoplasms

b. Known HIV positive with known end stage process and known CD4 count <50/mm3

c. Prior cardiac arrest requiring cardiopulmonary resuscitation without fully demonstrated neurologic recovery

d. New York Heart Association Class IV exercise restriction

e. Chronic condition making patient respirator dependent

8. Allogeneic bone marrow transplant in the last 5 years

9. Patient, surrogate, or physician not committed to full support (exception: a patient was not excluded if he/she would receive all supportive care except for attempts at resuscitation from cardiac arrest).

10. Severe chronic liver disease (Child-Pugh Score of 11-15)

11. Diffuse alveolar hemorrhage from vasculitis

12. Morbid obesity (a body weight of greater than 1kg/cm of body height) [this represents a body mass index of approximately 55-65 kg/m^2]

13. No consent/inability to obtain consent

14. Unwillingness or inability to utilize the ARDS network 6 ml/kg PBW lung protective ventilation protocol

15. Moribund patient not expected to survive 24 hours

16. No intent to obtain central venous access for monitoring intravascular pressures

17. Greater than 72 hours since initiation of mechanical ventilation

18. Refractory shock, defined by any of the following:

a. Dopamine infusion at rate >15 mcg/kg/min

b. Dobutamine infusion at rate >15 mcg/kg/min

c. Epinephrine or Norepinephrine infusion at rate >30 mcg/min

d. Phenylephrine infusion at rate >50 mcg/min

e. Milrinone infusion at rate >0.5 mcg/kg /min

f. Vasopressin infusion at rate >0.04 U/min

g. Intra-aortic Balloon Pump

19. Unable to obtain enteral access

20. Presence of partial or complete mechanical bowel obstruction, or ischemia, or infarction

21. Current TPN use or intent to use TPN within 7 days

22. Severe malnutrition with BMI <18.5 or loss of >30% total body weight in the previous 6 months

23. Laparotomy expected within 7 days

24. Unable to raise head of bed 30 degrees

25. Short-bowel syndrome or absence of gastrointestinal tract

26. Presence of high-output (>500 cc/day) enterocutaneous fistula

27. INR >5.0 or platelet count <30,000/mm3 or history of bleeding disorder

28. Intracranial hemorrhage within the previous month

29. Allergy to enteral formula, n-3 fatty acids, gamma-linolenic acid, vitamin E, vitamin C, betacarotene, taurine, or L-carnitine

30. Requirement for, or physician insistence on, enteral formula supplemented with n-3 fatty acids (ex: Oxepa®, Impact®) or providing n-3 fatty acid, GLA, or anti-oxidant supplementation

From: Rice TW, Wheeler AP, Thompson BT, Steingrub J, Hite RD, Moss M et al. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. JAMA 2012; 307(8):795-803.

ALTA Eligibility Criteria

ALTA Inclusion Criteria

1. PaO_2/FiO_2 ≤300 or equivalent adjusted for altitude where appropriate

2. Bilateral infiltrates consistent with pulmonary edema on frontal chest radiograph. The infiltrates could be patchy, diffuse, homogeneous, or asymmetric.

3. Requirement for positive pressure ventilation via endotracheal tube, and

4. No clinical evidence of left-sided cardiac failure to account for bilateral pulmonary infiltrates

ALTA Exclusion Criteria

1. Age <13 years

2. Greater than 48 hours since all inclusion criteria met

3. Neuromuscular disease that impairs ability to ventilate without assistance, such as:

    a. cervical spinal cord injury at level C5 or higher

    b. amyotrophic lateral sclerosis

    c. Guillain-Barré Syndrome

    d. myasthenia gravis

    e. kyphoscoliosis or chest wall deformity resulting in severe exercise restriction, secondary polycythemia, or respirator dependence

4. Pregnant or breast-feeding

5. Severe chronic respiratory disease, demonstrated by any of:

    a. FEV1 <20 ml/kg PBW

    b. FEV1/FVC <50% predicted

    c. Chronic hypercapnea with PaCO2 >45 mm Hg

    d. Chronic hypoxemia with PaO2 <55 mm Hg on FiO2 = 0.21

    e. Radiographic x-ray evidence of any chronic over-inflation or chronic interstitial infiltration

    f. Hospitalization within the past 6 months for respiratory failure

g. Chronic restrictive, obstructive, neuromuscular, chest wall, or pulmonary vascular disease resulting in severe exercise restriction, secondary polycythemia, severe pulmonary hypertension with mean PAP >40 mm Hg, or respirator dependency

6. Burns greater than 40% total body surface area

7. Malignancy or other irreversible disease or condition for which 6-month mortality is estimated to be greater than 50%:

a. Poorly controlled neoplasms

b. Known HIV positive with known end stage process and known CD4 count <50/mm3

c. Prior cardiac arrest requiring cardiopulmonary resuscitation without fully demonstrated neurologic recovery

d. New York Heart Association Class IV exercise restriction

e. Chronic condition making patient respirator dependent

8. Allogeneic bone marrow transplant in the last 5 years

9. Patient, surrogate, or physician not committed to full support (exception: a patient was not excluded if he/she would receive all supportive care except for attempts at resuscitation from cardiac arrest).

10. Severe chronic liver disease (Child-Pugh Score of 11-15)

11. Diffuse alveolar hemorrhage from vasculitis

12. Morbid obesity (a body weight of greater than 1kg/cm of body height)

13. No consent/inability to obtain consent

14. Unwillingness or inability to utilize the ARDS network 6 ml/kg PBW lung protective ventilation protocol

15. Moribund patient not expected to survive 24 hours.

16. No intent to obtain central venous access for monitoring intravascular pressures

17. Contraindication to aerosolized albuterol.

18. Daily use (prior to study hospitalization) of inhaled beta agonist, corticosteroid, or oral leukotriene modifier for reactive airway disease.

19. Unwillingness of primary physician to discontinue inpatient beta agonist use.

20. Acute myocardial infarction or acute coronary syndrome within 30 days.

21. Severe congestive heart failure.

22. Participation in other experimental medication trial within 30 days with the exception of EDEN/OMEGA.

23. Heart rate greater than 85% of maximal predicted heart rate (MGR85) as calculated by MHR85 = 85% x (220-age) or 140 beats per minute (whichever is lower).

24. Patients receiving high frequency ventilation.

25. Atrial fibrillation (new since hospital admission) requiring anticoagulation.

26. Greater than 5 PVCs per minute in the four hour period prior to randomization.

From: National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network, Matthay MA, Brower RG, Carson S, Douglas IS, Eisner M, Hite D, Holets S, Kallet RH, Liu KD, MacIntyre N, Moss M, Schoenfeld D, Steingrub J, Thompson BT. Randomized, placebo-controlled clinical trial of an aerosolized beta(2)-agonist for treatment of acute lung injury. *Am J Respir Crit Care Med* 2011; 184: 561-568.

ALTOS Eligibility Criteria

Patients were excluded from evaluation of post-discharge outcomes in ALTOS if (a) age <18 years old, (b) did not speak English, (c) had no fixed address (i.e., homeless), (d) had baseline cognitive impairment (based on chart review and/or interview with the patient and/or surrogate when necessary), or (e) failed to give consent for long-term follow-up.

From: Needham DM, Dinglas VD, Bienvenu OJ, Colantuoni E, Wozniak AW, Rice TW, Hopkins RO, Network NNA. One year outcomes in patients with acute lung injury randomised to initial trophic or full enteral feeding: prospective follow-up of EDEN randomised trial. *BMJ* 2013; 346: f1532.

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