TITLE: THE ARDS COGNITIVE OUTCOMES STUDY (ACOS): LONG-TERM NEUROPSYCHOLOGICAL FUNCTION IN ACUTE LUNG INJURY SURVIVORS

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Online Data Supplement

Methods

The study was reviewed and approved by the Institutional Review Boards of each participating hospital. It was also approved by the Natural History and Steering Committees of the NIH National Heart, Lung, and Blood Institute (NHLBI) Acute Respiratory Distress Syndrome Clinical Trials Network (ARDSNet) in 2002.

Study Design

The ARDS Cognitive Outcomes Study (ACOS) is a prospective, multi-center cohort study of survivors from the ARDSNet Fluid and Catheter Treatment Trial (FACTT). FACTT enrolled patients from 38 North American hospitals between June 2000 and October 2005. Between July 2002 and July 2003, FACTT was halted and new regulatory approval related to the study was prohibited. ACOS was coordinated and executed by investigators at the University of Pennsylvania and University of Pittsburgh. The regulatory process for ACOS began prior to the halt and testing was conducted between March 2003 and September 2006 in concert with the Economic Analysis of the Pulmonary-Artery Catheter (EA-PAC) study as a planned long-term assessment of neuropsychological function in FACTT survivors (E1). As a consequence of the regulatory halt of FACTT, ACOS ran partially concurrent with FACTT. Subjects gave informed consent for the telephone administration of neuropsychological tests.

Study Patients

To be eligible for ACOS, subjects had to be enrolled in FACTT and EA-PAC (E1) and ACOS-specific regulatory approval had to be in place. FACTT enrolled mechanically ventilated adults who met the American-European Consensus Conference criteria for ALI (E2). In FACTT, subjects were assigned at random to a conservative or liberal fluid management strategy (E3), and either a central venous catheter or PAC (E4) in a two-by-two factorial design. Baseline characteristics, including the presence of pre-existing dementia and site of enrollment, and medical data were collected prospectively as part of FACTT. We categorized the geographic region within the continental United States into one of five categories (Northeast, South, Southwest, Midwest, and West) based on the site of enrollment, consistent with prior studies (E5). On-study data, including hemodynamic, respiratory, renal and metabolic variables, were collected and recorded daily by the ARDS Network data coordinating center, as were cumulative fluid balance, organ-failure-free day assessments, ICU length of stay, and duration of mechanical ventilation (E3).

Cognitive and Psychiatric Function

A validated telephone battery of standardized neuropsychological tests was administered to consenting, English-speaking subjects at 2 and 12 months post-hospital discharge. Subjects were not required to undergo 2 month testing to be tested at 12 months. The test administration call center was centralized at the University of Pittsburgh. The telephone battery was administered using a

detailed standardized script by two non-neuropsychologists at the University of Pittsburgh who were blinded to group randomization. These two investigators received formal training from neuropsychologists and were evaluated for competence during the pilot interview stage prior to administering tests to subjects. The details of formation and validation of the battery used in this study have been presented previously (E6-8).

The following cognitive domains were assessed: vocabulary, reasoning, memory, verbal fluency and executive function. Executive function is a set of cognitive abilities that enable individuals to engage in purposeful, goal-directed behaviors, cognitive flexibility, abstract thinking, initiate behavior and are necessary for effective daily functioning. Memory, verbal fluency, and executive function were hypothesized to be domains susceptible to impairment in ALI survivors based on previous investigations in this population (E6, E8-E10). Anxiety, depression, and post-traumatic stress disorder (PTSD) symptoms were assessed using standardized measures (E11-14). Neuropsychological tests were reviewed, scored, and standardized by neuropsychologists at the University of Pennsylvania. Instruments used to assess each neuropsychological domain are presented in Table E1 (E11-18). To minimize the effect of order presentation, the tests were administered in random sequence (E6-E8).

Data Analysis

The cognitive battery yielded scaled scores for each domain which were normalized to allow for comparisons across tests and subjects (E19-20). We

report the median and interquartile range of results as percentiles. We defined impairment in a single domain as a score > 2 SD below the population normative data (E9-10, 21-22), a conservative definition of cognitive impairment that represents significant deficits outside the normal range of cognitive function. Cognitive impairment at the subject level was defined as impairment in memory, verbal fluency, and/or executive function in subjects who completed tests in each of these domains. We used the most conservative criteria to define impairment in a single domain and limited our cognitive assessment *a priori* to three domains shown to be affected in ALI survivors in previous studies (E6, E8-10) to minimize the probability of a Type I error to an acceptable alpha level of < 0.05 (E22).

The Beck Anxiety Inventory and the Zung Self-Rating Depression Scale are scored as none, mild, moderate and severe (E11-13). Patients with moderate or severe anxiety or depression were classified as impaired similar to previous studies (E6, E8, E21). The modified Post-traumatic Stress Syndrome 10-Questions Inventory (PTSS-10) is scored as normal or impaired (E14). Psychiatric impairment was defined as impairment in any, or multiple, of the three psychiatric measures (anxiety, depression, and PTSD) in subjects completing tests in each of these domains. We focused our study on survivors tested at approximately 12 months post-discharge to assess long-term neuropsychological function.

Based on prior studies, we *a priori* hypothesized that cognitive impairment would be associated with duration of mechanical ventilation, either conservative or liberal fluid-management strategy (E3), hypotension (E10), hypoxemia (E9),

PAC use (E4, E23), sepsis as the primary cause of lung injury (E24-25), and severity of illness (E26). PAC use was considered as a candidate risk factor given its association with arrhythmias and the potential risk of paradoxical air and/or microthrombotic embolism given the prevalence of moderate-to-large patient foramen ovale shunting in patients with ARDS (E23, E27-E28). There was no standardized delirium assessment in FACTT (E3-4) to permit adjusting for duration of delirium, which was recently shown to be associated with long-term cognitive impairment (E29-30). The pre-specified potential confounding variables included: age, gender, race, history of heavy alcohol use or cerebrovascular disease, level of education, the presence of concomitant psychiatric impairment, hospital length of stay prior to enrollment, and the time to testing (E6, E8-10, E21, E31-33).

We used baseline measures and daily measurements during the study ("on-study" data) to explore our hypotheses. On-study data from FACTT were summarized at the subject level as means to account for influential observations. We used hemodynamic values (systolic blood pressure (SBP), vasopressor use, cardiac index) and protocol assignment to shock cells from FACTT (E3-E4) to explore the potential causative role of hypotension (E10) and central venous pressure (CVP) to explore the potential role of fluid-management strategy. Respiratory values (partial pressure of arterial oxygen, PaO_2, partial pressure of arterial oxygen to fraction of inspired oxygen, PaO_2:FiO_2, oxygenation index, and oxygen saturation) were assessed to explore the potential causative role of hypoxemia (E9). We used Acute Physiologic and Chronic Health Evaluation

(APACHE) III scores and intensive care unit (ICU) length of stay for severity of illness measures.

With the exception of the shock assessment, which was measured as often as every 4 hours, and SBP and PaO_2:FiO_2, in which the worst values over the preceding 24 hours were recorded to derive the Brussels organ failure score, values were measured and recorded daily (measure closest to 8 am) during the study.

In addition, serum sodium, bicarbonate, blood urea nitrogen, creatinine, glucose (E34), organ-failure-free (cardiovascular, central nervous system, and renal) days (E35), and cumulative furosemide and corticosteroid dose given their potential anticholinergic activity (E36-37), were assessed in exploratory analyses (see Table E5).

Based on prior studies and/or plausibility, we tested the following candidate risk factors for the development of psychiatric morbidity: age (E38-E40), gender (E38-41), race/ethnicity, level of education (E39, E42), APACHE III, the trial interventions (fluid-management strategy, PAC), hypotension, hypoxemia (E38-39), any episode of hypoglycemia during the hospitalization (E43), corticosteroid administration (E43), ICU length of stay (E45-E46), and duration of mechanical ventilation (E38, E45).

Comparisons between groups were made using Student's t-test or Wilcoxon's rank-sum test for continuous variables and the chi-squared statistic or Fisher's exact test for categorical variables. In the presence of a significant association, continuous measurements were categorized based on the

distribution into quartiles to assess for dose-response effects. Quality of life was assessed at 12 months post-discharge as part of the EA-PAC study (E1). Quality of life was measured using the Health Utilities Index Mark 2 (E47).

Statistical Analysis:

Multivariable logistic regression was used to investigate the relationship between candidate risk factors and long-term neuropsychological impairment (cognitive impairment and psychiatric morbidity). We adjusted for each candidate risk factor and potential covariates with an alpha level of significance < 0.20 in univariate analyses (E48). Age and level of education were forced into the final cognitive models to account for potential differences in pre-morbid cognitive impairment. Time to testing and race were forced into the final cognitive models to account for potential time and survival biases. To avoid over-fitting the model, adjustment for potential confounding was performed one covariate at-a-time (E49). Multivariable logistic regression was also used to investigate the relationship between sociodemographic factors and consent to participate in a study of long-term neuropsychological function. For all analyses, associations were reported as an OR with 95% confidence intervals (CI). A standard two-tailed p-value of ≤ 0.05 was used to signify statistical significance. Statistical analyses were performed using Stata 10.0 software (Stata Datacorp, College Station, TX).

The primary analysis was limited to 75 survivors who completed testing in all three cognitive domains of interest at 12 months: memory, verbal fluency, and

executive function. The Hayling Sentence Completion Test (HSCT) assesses executive function with an error score and response latency component to produce an overall score. The response times for the HSCT were not measured before February, 2005 due to an error in the administration of the timing of the test. This error effected 21 of 102 survivors (8 randomized to the liberal-strategy group and 13 to the conservative-strategy group) at 12 months. In secondary analyses, 90 survivors who completed assessments in memory, verbal fluency, and the error score of the HSCT at 12 months were carried out.

Sensitivity Analyses:

We performed multiple sensitivity analyses to determine the effects of missing data on the observed association between fluid-management strategy and long-term cognitive impairment. To assess the potential effects of morbidity and mortality post-consent, we assumed that all 31 subjects who died post-consent or were classified as incapable to have the tests administered were impaired. To assess the potential effects of loss to follow-up post-consent, we first assumed that all 50 survivors reported as lost to follow-up were impaired, then we assumed that all 50 survivors reported as lost to follow-up were not impaired, and finally we assumed that impairment in those lost to follow-up was similar to the 55% incidence observed for the full cohort. To assess the potential effects of the 25 survivors who refused testing, we performed separate analyses using these same three assumptions. Finally, to gauge the potential effects of incomplete cognitive assessments on the associations identified in the primary

analysis, we assumed that all 27 survivors without a complete cognitive assessment were impaired, and then assumed that survivors without a complete cognitive assessment were not impaired. To minimize the assumptions of the latter scenario, survivors were categorized as impaired if the subject was impaired in a tested domain.

Results

Association between Risk Factors and Cognitive Domain Performance:

Lower PaO_2 values correlated with worse executive function (rho=0.24, p=0.05), but not verbal fluency (rho=0.16, p=0.14) or memory (rho=0.14, p=0.20). Similarly, lower central venous pressures correlated with worse executive function (rho=0.28, p=0.02), but not verbal fluency (rho= -0.07, p=0.47) or memory (rho=0.14, p=0.20). Enrollment in the conservative fluid-strategy group correlated with worse executive function (rho= -0.39, p<0.001), but not verbal fluency (rho= -0.01, p=0.89) or memory (rho= -0.12, p=0.25).

Association between Risk Factors and Anxiety, Depression, and PTSD:

Lower PaO_2 values were associated with anxiety (p=0.05), as were lower systolic blood pressures (p=0.04). Neither lower PaO_2 values, nor lower systolic blood pressures, were found to be associated with depression or PTSD. An episode of hypoglycemia was associated with anxiety at 12 months (p=0.01), but not depression (p=0.28), or PTSD (p=0.31).

Sensitivity Analyses:

Given the potential bias due to the effects of dropouts, we performed several sensitivity analyses. Under the assumption that all 31 subjects who consented for ACOS but died before testing (N=22) or were classified as incapable of test performance (N=9) were impaired (Figure 1), the association between conservative fluid-management strategy and long-term cognitive impairment remained significant (N=106, OR=3.48, 95% CI: 1.48, 8.16, p=0.004). The association also persisted if we assumed that the 50 survivors lost to follow-up post-consent were all impaired (N=125, OR=2.92, 95% CI: 1.28, 6.61, p=0.01), were all not impaired (N=125, OR=2.45, 95% CI: 1.14, 5.28, p=0.02), or were impaired to a similar degree (55% incidence) as the overall cohort of long-term survivors (N=125, OR=2.24, 95%CI: 1.10, 4.59, p=0.03). The association also persisted if we assumed that the 25 patients who refused after initially consenting were all impaired (N=100, OR=2.51, 95% CI: 1.05, 5.97, p=0.04), were all not impaired (N=100, OR=3.76, 95% CI: 1.62, 8.72, p=0.002), or were impaired to a similar degree (55% incidence) as the overall cohort of long-term survivors (N=100, OR=2.78, 95% CI: 1.23, 6.31, p=0.01).

Assuming that survivors with an incomplete cognitive assessment were *not* impaired, we found the association between the conservative fluid management strategy and long-term cognitive impairment remained (N=102, OR=2.76, 95% CI: 1.22, 6.21, p=0.014); as did the association between lower PaO_2 values and long-term cognitive impairment (N=93, OR=1.36, 95% CI: 1.03, 1.81, p=0.033). Under the assumption that survivors with an incomplete cognitive

assessment were impaired, we observed an association similar to the unadjusted association between the conservative-strategy group and long-term cognitive impairment (N=102, OR=4.09, 95% CI: 1.70, 9.83, p=0.002). The association between lower PaO_2 values and long-term cognitive impairment was no longer significant (N=93, OR=1.26, 95% CI: 0.95, 1.66, p=0.10).

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Figure E1. Enrollment and outcomes by fluid-management strategy. Abbreviations: ACOS=ARDS Cognitive Outcomes Study

Table E1. Outcomes measured in the neuropsychological test battery and cognitive domain performance at 12 months. Cognitive domains are listed by increasing prevalence of impairment in the 102 long-term ALI survivors.

Cognitive Domain	Instrument	No.	Percentile
Vocabulary *	WAIS-III: Vocabulary [E14]	98	25 (9 – 50)
Reasoning *	WAIS – III: Similarities [E14]	98	37 (16 – 63)
Memory †	WMS – III: Logical Memory I [E15]	92	37 (5 – 63)
Verbal Fluency †	Controlled Oral Word Association Test [E16]	96	19 (4 – 34)
Executive Functioning †	Hayling Sentence Completion Test (HSCT) [E17]	76	5 (<1 – 25)
Psychiatric Domain	Instrument		
Anxiety	Beck Anxiety Inventory [E12]	102	
Depression	Zung Self-Rating Depression Scale [E10-E11]	102	
Post-traumatic stress disorder	Post-traumatic Stress Syndrome 10-Questions Inventory [E13]	102	

Definition of abbreviation: HSCT=Hayling Sentence Completion Test; WAIS-III=Wechsler Adult Intelligence Scale-III; WMS-III: Wechsler Memory Scale-III.

* Domain a priori hypothesized to be resilient to effects of acute lung injury.

† Domain a priori hypothesized to be susceptible to effects of acute lung injury.

‡ The error score of the HSCT was completed in 100 long-term survivors.

Individual cognitive domain performance expressed as percentiles based on normative data.

Table E2. Patient characteristics and consent to participate in a study to assess long-term neuropsychological outcomes.

Variable*	Consent Rate †	p-value	Adjusted Odds Ratio (95% CI) ‡	p-value
Age, years (%)				
Age < 39	47/156 (30)		Reference	Reference
Age 40 – 48	65/162 (40)	0.02	1.59 (0.93 – 2.69)	0.09
Age 49 – 59	58/166 (35)		1.28 (0.75 – 2.18)	0.37
Age ≥ 60	43/171 (25)		1.23 (0.70 – 2.19)	0.47
Gender (%)				
Female sex	114/308 (37)	0.02	Reference	Reference
Male sex	99/347 (28)		0.75 (0.52 – 1.11)	0.15
Race or ethnic group (%)				
White non-Hispanic	166/446 (37)		Reference	Reference
Black non-Hispanic	34/136 (25)	0.001	0.73 (0.44 – 1.22)	0.23
Hispanic §	12/60 (20)		0.55 (0.26 – 1.13)	0.10
Other §	1/13 (8)			
United States geographic region (%)				
Northeast	49/128 (38)		Reference	Reference
Southeast	70/192 (36)	0.001	1.78 (0.90 – 3.55)	0.10
Southwest	22/124 (18)		0.64 (0.32 – 1.25)	0.19
Midwest	32/83 (38)		1.28 (0.74 – 2.21)	0.37
West	40/128 (31)		1.62 (0.90 – 2.93)	0.11

* Sociodemographic and hospital-level information in those 655 subjects who consented to long-term follow-up as part of EA-PAC (E1). Age was categorized into quartiles based on the observed distribution.

† Of 442 subjects who consented to EA-PAC, but not ACOS, 194 died between EA-PAC consent and completion of long-term follow-up, 55 were ineligible as the time window to be tested had elapsed due to the regulatory halt, 48 declined, and the remaining 145 were categorized as “not consented.”

‡ Adjusted for each variable and whether patient died during long-term follow-up after excluding the 55 ineligible subjects.

§ Hispanic and other race/ethnicity were collapsed into one group in the multivariable logistic regression model.

Table E3. Characteristics of long-term survivors with complete cognitive testing, by fluid-management strategy.

	Liberal (N=37)	Conservative (N=38)	p-value
Age, years	53 (43 – 60)	50 (47 – 56)	0.75
Male sex (%)	43	42	0.92
Race or ethnic group (%)			
White non-Hispanic	92	89	1.00
Black non-Hispanic	8	8	
Hispanic	0	3	
Level of education, years	12 (12 – 16)	12 (12 – 16)	0.43
Time from enrollment to testing, months	13 (12 – 13)	12 (12 – 14)	0.64
Time from discharge to testing, months	12 (11 – 13)	12 (11 – 13)	0.97
Previously Tested	24	37	0.24
Primary lung injury (%)			
Pneumonia	30	42	
Sepsis	30	18	
Aspiration	11	16	0.20
Trauma	5	16	
Multiple transfusions	5	3	
Other	19	5	
Coexisting conditions (%)*			
Diabetes	16	19	0.76
HIV infection or AIDS	0	0	–
Cirrhosis	5	3	1.00
Solid tumors	0	3	1.00
Leukemia	0	3	1.00
Lymphoma	5	0	0.49
Immunosuppression	8	11	1.00
Medical ICU (%)	59	53	0.87
APACHE III †	90 (64 – 107)	65 (58 – 89)	0.04
Glasgow Coma Scale	7 (3 – 11)	8 (7 – 11)	0.44
Mean arterial pressure, mm Hg *	74 (66 – 84)	77 (65 – 86)	0.68
Met shock criteria at baseline (%)	46	39	0.57
Vasopressor use at baseline (%)	43	32	0.30
Pre-randomization fluid balance, mL †	1869 (522 – 5564)	1261 (450 – 3744)	0.29
PaO_2:FiO_2 ‡	120 (87 – 162)	124 (80 – 180)	0.61

PaO_2[¶]	80 (67 – 105)	82 (67 – 97)	0.81
Pulmonary artery catheter (%)	62	53	0.40

Definition of abbreviation: HIV=human immunodeficiency virus; AIDS=acquired immunodeficiency syndrome; ICU=intensive care unit; APACHE III= Acute Physiologic and Chronic Health Evaluation III scores; PaO_2:FiO_2=ratio of partial pressure of arterial oxygen to fraction of inspired oxygen.
Values expressed as a percentage or median (interquartile range).
* Measured in 74 survivors; [†] measured in 73 survivors; [‡] measured in 71 survivors; [¶] measured in 72 survivors. Shock at baseline present if mean arterial pressure < 60 at baseline or vasoactive agent administered.

Table E4. On-study physiologic variables and outcomes of long-term survivors with complete cognitive testing, by fluid-management strategy.

	Fluid-Management Strategy		
	Liberal (N=37)	Conservative (N=38)	p-value
Hemodynamic variables			
Systolic Blood Pressure (mm Hg) *	108 (102 – 114)	102 (96 – 112)	0.11
Cardiac index (liters/min/m^2) †	4.8 (4.2 – 5.5)	4.2 (3.3 – 4.7)	0.06
CVP (mm Hg)	12.0 (10.4 – 13.8)	9.4 (6.6 – 11)	<0.001
CVP < 8 mm Hg (1st quartile) (%)	16	37	
CVP 8 – 12 mm Hg	43	50	0.015
CVP > 12 mm Hg (4th quartile)	40	13	
Shock ‡ (%)	27	34	0.50
Vasopressor use (%)	19	32	0.21
Ineffective circulation (%)	16	8	0.31
Fluid balance (cumulative over 7 days, mL)	1659 (-4236 – 6244)	-2706 (-7970 – -336)	0.02
Respiratory variables			
PaO_2:FiO_2	158 (128 – 191)	156 (133 – 191)	0.60
Oxygenation index	7.50 (5.11 – 10.3)	7.30 (5.16 – 10.05)	0.94
PaO_2	79 (70 – 97)	72 (68 – 84)	0.14
$PaCO_2$	43 (35 – 46)	42 (36 – 48)	0.59
PEEP	7 (6.2 – 8.4)	6.9 (5 – 8)	0.39
Oxygen saturation (%)	95 (92.8 – 96.6)	94.5 (92.7 – 96)	0.54
pH	7.41 (7.37 – 7.44)	7.44 (7.40 – 7.45)	0.01
ICU length of stay (days)	12 (9 – 18)	9 (7 – 13)	0.07
Duration of mechanical ventilation (days)	8.5 (4.5 – 12)	6 (4 – 9)	0.04
Glasgow coma scale ‡	11 (11 – 12)	12 (10 – 14)	0.59
Renal and metabolic variables			
Sodium	140 (139 – 143)	142 (139 – 144)	0.32
Blood urea nitrogen (mg/dL)	17.8 (15.7 – 31.6)	22.4 (17.0 – 32.8)	0.32
Creatinine (mg/dl)	0.98 (0.77 – 1.16)	0.92 (0.68 – 1.24)	0.63
Bicarbonate (mmol/L)	25.8 (24.0 – 28.9)	27.4 (23.0 – 32.2)	0.15
Glucose (mg/dL)	118 (110 – 144)	121 (108 – 134)	0.44

Dialysis to day 60 (%)	0	5	0.49
Therapy (cumulative dose)			
Furosemide (mg)	120 (60 – 260)	340 (160 – 620)	<0.001
Corticosteroids (mg of Methylprednisolone)	0 (0 – 96)	0 (0 – 144)	0.38
Organ-Failure-Free Days			
Days 1 to 7			
Cardiovascular failure	6 (5 – 7)	6 (4 – 7)	0.24
CNS failure	7 (0 – 7)	7 (0 – 7)	0.30
Renal failure	7 (7 – 7)	7 (7 – 7)	0.81
Days 1 to 28			
Cardiovascular failure	27 (25 – 28)	26 (24 – 27)	0.17
CNS failure	28 (21 – 28)	28 (21 – 28)	0.29
Renal failure	28 (28 – 28)	28 (28 – 28)	0.71
Psychiatric impairment, 12 months post-hospital discharge (%)	65	76	0.28

Definition of abbreviation: CVP=central venous pressure; ICU=intensive care unit; PaO_2:FiO_2=ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; PaO_2=partial pressure of arterial oxygen; $PaCO_2$=partial pressure of arterial carbon dioxide; PEEP=positive end-expiratory pressure; ICU=intensive care unit; CNS=central nervous system.
Values expressed as a frequency (percent) or median (interquartile range).
On-study variables were summarized at the subject level as means to account for influential observations. With the exception of systolic blood pressure measurements, values were measured and recorded daily (measure closest to 8 am) during the study.
* Lowest systolic blood pressure was recorded daily to determine the cardiovascular component of the Brussels organ failure score.
† Cardiac index was measured in 39 survivors (20 in the liberal-strategy group and 19 in the conservative-strategy group).
‡ Shock defined as mean arterial pressure < 60 or vasoactive agent use (assignment to FACTT protocol cells 1 or 2) at any time during FACTT (E3). Ineffective circulation was defined as a cardiac index of less than 2.5 liters per minute per square meter in the PAC group and as cold, mottled skin with a capillary re-filling time of greater than 2 seconds in the non-PAC group (E3).

Table E5. Associations with long-term cognitive impairment in ALI survivors. Cognitive impairment at the subject level was defined as impairment in memory, verbal fluency, and/or executive function in the 75 subjects who completed tests in each of these domains.

	Cognitive Impairment		
	Not Impaired (n=34)	Impaired (n=41)	p-value
Baseline characteristics			
Age, years	50 (43 – 58)	51 (45 – 60)	0.51
Male sex (%)	32	51	0.10
Race or ethnic group (%)			
White	91	90	0.53
Black	6	10	
Hispanic	3	0	
Level of education, years	13 (12 – 16)	12 (12 – 15)	0.36
Hospital length of stay prior to enrollment, days	2 (1 – 3)	3 (1 – 4)	0.22
ARDS at enrollment	88	90	1.00
Primary lung injury (%)			
Pneumonia	24	46	
Sepsis	29	20	
Aspiration	9	17	0.10
Trauma	12	10	
Multiple transfusions	6	2	
Other	21	5	
Coexisting conditions (%)			
Diabetes	18	17	1.00
HIV infection or AIDS	0	0	–
Cirrhosis	0	7	0.25
Solid tumors	0	2	1.00
Leukemia	3	0	0.45
Lymphoma	6	0	0.20
Immunosuppression	9	10	1.00
Heavy alcohol use	3	13	0.21
Cerebrovascular disease	0	2	1.00
Medical ICU (%)	59	54	0.56
APACHE III	87 (60 – 106)	72 (60 – 94)	0.42
Glasgow Coma Scale	8 (6 – 9)	8 (6 – 11)	0.39
Mean arterial pressure, mm Hg	80 (72 – 87)	72 (62 – 84)	0.12
Met shock criteria * (%)	44	41	0.82
Vasopressor use (%)	44	32	0.27
Pre-randomization fluid balance, mL	2109 (450 – 5189)	1437 (679 – 3744)	0.44

PaO_2:FiO_2	122 (76 – 170)	126 (87 – 166)	0.75
PaO_2	81 (66 – 104)	81 (67 – 99)	0.97
Conservative strategy (%)	32	66	0.004
Pulmonary artery catheter (%)	53	61	0.48
On-study variables			
Hemodynamic variables			
Systolic Blood Pressure (mm Hg) †	108 (102 – 113)	104 (96 – 112)	0.32
Cardiac index (liters/min/m^2) ‡	4.5 (3.8 – 5.3)	4.5 (3.7 – 5.0)	0.49
CVP (mm Hg)	11.0 (8.7 – 12.7)	9.7 (6.6 – 12.0)	0.038
CVP < 8 mm Hg (1st quartile) (%)	12	39	
CVP 8 – 12 mm Hg	53	41.5	0.02
CVP > 12 mm Hg (4th quartile)	35	19.5	
Shock * (%)	32	29	0.77
Vasopressor use	26	24	0.84
Ineffective circulation *	9	15	0.50
Fluid balance (cumulative over 7 days, mL)	-2352 (-5236 – 3598)	-503 (-4236 – 5698)	0.24
Respiratory variables			
PaO_2:FiO_2 §	152 (132 – 192)	157 (133 – 190)	0.63
Oxygenation index	7.38 (4.55 – 10.42)	7.67 (5.97 – 10.02)	0.57
PaO_2	86 (70 – 98)	71 (67 – 80)	0.02
PaO_2 < 68 (1st quartile) (%)	13	27	
PaO_2 68 – 93	50	65	0.014
PaO_2 > 93 (4th quartile)	37	8	
$PaCO_2$	43 (36 – 47)	42 (35 – 48)	0.96
PEEP	7 (5 – 9)	7 (6 – 7.8)	0.84
Oxygen saturation (%)	95.1 (93.3 – 96.8)	94.2 (92.6 – 95.8)	0.10
pH	7.42 (7.38 – 7.44)	7.43 (7.40 – 7.45)	0.27
ICU length of stay (days)	11 (8 – 18)	10 (7 – 16)	0.65
Duration of mechanical ventilation (days)	8 (4 – 11)	6 (4 – 9)	0.43
Glasgow coma scale	11 (11 – 13)	12 (11 – 14)	0.66
Renal and metabolic variables			
Sodium	141 (139 – 144)	142 (139 – 144)	0.49
Blood urea nitrogen (mg/dL)	20.6 (15.7 – 32.8)	19.8 (15.7 – 31.6)	0.94
Creatinine (mg/dl)	0.98 (0.69 – 1.24)	0.86 (0.70 – 1.14)	0.36
Bicarbonate (mmol/L)	26.6 (24.1 – 29.6)	25.9 (23.0 – 30.4)	0.95
Glucose (mg/dL)	124 (110 – 138)	118 (108 – 135)	0.74
Hypoglycemia, < 60 mg/dL (%)	6	12	0.45
Hyperglycemia, > 180 mg/dL (%)	26	37	0.35

Dialysis to day 60 (%)	0	5	0.50
Therapy (cumulative dose)			
Furosemide (mg)	200 (120 – 420)	200 (80 – 440)	0.62
Corticosteroids (mg of Methylprednisolone)	0 (0 – 144)	0 (0 – 136)	0.80
Organ-Failure-Free Days			
Days 1 to 7			
Cardiovascular failure	6 (5 – 7)	6 (4 – 7)	0.98
CNS failure	7 (0 – 7)	7 (0 – 7)	0.82
Renal failure	7 (7 – 7)	7 (7 – 7)	0.25
Days 1 to 28			
Cardiovascular failure	26 (24 – 28)	27 (24 – 27)	0.97
CNS failure	28 (21 – 28)	28 (21 – 28)	0.59
Renal failure	28 (28 – 28)	28 (28 – 28)	0.79
Time from enrollment to testing, months	13 (12 – 13)	12 (12 – 14)	0.53
Time from discharge to testing, months	12 (11 – 13)	12 (11 – 13)	0.51
Previously Tested (%)	38	24	0.20
Neuropsychiatric impairment, 1 year (%)	59	80	0.04

Definition of abbreviation: HIV=human immunodeficiency virus; AIDS=acquired immunodeficiency syndrome;ARDS=acute respiratory distress syndrome (PaO_2:$FiO_2 \leq 200$); ICU=intensive care unit; APACHE III= Acute Physiologic and Chronic Health Evaluation III scores; PaO_2:FiO_2=ratio of partial pressure of arterial oxygen to fraction of inspired oxygen; CVP=central venous pressure; ICU=intensive care unit; PaO_2=partial pressure of arterial oxygen; $PaCO_2$=partial pressure of arterial carbon dioxide; PEEP=positive end-expiratory pressure; ICU=intensive care unit; CNS=central nervous system.

Values expressed as a frequency (percent) or median (interquartile range).

On-study variables were summarized at the subject level as means to account for influential observations. With the exception of systolic blood pressure measurements, values were measured and recorded daily (measure closest to 8 am) during the study. Hypo- and hyperglycemia were defined as any episode of serum glucose < 60 mg/dL or > 180 mg/dL, respectively, during the hospitalization.

* Shock defined as mean arterial pressure < 60 or vasoactive agent use (assignment to FACTT protocol cells 1 or 2) at any time during FACTT (E3). Ineffective circulation was defined as a cardiac index of less than 2.5 liters per minute per square meter in the PAC group and as cold, mottled skin with a capillary re-filling time of greater than 2 seconds in the non-PAC group (E4).

† Lowest systolic blood pressure was recorded daily to determine the cardiovascular component of the Brussels organ failure score.

‡ Cardiac index was measured in 39 survivors (20 in the liberal-strategy group and 19 in the conservative-strategy group).

§ Using mean PaO_2:FiO_2 on-study to categorize subjects as ALI or ARDS, 77% met criteria for ARDS (PaO_2:$FiO_2 \leq 200$), 23% met criteria for ALI, and there was no association with cognitive impairment (p=0.82).

Table E6. Association between identified candidate risk factors and long-term cognitive impairment, adjusted for each potential covariate, one covariate at-a-time.* Cognitive impairment at the subject level was defined as impairment in memory, verbal fluency, and/or executive function in the 75 subjects who completed tests in each of these domains.

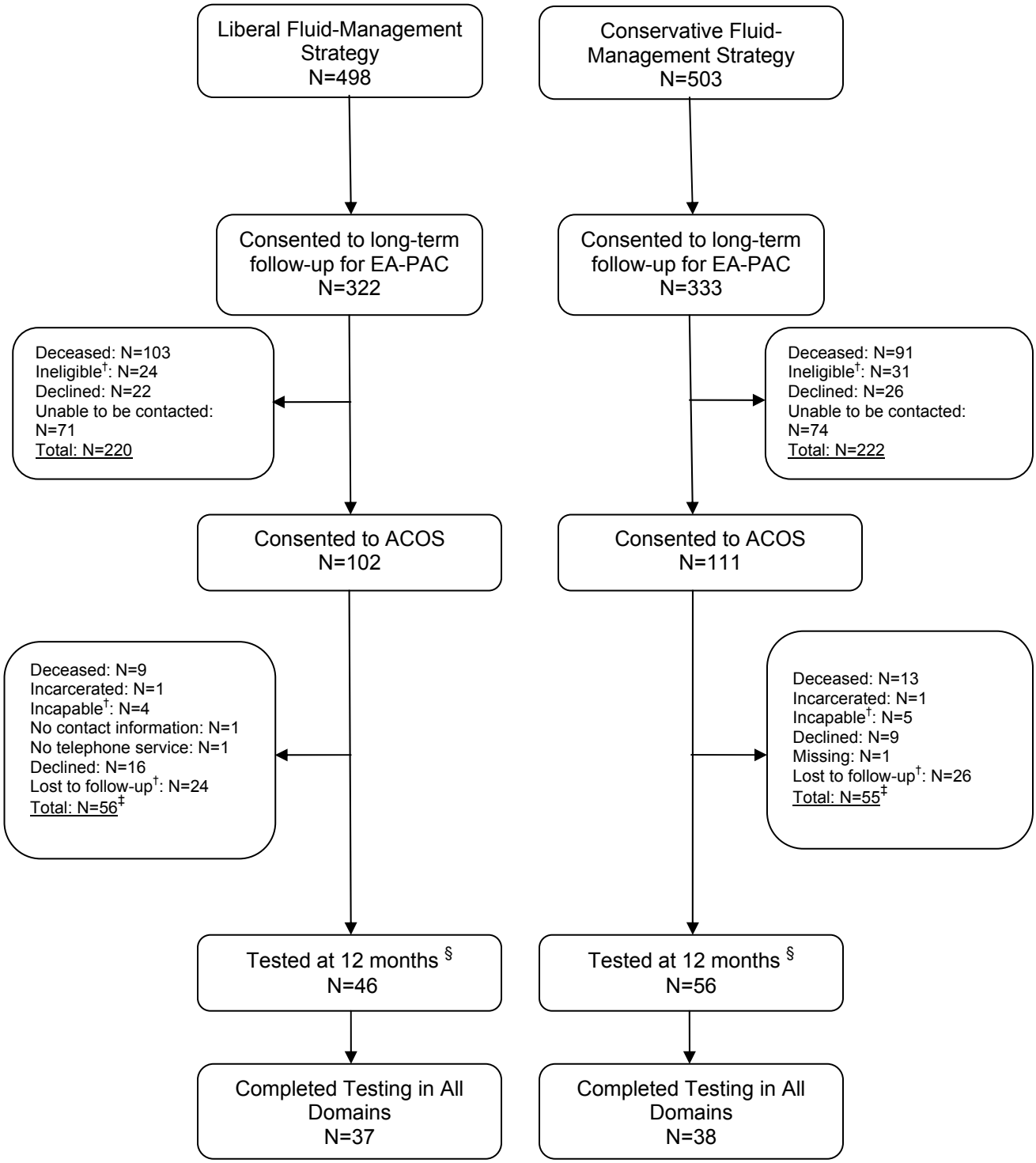
Hypoxemia Logistic Regression Model	Total N in Model	Odds Ratio (95% CI)	p-value
PaO_2 (base model) † ‡ §	67	1.56 (1.09 – 2.24)	0.015
Adjusted for: Age	67	1.57 (1.08 – 2.28)	0.017
Gender	67	1.53 (1.07 – 2.20)	0.021
Race	67	1.52 (1.05 – 2.19)	0.026
Level of education	67	1.57 (1.09 – 2.25)	0.015
Time to testing	67	1.56 (1.09 – 2.24)	0.015
Psychiatric impairment	67	1.49 (1.03 – 2.16)	0.033
Mean arterial pressure (baseline)	66	1.51 (1.05 – 2.18)	0.028
Vasopressor use (baseline)	67	1.57 (1.06 – 2.32)	0.023
Vasopressor use ‡	67	1.68 (1.14 – 2.49)	0.009
Central venous pressure ‡	67	1.60 (1.11 – 2.32)	0.012
Primary lung injury	67	1.51 (1.01 – 2.26)	0.043
Conservative fluid-management	67	1.48 (1.02 – 2.15)	0.037
Fluid-Management Logistic Regression Model	**Total N in Model**	**Odds Ratio (95% CI)**	**p-value**
Conservative fluid-management strategy (base model)	75	4.03 (1.53 – 10.59)	0.005
Adjusted for: Age	75	4.15 (1.56 – 11.00)	0.004
Gender	75	4.36 (1.60 – 11.85)	0.004
Race	75	4.47 (1.66 – 12.01)	0.003
History of heavy alcohol use †	72	5.46 (1.92 – 15.53)	0.001
History of cerebrovascular disease †	73	4.78 (1.77 – 12.91)	0.002
Level of education	75	4.45 (1.64 – 12.07)	0.003
Time to testing	75	4.00 (1.52 – 10.53)	0.005
Psychiatric impairment	75	3.84 (1.43 – 10.31)	0.008
Mean arterial pressure (baseline) †	74	4.88 (1.76 – 13.58)	0.002
Vasopressor use (baseline)	75	3.89 (1.47 – 10.28)	0.006
Vasopressor use ‡	75	4.28 (1.59 – 11.51)	0.004
Central venous pressure ‡	75	3.40 (1.21 – 9.58)	0.021
Primary lung injury	75	3.51 (1.24 – 9.94)	0.018
PaO_2 † ‡	67	3.35 (1.16 – 9.70)	0.026

***** Potential covariates were included in the multivariable logistic regression models if the variable was found to be associated with cognitive impairment in the univariate analyses ($p<0.20$) and to assess whether inclusion of the potential covariate altered the odds ratio for the candidate risk factor by > 10%. Age, race, level of education, and time from enrollment to testing were forced into the models. See methods for details.

† History of heavy alcohol use was missing in 3 survivors; history of cerebrovascular disease was missing in 2 survivors; baseline mean arterial pressure missing in 1 survivor. On-study PaO_2 measurements were missing in 8 survivors.

‡ On-study values. Daily measurements on-study were summarized, at the subject level, as means.
§ For each 10-unit decrease in partial pressure of oxygen in arterial blood (PaO_2), odds ratio for the development of cognitive impairment increases by 1.56 in the base model.

Figure E1.


Liberal Fluid-Management Strategy N=498
Conservative Fluid-Management Strategy N=503
Consented to long-term follow-up for EA-PAC N=322
Consented to long-term follow-up for EA-PAC N=333
Deceased: N=103
Ineligible†: N=24
Declined: N=22
Unable to be contacted: N=71
Total: N=220
Deceased: N=91
Ineligible†: N=31
Declined: N=26
Unable to be contacted: N=74
Total: N=222
Consented to ACOS N=102
Consented to ACOS N=111
Deceased: N=9
Incarcerated: N=1
Incapable†: N=4
No contact information: N=1
No telephone service: N=1
Declined: N=16
Lost to follow-up†: N=24
Total: N=56‡
Deceased: N=13
Incarcerated: N=1
Incapable†: N=5
Declined: N=9
Missing: N=1
Lost to follow-up†: N=26
Total: N=55‡
Tested at 12 months § N=46
Tested at 12 months § N=56
Completed Testing in All Domains N=37
Completed Testing in All Domains N=38

* Of 1001 FACTT subjects who underwent randomization, 227 were ineligible for long-term follow-up as part of EA-PAC as no regulatory approval was in place and 119 refused consent (21).

† Subjects were categorized as ineligible if the time window to be tested had elapsed due to the regulatory halt, as incapable if self-determined or determined by a surrogate to be physically or mentally incapable of telephone-based neuropsychological testing, and as lost to follow-up if consent was obtained but the subject was not tested.

‡ Reasons for not being testing, in those who consented, are categorized initially as causes outside of investigator control and then as causes which may be potentially remediable by future investigators.

§ Of 52 subjects tested at 2 months (20 from liberal arm and 32 from conservative arm), 32 were re-tested at 12 months. Subjects were not required to undergo testing at 2 months to be tested at 12 months.