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Psychiatric Symptoms in Acute Respiratory Distress Syndrome Survivors: A One-Year National Multi-Center Study

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Abstract

Objective—To evaluate prevalence, severity, and co-occurrence of, and risk factors for depression, anxiety, and post-traumatic stress disorder (PTSD) symptoms over the first year after ARDS.

Design—Prospective longitudinal cohort study.

Settings—41 ARDS Network hospitals across the U.S.

Patients—698 ARDS survivors.

Interventions—None.

Measurements and Main Results—Psychiatric symptoms were evaluated using the Hospital Anxiety and Depression Scale (HADS) and Impact of Event Scale–Revised (IES-R) at 6 and 12 months. Adjusted prevalence ratios for substantial symptoms (binary outcome) and severity scores were calculated using Poisson and linear regression, respectively. During 12 months, a total of 416 of 629 patients (66%) with at least one psychiatric outcome measure had substantial symptoms in at least one domain. There was a high and almost identical prevalence of substantial symptoms (36%, 42%, and 24% for depression, anxiety and PTSD) at 6 and 12 months. The most common pattern of co-occurrence was having symptoms of all 3 psychiatric domains *simultaneously*. Younger age, female sex, unemployment, alcohol misuse, and greater opioids use in the ICU were significantly associated with psychiatric symptoms, while greater severity of illness and ICU length of stay were not associated.

Conclusions—Psychiatric symptoms occurred in two-thirds of ARDS survivors with frequent co-occurrence. Sociodemographic characteristics and in-ICU opioids administration, rather than traditional measures of critical illness severity, should be considered in identifying patients at highest risk for psychiatric symptoms during recovery. Given high co-occurrence, ARDS survivors should be simultaneously evaluated for a full spectrum of psychiatric sequelae to maximize recovery.

Keywords

Depression; Anxiety; Stress Disorder; Post-Traumatic; Prospective Studies; Critical Illness; Respiratory Distress Syndrome; Adult

INTRODUCTION

Survivors of acute respiratory distress syndrome (ARDS) frequently experience substantial long-term psychiatric symptoms after hospital discharge.(1–10) Pro-inflammatory cytokines, frightening memories experienced in the intensive care unit (ICU), and stressful life changes after hospital discharge may be potential causes for psychiatric symptoms.(6) In ARDS survivors, systematic reviews have reported point prevalences of 17% to 43% for depression, 23% to 48% for anxiety, and 8% to 35% for post-traumatic stress disorder (PTSD) symptoms,(6;7;9) with common risk factors including younger age, female sex, obesity, pre-existing psychiatric illness, lower educational attainment, baseline unemployment, and lower blood glucose in the ICU.(1;3;4;7;9)

However, most existing publications are single-center studies with modest sample sizes that evaluate a single psychiatric domain in isolation. Few studies have evaluated multiple psychiatric outcomes in multiple institutions with large sample sizes.(6;11) These limitations contribute, in part, to conflicting results in evaluating risk factors for psychiatric symptoms after ARDS. To better inform clinicians' and researchers' efforts to effectively identify and treat these important morbidities, additional research is required regarding the prevalence, severity, co-occurrence and risk factors for psychiatric symptoms, using larger-sized, multi-centered, longitudinal studies to simultaneously evaluate commonly reported symptoms.

Hence, our study longitudinally evaluates, over the first year after ARDS, the prevalence, severity and co-occurrence of depression, anxiety, and PTSD symptoms, as well as patient- and critical illness-related risk factors for these symptoms.

METHODS

Study Population

Participants were part of the ARDS Network (ARDSNet) Long-term Outcome Study (ALTOS), a national, multi-center, prospective cohort study evaluating outcomes at 6 and 12 months after enrollment into three recent ARDSNet clinical trials evaluating ICU-based therapies for ARDS patients. The eligibility criteria for these three ARDSNet trials have been published previously and are summarized herein.(12;13) Patients were eligible for recruitment within 48 hours of ARDS onset and within 72 hours of initiation of mechanical ventilation. Major exclusion criteria included severe comorbid malnutrition; lung, liver or neuromuscular diseases; or limitations in life support at time of eligibility.(12;13) For follow-up evaluations in ALTOS, we further excluded survivors from the ARDSNet trials if they had potential cognitive impairment prior to admission (ascertained via medical records and/or patient/proxy report), or were non-English speaking, homeless, or younger than 18 years old. Across all participating sites, patients were managed with simplified versions of lung protective mechanical ventilation and fluid conservative hemodynamic management protocols, with blood glucose control aimed at 80–150 mg/dL (tighter glucose control was permitted). Informed consent was obtained from the patient or a proxy. This study was approved by the Institutional Review Board at Johns Hopkins University and all participating hospitals.

Measurement of Patient- and Critical Illness-Related Exposures

Both patient- and critical illness-related exposures were obtained from ALTOS and the ARDSNet trials. Patient-related baseline exposures included demographics, employment status (unemployed vs. employed), body mass index (BMI), medical comorbidities (diabetes mellitus, prior stroke, and use of hemodialysis), and alcohol misuse. Alcohol misuse was defined by zones 3 and 4 from the Alcohol Use Disorders Identification Test (AUDIT), which indicate alcohol consumption in excess of recommended limits. (14) Critical illness-related baseline exposures included admission to a medical (versus surgical) ICU, severity of illness (i.e., Acute Physiology and Chronic Health Evaluation (APACHE) III score, and partial pressure of oxygen in arterial blood to fraction of inspired oxygen (PaO2/FiO2) ratio), and ARDS risk factor (sepsis versus all others). While in the ICU, the following were collected daily for up to 12 days after enrollment: (1) the Brussels organ failure status for the cardiovascular, pulmonary, coagulation, renal and hepatic systems(15) (modeled as the mean number of organ failures during data collection), (2) use of hemodialysis and vasopressors (modeled as binary variables), (3) use of opioids, corticosteroids, and neuromuscular blockers (modeled as the percentage of ICU days with use), and (4) morning and daily minimum blood glucose (modeled as mean values). Mechanical ventilation duration and ICU length of stay data were also collected.

Measurement of Psychiatric Symptoms

The outcome variables of interest were symptoms of depression, anxiety, and PTSD at 6 and 12 months after ARDS. Depression and anxiety symptoms were measured using the respective subscales of the Hospital Anxiety and Depression Scale (HADS) instrument.(16) Each HADS subscale ranges from 0 to 21, with a higher score indicating worse symptoms and a score ≥8 indicating substantial symptoms.(16) PTSD symptoms were measured using the Impact of Event Scale-Revised (IES-R). The IES-R score ranges from 0 to 4, with a higher score indicating worse PTSD symptoms(17) and a score ≥1.6 indicating substantial PTSD symptoms in ARDS survivors.(18) Both scales were administered to patients only (i.e. no proxy respondents) by trained research staff via phone for 98% of assessments, otherwise via mail or in-person administration. These scales have evidence of good reliability and validity, and have been frequently used in prior studies evaluating survivors of critical illness.(1;9;18;19)

Statistical Analysis

We compared all exposure variables (see Table 1) by binary categorization of the three psychiatric domains at 6 months using Fisher’s exact tests and t-tests. For both the 6- and 12-month time points, correlations of continuous psychiatric symptom scores were calculated using the Spearman correlation coefficient, and co-occurrence of substantial psychiatric symptoms was evaluated by calculating the proportion of patients who had substantial symptoms in more than one domain. The prevalence and co-occurrence were illustrated via a proportioned Venn diagram utilizing the “pvenn” command (Stata version 13.0, StataCorp, College Station, TX).

Associations between each exposure variable and substantial symptoms for each of the three psychiatric domains (binary outcome variables, as previously defined) were evaluated using

Poisson regression. We evaluated these associations separately at 6- and 12-month follow-up; however, due to statistically similar associations at both time points, we adopted a simplified approach combining 6- and 12-month follow-up visits. For this combined approach, the models included an indicator for time (12- vs. 6-month) and were fitted using generalized estimating equations (GEE), with an exchangeable correlation structure and robust variance estimate to account for within-patient clustering over 6- and 12-month follow-ups. For continuous measures of symptom severity for each of the three psychiatric domains, a similar statistical approach was employed using linear regression models. Multivariable regression models were constructed in the same manner as the bivariable models and included all exposure variables that had a potentially significant bivariable association of $p<0.20$ with each psychiatric domain. Regardless of bivariable association, ICU length of stay was included in the multivariable models to standardize evaluation of daily ICU exposure variables, and baseline use of hemodialysis was included to adjust for pre-existing renal disease when including hemodialysis in the ICU in the multivariable models. To evaluate the effect of potential confounding by pre-existing psychiatric comorbidity on the results, we conducted sensitivity analysis using a subgroup of patients (n=203) from 5 of the 12 study sites on whom we prospectively collected baseline psychiatric comorbidity based on medical records. In this analysis, we evaluated the exposure-outcome assessments with vs. without this comorbidity in the original multivariable model.

Standard regression diagnostics were conducted for all models. The linearity assumption was verified by assessing locally weighted scatterplot smoothing of each exposure variable against residuals from the regression model. Only age demonstrated a non-linear relationship with outcomes, so we categorized age into four quartiles (18–39, 40–49, 50–59, and 60–89 years), with the last quartile (60–89) as the reference. We confirmed that there was no multi-collinearity by evaluating variance inflation factors.(20) Since missing data were rare (<5% of all survivors at each of 6 and 12 months), regression analysis was done using the available data without imputation. P-values were two-sided, and statistical significance was defined as $p<0.05$. All statistical analyses were performed using Stata 13.0 (StataCorp, College Station, TX).

RESULTS

Among 1,176 patients enrolled in the three ARDSNet trials, 247 (21%) died by hospital discharge, an additional 44 (5% of hospital survivors) died before re-consent, and 187 (20% of hospital survivors) met ALTOS exclusion criteria, leaving a total of 698 (59%) who survived hospital stay and were eligible and consented for follow-up (Figure 1). A total of 645 (98%) of 656 and 606 (95%) of 635 survivors had follow-up visits at 6 and 12 months, respectively. Among them, 613 (95%) and 576 (95%) completed at least one psychiatric instrument at 6- and 12-month follow-up, respectively, with 629 patients completing at least one psychiatric instrument over one-year longitudinal follow-up.

Participating patients had a mean (standard deviation) age of 49 (15) years, with 52% female, 82% white and 49% unemployed prior to hospital admission (Table 1). Patients with substantial psychiatric symptoms during follow-up were more likely ($p<0.05$ based on

Fisher's exact and t-tests) to be younger, female, unemployed prior to ARDS, have alcohol misuse history, be less acutely ill (i.e. lower APACHE III score at ICU admission), and receive opioids for a greater proportion of ICU stay (Table 1).

Individual Psychiatric Domains and their Co-occurrence

Among 629 patients with at least one psychiatric measure, 416 (66%) had substantial symptoms in ≥1 domain during one-year follow-up. At 6 months (Table 1), the prevalence of substantial symptoms of depression, anxiety, and PTSD was 36% (222/613), 42% (260/613), and 24% (148/605), respectively, with almost identical prevalence at 12 months (36% (204/574), 42% (241/575), and 23% (132/573)). Across all three domains, the multivariable models demonstrated no significant change in prevalence or severity of psychiatric morbidity over time (Tables 2 and 3). Of patients who had substantial symptoms of depression, anxiety, and PTSD at 6 months, 57%–66% still had the same symptoms at 12 months, and <15% of patients without substantial symptoms at 6 months developed symptoms later.

Continuous scores for psychiatric symptoms during follow-up were correlated as follows: depression and anxiety (Spearman's rho: 0.70–0.72, $p<0.001$), anxiety and PTSD (0.69 at both time points, $p<0.001$), and depression and PTSD (0.58–0.59, $p<0.001$). The majority of survivors (63%) with any psychiatric morbidity (i.e. depression, anxiety, and/or PTSD symptoms) had substantial symptoms in two or more domains. At 6 months, 325 (53%) of 613 patients had substantial symptoms in at least 1 of the 3 domains assessed in this study. Among these symptomatic patients, the most common pattern of co-occurrence of symptoms involved simultaneously having substantial symptoms of depression, anxiety, and PTSD (n=106, 33%), followed by substantial depression and anxiety symptoms (18%), substantial anxiety and PTSD symptoms (7%), and substantial depression and PTSD symptoms (3%) (Figure 2). Similar results were observed at 12 months.

Risk Factors for Substantial Psychiatric Symptoms and Severity

The bivariable and multivariable prevalence ratios for each psychiatric domain by risk factors are reported in Table 2. Female sex, unemployment prior to hospital admission, and alcohol misuse were associated with substantial symptoms in all three psychiatric domains. Younger age was significantly associated with substantial anxiety and PTSD symptoms, and a greater proportion of ICU days with opioids administration was significantly associated with substantial anxiety and depression symptoms (Table 2). Risk factor associations were similar when psychiatric symptoms were modeled as continuous variables (Table 3). Specifically, female sex, unemployment, and a greater in-ICU opioid use were associated with symptoms in all three domains. Younger age, alcohol misuse, and greater in-ICU neuromuscular blocker use were associated with more severe anxiety and PTSD symptoms.

Sensitivity analysis demonstrated that pre-existing psychiatric comorbidity was associated with each psychiatric domain in continuous analyses and only with anxiety in binary analyses. Adding psychiatric comorbidity in both continuous and binary multivariable models demonstrated relatively little change in the overall results with the risk factors for

depression remaining significant, unemployment no longer being significant for anxiety, and female sex no longer being significant for PTSD.

In both binary and continuous analyses, greater severity of illness (i.e., APACHE III, PaO2/FiO2 ratio, number of organ failures, hemodialysis, and vasopressors), consistently was not associated with, or was negatively associated with, psychiatric symptoms. Moreover, there was no association between type of ICU, ARDS risk factor (sepsis vs. others), mechanical ventilation duration, and ICU length of stay with psychiatric symptoms in any analysis (Tables 2 and 3).

DISCUSSION

In this national, multicenter, longitudinal follow-up study evaluating psychiatric symptoms in over 600 ARDS survivors, two-thirds of participants had substantial symptoms in at least one psychiatric domain during 12-month follow-up. There was high prevalence, persistence, and co-occurrence of depression, anxiety, and PTSD symptoms. Severity of illness, mechanical ventilation duration and ICU length of stay were not associated with worse psychiatric symptoms. Younger age, female sex, baseline unemployment, alcohol misuse, and greater in-ICU use of opioids were consistently significant markers for post-ICU psychiatric symptoms.

At 6 months, the prevalence of substantial symptoms of depression, anxiety, and PTSD were high at 36%, 42%, and 24%, without improvement at 12 months. These prevalence rates are much higher than those in the general population,(21;22) but comparable with prior smaller, single-centered studies of ICU survivors.(4–7) Moreover, our findings of the persistence, frequent co-occurrence, and moderate to high correlation of psychiatric symptoms are also built upon prior studies of ICU survivors.(2;5;8;23–26)

Notably, anxiety and depression symptoms observed in this study may reflect pre-ARDS psychiatric morbidity; however, when accounting for pre-ICU psychiatric status, critical illness may remain an independent risk factor for new post-ICU psychiatric morbidity.(27;28) Moreover, PTSD symptoms, reported in approximately one-quarter of survivors in this study, likely represent incident psychiatric symptoms post-ARDS, since the IES-R instrument used in this study specifically addresses patients' symptoms in relation to their critical illness and ICU experience.

Our findings add to the growing body of evidence that psychiatric symptoms are a significant and prolonged burden for ICU survivors, and that patient and critical illness factors may be markers for these symptoms. The positive associations of younger age, female sex and unemployment with psychiatric symptoms are recognized in ICU survivors and other patient populations.(1;4;29–35) Notably, however, our sensitivity analysis suggests that the association of unemployment with anxiety and female sex with PTSD may be a marker for patients who have pre-existing psychiatric comorbidity rather than independent risk factors. While existing findings have been inconsistent about alcohol use disorder as a predictor for developing psychiatric conditions, our study suggests that it is strongly associated with psychiatric symptoms and severe outcomes.(36–40)

A longer duration of opioid exposure was the only ICU-related risk factor consistently and positively associated with symptoms in all three psychiatric domains. A prior study of ARDS survivors demonstrated that a high mean daily dose of opioids (≥100mg of morphine equivalents per day) was positively associated with PTSD symptoms measured by IES-R, but a greater proportion of ICU days with opioid was negatively associated with PTSD symptoms.(9) It has been speculated that adequate pain control using opioids may have a preventive effect on PTSD.(9;41–43) Unfortunately, data on opioid dosing was not available to further evaluate this issue in our study. Future research in survivors of critical illness should investigate, in greater detail, the potentially complex role of in-ICU opioid administration and dosage.

Of note, our study demonstrated that five different measures of severity of illness, along with mechanical ventilation duration and ICU length of stay, had no positive association with psychiatric symptoms. Notably, a higher APACHE III score was associated with lower symptom scores, which might reflect that patients with higher severity of illness who survived their ICU stay had less pre-existing psychiatric illness or had another unmeasured factor that was protective against post-ICU psychiatric symptoms. Despite these findings contradicting positive associations of illness severity with post-ARDS physical impairments and mortality,(11;44–48) our findings agree with prior studies evaluating psychiatric symptoms in both ARDS and other ICU survivors.(30–32;49;50) Hence, it is critical for clinicians to recognize that patients with anticipated better physical outcomes, due to a lower severity of illness and shorter length of stay, should not be overlooked when considering risk for post-ICU psychiatric symptoms.(9;49;50)

The strengths of this study include being a national, longitudinal, prospective study with large sample size, high retention rate (≥95%), and simultaneous evaluation of prevalence, severity, co-occurrence and risk factors for three common psychiatric morbidities. However, the study has potential limitations. First, our study focused on relatively young ARDSNet trials survivors with exclusions for severe comorbid diseases. Hence, the findings may not be generalizable to other populations. However, comparisons of our findings to the existing literature generally revealed consistency of results, which may support generalizability. Second, this evaluation was restricted to the variables collected as part of the ARDSNet trials, omitting potentially relevant variables, such as baseline neuropsychological and physical functioning status, ICU exposure to sedatives, dose-related data for the opioid and corticosteroid, and daily pain, sedation and delirium assessments. Inclusion of such variables in future large-scale studies is highly recommended. Third, given its observational design, our study cannot demonstrate cause-effect relationships; hence, the results should be recognized as markers of risk for post-ARDS psychiatric symptoms, rather than as direct causal associations. We could be underpowered to identify a true association between severity of illness and psychiatric symptoms, but prior literature supports our findings. Finally, we used self-reported measures of psychiatric symptoms without ascertaining clinical psychiatric diagnoses and could only determine the prevalence, rather than incidence of depression and anxiety symptoms. However, the HADS and IES-R are commonly used and well-validated instruments.(1;9;18;19) Moreover, they have the advantages of providing both a binary result and a continuous measure of symptom severity, and being feasible to administer to a large geographically dispersed national patient cohort.(9) In addition, the

IES-R instrument used in this study evaluates PTSD symptoms with respect to patients' critical illness, thus likely evaluating incident symptoms. The IES-R instrument has high discrimination (area under the receiver operating characteristics = 95%) in screening for a clinical diagnosis of PTSD in ARDS survivors.(18)

CONCLUSION

Two-thirds of ARDS survivors had substantial symptoms of depression, anxiety or PTSD during 12-month follow-up. We observed high co-occurrence among these psychiatric domains, particularly co-occurrence of all three morbidities. Younger age, female sex, unemployment prior to hospital admission, alcohol misuse, and greater in-ICU use of opioids were significant markers for these symptoms. However, traditional risk factors for post-ICU physical impairment were not associated with worse symptoms. These findings have value in identifying patients at greatest risk of psychiatric symptoms during recovery from critical illness, and emphasize the need to simultaneously evaluate for a full spectrum of potential sequelae to maximize patient recovery.

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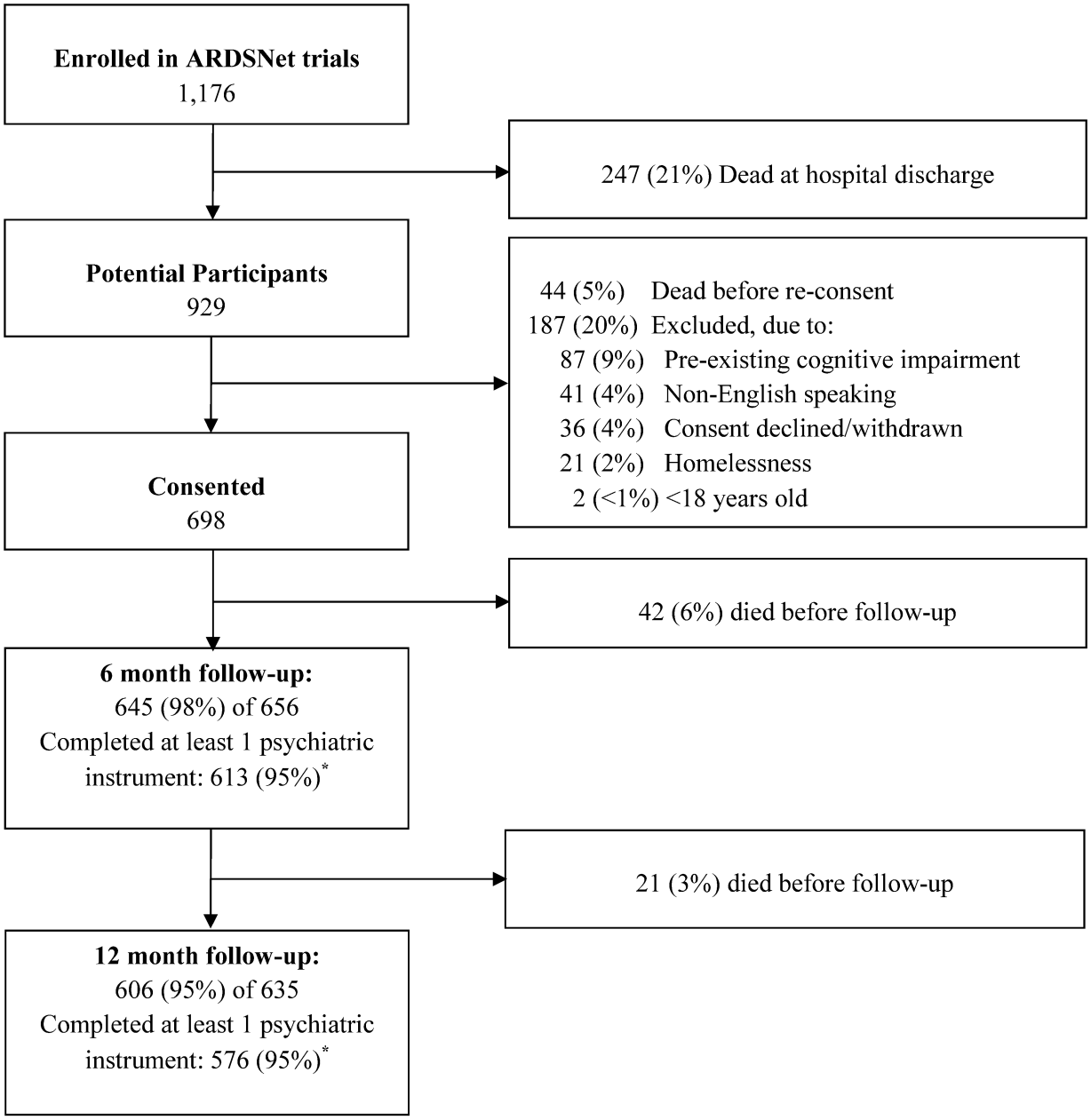

Figure 1.
Patient flow diagram.
*Reasons for not completing psychiatric assessments at 6 and 12 months, respectively: declined 8 and 7, physically incapable 7 and 5, cognitively incapable 6 and 4, receiving mechanical ventilation 3 and 3, psychiatric issues 2 and 3, incarcerated 2 and 2, unable to contact 3 and 1, lack of time 0 and 1, and other reason 1 and 4.

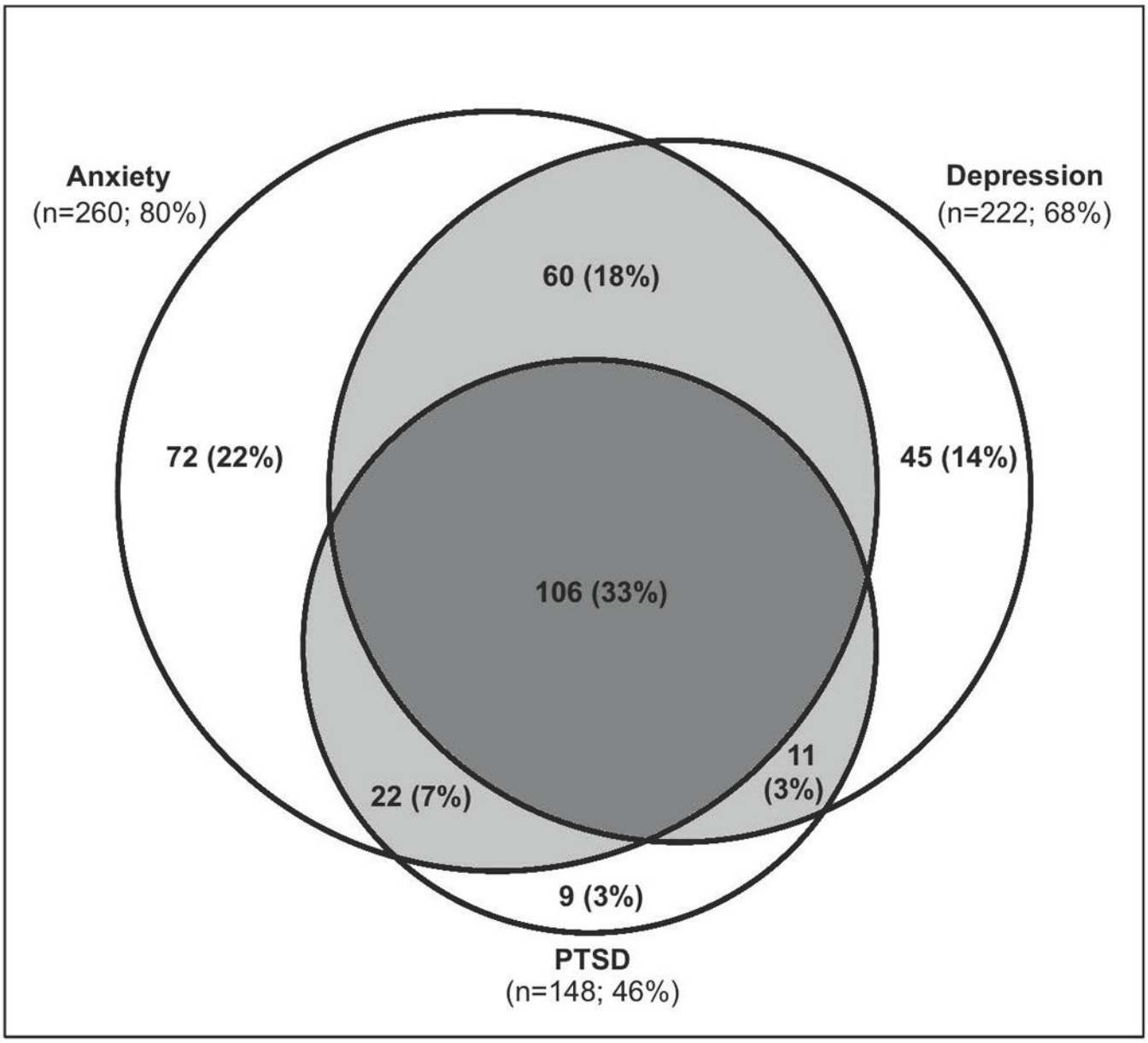

Figure 2.

Venn diagram of co-occurrence of anxiety, depression, and PTSD symptoms among 325 patients with any psychiatric morbidity at 6-month follow-up. (Light grey area indicates co-occurrence of two psychiatric symptoms; dark grey area indicates co-occurrence of all three psychiatric symptoms).

Table 1

Baseline characteristics for all patients and by psychiatric symptoms at 6 months after acute respiratory distress syndrome

		Depression Symptoms, n (%)		Anxiety Symptoms, n (%)		PTSD Symptoms[b], n (%)	
Variable[a]	**Total (n=613)**	**Positive (HADS ≥8) n=222 (36%)**	**Negative (HADS <8) n=391 (64%)**	**Positive (HADS ≥8) n=260 (42%)**	**Negative (HADS <8) n=353 (58%)**	**Positive (IES-R ≥1.6) n=148 (24%)**	**Negative (IES-R <1.6) n=457 (76%)**
Baseline patient data							
Age, mean (SD) year	49 (15)	48 (12)	49 (16)	48 (12)	50 (16)	47 (12)	50 (15)
Female, N (%)	316 (52)	127 (57)	189 (48)	155 (60)	161 (46)	100 (68)	213 (47)
White, N (%)	485 (82)	174 (81)	311 (82)	211 (84)	274 (80)	108 (78)	371 (83)
Unemployed, N (%)	296 (49)	130 (59)	166 (43)	143 (56)	153 (44)	88 (60)	205 (45)
BMI, mean (SD) kg/m^2	30 (8)	31 (8)	30 (8)	31 (8)	30 (8)	31 (8)	30 (8)
Diabetes, N (%)	146 (24)	52 (23)	94 (24)	62 (24)	84 (24)	32 (22)	110 (24)
Stroke, N (%)	9 (2)	5 (2)	4 (1)	4 (2)	5 (1)	4 (3)	4 (1)
Hemodialysis, N (%)	14 (2)	9 (4)	5 (1)	7 (3)	7 (2)	6 (4)	8 (2)
Alcohol misuse, N (%)	126 (22)	52 (25)	74 (20)	60 (24)	66 (20)	36 (26)	88 (21)
Baseline intensive care data							
Admission to medical ICU, N (%)	350 (57)	124 (56)	226 (58)	151 (58)	199 (56)	86 (58)	259 (57)
APACHE III, mean (SD)	86 (26)	82 (25)	88 (26)	83 (26)	88 (25)	83 (26)	87 (25)
PaO2/FiO2, mean (SD)	204 (73)	209 (76)	200 (72)	202 (65)	205 (79)	207 (71)	202 (74)
Sepsis as ARDS risk factor, N (%)	467 (76)	157 (71)	310 (79)	195 (75)	272 (77)	108 (73)	352 (77)
Daily intensive care data							
No. of organ failures[c], mean (SD)	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)	2 (1)
Any hemodialysis, N (%)	76 (14)	22 (11)	54 (15)	24 (10)	52 (17)	19 (14)	56 (14)
Any vasopressor use, N (%)	325 (53)	110 (50)	215 (55)	137 (53)	188 (53)	81 (55)	240 (53)
% of days with opioids, mean (SD)	73 (30)	78 (28)	70 (31)	76 (28)	70 (32)	79 (27)	71 (31)
% of days with corticosteroids, mean (SD)	21 (35)	23 (37)	20 (34)	21 (36)	20 (34)	24 (37)	20 (34)
% of days with neuromuscular blocker, mean (SD)	5 (13)	5 (14)	5 (13)	6 (14)	4 (13)	6 (15)	5 (13)
Morning glucose, mean (SD) mg/dl,	127 (26)	127 (26)	127 (26)	126 (26)	128 (26)	126 (26)	128 (26)
Minimum glucose, mean (SD) mg/dl	110 (23)	110 (25)	111 (21)	108 (23)	112 (22)	108 (20)	111 (23)
Other intensive care data							

Variable[a]	Total (n=613)	Depression Symptoms, n (%)		Anxiety Symptoms, n (%)		PTSD Symptoms[b], n (%)	
		Positive (HADS ≥8) n=222 (36%)	Negative (HADS <8) n=391 (64%)	Positive (HADS ≥8) n=260 (42%)	Negative (HADS <8) n=353 (58%)	Positive (IES-R ≥1.6) n=148 (24%)	Negative (IES-R <1.6) n=457 (76%)
Ventilation duration, mean (SD) day	11 (10)	11 (10)	11 (10)	10 (8)	11 (11)	11 (9)	11 (10)
ICU length of stay, mean (SD) day [d]	14 (11)	14 (11)	14 (11)	13 (10)	15 (12)	14 (10)	14 (11)

Abbreviations: ARDS (acute respiratory distress syndrome), PTSD (post-traumatic stress disorder), HADS (Hospital Anxiety and Depression Scale), IES-R (Impact of Event Scale – Revised), SD (standard deviation), BMI (body mass index), ICU (intensive care unit), APACHE III (Acute Physiology and Chronic Health Evaluation III), PaO2/FiO2 (ratio between partial pressure of oxygen in arterial blood and fraction of inspired oxygen).

[a]Percentages may not add up to 100% due to rounding. Missing data for each variable (N): white (19), unemployed (10), BMI (2), alcohol misuse (42), APACHE III score (17), PaO2/FiO2 ratio (19), any hemodialysis (58), % of days with opioids (130), % of days with corticosteroids (120), % of days with neuromuscular blocker (130), morning glucose (1), and minimum glucose (101).

[b]Missing PTSD assessments for 8 (1%) of 613 patients.

[c]Data represent the average number of organ failures during ICU stay, using the Brussels scoring system(20) for the following five organ systems (with definition of organ failure): cardiac (systolic blood pressure ≤90 mmHg or use of vasopressor), pulmonary (PaO2/FiO2 ratio ≤300), coagulation (platelets ≤80 × 10^9/L), renal (creatinine ≥2.0 mg/dL) and hepatic (bilirubin ≥2.0 mg/dL).

[d]Median and inter-quartile range (IQR) of ICU length of stay was 10 (7–16) days.

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Table 2

Variables associated with presence versus absence of substantial psychiatric symptoms

	Prevalence ratio (95% CI) of substantial psychiatric symptoms[a,b,c]					
	Depression		Anxiety		PTSD	
Variables	**Bivariable**	**Multivariable**	**Bivariable**	**Multivariable**	**Bivariable**	**Multivariable**
Baseline patient data						
Age quartile (younger vs. older)[d]	1.03 (0.95, 1.12)		1.13 (1.05, 1.21)	**1.16 (1.07, 1.26)**	1.22 (1.10, 1.36)	**1.23 (1.08, 1.41)**
Female	1.24 (1.02, 1.50)	**1.26 (1.01, 1.58)**	1.41 (1.19, 1.66)	**1.43 (1.18, 1.74)**	1.78 (1.37, 2.32)	**1.80 (1.31, 2.48)**
White	0.99 (0.78, 1.26)		1.12 (0.89, 1.40)		0.83 (0.62, 1.13)	
Unemployed	1.50 (1.24, 1.83)	**1.35 (1.09, 1.69)**	1.31 (1.11, 1.55)	**1.26 (1.05, 1.52)**	1.51 (1.17, 1.95)	**1.40 (1.03, 1.90)**
BMI, per 10 kg/m^2	1.07 (0.96, 1.20)		1.11 (1.01, 1.22)	**1.14 (1.03, 1.26)**	1.07 (0.93, 1.24)	
Diabetes	1.06 (0.86, 1.30)		0.99 (0.82, 1.20)		0.85 (0.63, 1.14)	
Stroke	1.39 (0.74, 2.58)		1.04 (0.49, 2.18)		1.61 (0.76, 3.43)	
Hemodialysis	1.29 (0.82, 2.03)	1.54 (0.86, 2.75)	1.05 (0.63, 1.77)	1.26 (0.75, 2.12)	1.39 (0.72, 2.67)	
Alcohol misuse	1.22 (0.99, 1.50)	**1.39 (1.09, 1.77)**	1.19 (0.99, 1.44)	**1.45 (1.18, 1.79)**	1.35 (1.02, 1.79)	**1.79 (1.31, 2.46)**
Baseline intensive care data						
Admission to medical ICU	0.99 (0.82, 1.20)		1.02 (0.87, 1.21)		1.00 (0.77, 1.28)	
APACHE III, per 20 unit	0.90 (0.83, 0.97)	**0.90 (0.82, 0.99)**	0.89 (0.84, 0.96)	0.95 (0.88, 1.02)	0.89 (0.80, 0.98)	**0.88 (0.79, 0.98)**
PaO2/FiO2, per 20 unit	1.01 (0.98, 1.04)		0.99 (0.97, 1.01)		1.01 (0.98, 1.04)	
Sepsis as ARDS risk factor	0.88 (0.71, 1.08)		0.99 (0.82, 1.20)		0.91 (0.68, 1.21)	
Daily intensive care data						
No. of organ failures	0.90 (0.78, 1.05)	0.94 (0.76, 1.18)	0.84 (0.73, 0.96)	0.88 (0.73, 1.07)	0.99 (0.81, 1.21)	
Any hemodialysis	0.66 (0.47, 0.92)	0.69 (0.45, 1.04)	0.67 (0.48, 0.91)	0.77 (0.53, 1.12)	0.95 (0.64, 1.43)	
Any vasopressor use	0.94 (0.78, 1.14)		0.98 (0.83, 1.16)		1.12 (0.87, 1.44)	
% of days with opioids, per 20%	1.10 (1.02, 1.19)	**1.11 (1.03, 1.20)**	1.07 (1.01, 1.14)	**1.08 (1.01, 1.15)**	1.13 (1.02, 1.25)	1.09 (0.98, 1.22)
% of days with corticosteroids, per 20%	1.02 (0.96, 1.08)		1.02 (0.97, 1.07)		1.05 (0.98, 1.13)	1.04 (0.96, 1.12)
% of days with neuromuscular blocker, per 20%	1.00 (0.87, 1.17)		1.12 (1.02, 1.24)	1.12 (0.99, 1.27)	1.14 (0.96, 1.35)	**1.23 (1.02, 1.49)**
Morning glucose, per 20 mg/dL	1.01 (0.94, 1.09)		0.98 (0.92, 1.05)		0.96 (0.87, 1.06)	
Minimum glucose, per 20 mg/dL	1.00 (0.91, 1.10)		0.96 (0.87, 1.05)		0.94 (0.84, 1.06)	
Other intensive care data						

	Prevalence ratio (95% CI) of substantial psychiatric symptoms[a,b,c]					
	Depression		Anxiety		PTSD	
Variables	**Bivariable**	**Multivariable**	**Bivariable**	**Multivariable**	**Bivariable**	**Multivariable**
Mechanical ventilation duration, per week	1.02 (0.95, 1.08)		0.99 (0.93, 1.05)		1.02 (0.94, 1.11)	
ICU length of stay, per week	1.01 (0.95, 1.07)	1.00 (0.93, 1.08)	0.98 (0.93, 1.03)	0.95 (0.88, 1.02)	1.00 (0.92, 1.08)	0.93 (0.83, 1.04)
Change at 12 vs. 6 month follow-up[e]		1.00 (0.89, 1.13)		0.91 (0.83, 1.01)		0.90 (0.77, 1.06)

Abbreviations: CI (confidence interval), PTSD (post-traumatic stress disorder), BMI (body mass index), ICU (Intensive Care Unit), APACHE III (Acute Physiology and Chronic Health Evaluation III), PaO2/FiO2 (ratio between partial pressure of oxygen in arterial blood and fraction of inspired oxygen), ARDS (acute respiratory distress syndrome).

[a]Presence of substantial symptoms of depression, anxiety and PTSD was defined by Hospital Anxiety and Depression Scale (HADS) depression and anxiety subscale scores ≥8 and an Impact of Event Scale – Revised (IES-R) score ≥1.6. Results are presented as prevalence ratios, calculated by Poisson regression models using generalized estimating equations (GEE) with robust variance estimate, an exchangeable correlation structure, and an indicator for time (12- vs. 6-month follow-up).

[b]Variables included in multivariable analyses are those from bivariable analyses that were associated (at $p < 0.20$) with each outcome measure of depression, anxiety, or PTSD symptoms.

[c]All the significant associations ($p<0.05$) in multivariable models are highlighted in bold.

[d]Age quartiles in years: 18–39 (quartile 1), 40–49 (quartile 2), 50–59 (quartile 3), 60–89 (quartile 4). Quartile 4 (60–89) was used as the reference group.

[e]Represents the change in outcome proportions, between 12- vs. 6-month follow-up, after adjusting for the other variables.

Table 3

Variables associated with severity of psychiatric symptoms

	Increase (95% CI) in psychiatric symptom score[a,b,c]					
	HADS-Depression		HADS-Anxiety		IES-R	
Variables	**Bivariable**	**Multivariable**	**Bivariable**	**Multivariable**	**Bivariable**	**Multivariable**
Baseline patient data						
Age quartile (younger vs. older) [d]	0.03 (−0.30, 0.36)		0.67 (0.34, 1.01)	**0.70 (0.30, 1.10)**	0.13 (0.07, 0.19)	**0.14 (0.07, 0.21)**
Female	1.28 (0.57, 1.99)	**0.91 (0.11, 1.71)**	1.63 (0.90, 2.36)	**1.81 (0.94, 2.67)**	0.33 (0.19, 0.46)	**0.38 (0.22, 0.54)**
White	−0.13 (−1.06, 0.81)		0.24 (−0.72, 1.20)		−0.08 (−0.25, 0.09)	
Unemployed	2.04 (1.34, 2.75)	**1.74 (0.95, 2.54)**	1.30 (0.56, 2.04)	**1.22 (0.36, 2.09)**	0.21 (0.08, 0.35)	**0.20 (0.05, 0.36)**
BMI, per 10 kg/m^2	0.47 (0.03, 0.91)	0.15 (−0.35, 0.65)	0.33 (−0.12, 0.79)	0.39 (−0.16, 0.95)	0.06 (−0.02, 0.14)	0.10 (−0.01, 0.20)
Diabetes	0.16 (−0.68, 1.00)		−0.39 (−1.26, 0.48)		−0.13 (−0.29, 0.02)	−0.02 (−0.21, 0.17)
Stroke	0.95 (−2.08, 3.99)		0.47 (−2.66, 3.61)		0.14 (−0.45, 0.73)	
Hemodialysis	0.42 (−2.01, 2.85)	0.82 (−1.91, 3.55)	−0.92 (−3.42, 1.59)	0.03 (−3.06, 3.12)	0.19 (−0.26, 0.64)	
Alcohol misuse	0.55 (−0.34, 1.43)		0.88 (−0.04, 1.80)	**1.88 (0.81, 2.95)**	0.20 (0.03, 0.36)	**0.40 (0.21, 0.60)**
Baseline intensive care data						
Admission to medical ICU	0.13 (−0.60, 0.85)		−0.01 (−0.75, 0.74)		−0.04 (−0.17, 0.10)	
APACHE III, per 20 unit	−0.39 (−0.67, −0.12)	**−0.36 (−0.68, −0.03)**	−0.52 (−0.81, −0.23)	**−0.44 (−0.79, −0.08)**	−0.06 (−0.11, −0.01)	**−0.07 (−0.13, −0.01)**
PaO2/FiO2, per 20 unit	0.05 (−0.05, 0.15)		−0.01 (−0.12, 0.09)		0.00 (−0.02, 0.02)	
Sepsis as ARDS risk factor	−0.41 (−1.25, 0.43)		−0.22 (−1.09, 0.65)		−0.12 (−0.27, 0.04)	−0.03 (−0.23, 0.17)
Daily intensive care data						
No. of organ failures	−0.61 (−1.18, −0.04)	−0.51 (−1.30, 0.28)	−0.69 (−1.28, −0.11)	−0.28 (−1.13, 0.57)	−0.04 (−0.15, 0.07)	
Any hemodialysis	−1.45 (−2.55, −0.35)	−0.64 (−2.01, 0.74)	−1.31 (−2.43, −0.18)	−0.69 (−2.16, 0.78)	−0.03 (−0.24, 0.17)	
Any vasopressor use	−0.06 (−0.78, 0.65)		0.30 (−0.44, 1.04)		0.07 (−0.06, 0.21)	
% of days with opioids, per 20%	0.41 (0.14, 0.67)	**0.42 (0.16, 0.69)**	0.39 (0.12, 0.67)	**0.39 (0.10, 0.68)**	0.09 (0.04, 0.13)	**0.07 (0.02, 0.12)**
% of days with corticosteroids, per 20%	0.09 (−0.14, 0.32)		0.08 (−0.16, 0.32)		0.03 (−0.01, 0.08)	0.02 (−0.02, 0.06)
% of days with neuromuscular blocker, per 20%	0.10 (−0.50, 0.70)		0.68 (0.07, 1.30)	**0.67 (0.03, 1.31)**	0.12 (0.01, 0.23)	**0.14 (0.02, 0.25)**
Morning glucose, per 20 mg/dL	0.01 (−0.27, 0.28)		−0.17 (−0.46, 0.11)		−0.01 (−0.07, 0.04)	
Minimum glucose, per 20 mg/dL	−0.13 (−0.48, 0.22)		−0.31 (−0.67, 0.06)	−0.32 (−0.73, 0.10)	−0.03 (−0.09, 0.04)	
Other intensive care data						

	Increase (95% CI) in psychiatric symptom score[a,b,c]					
	HADS-Depression		HADS-Anxiety		IES-R	
Variables	**Bivariable**	**Multivariable**	**Bivariable**	**Multivariable**	**Bivariable**	**Multivariable**
Mechanical ventilation duration, per week	0.07 (−0.19, 0.33)		−0.07 (−0.34, 0.19)		0.02 (−0.03, 0.07)	
ICU length of stay, per week	0.03 (−0.20, 0.26)	0.01 (−0.26, 0.27)	−0.09 (−0.33, 0.14)	−0.25 (−0.54, 0.05)	0.01 (−0.03, 0.06)	−0.04 (−0.09, 0.01)
Change at 12 vs. 6 month follow-up [e]		−0.01 (−0.35, 0.33)		−0.30 (−0.70, 0.09)		−0.06 (−0.14, 0.01)

Abbreviations: CI (confidence interval), HADS (Hospital Anxiety and Depression Scale), IES-R (Impact of Event Scale – Revised), BMI (body mass index), ICU (Intensive Care Unit), APACHE III (Acute Physiology and Chronic Health Evaluation III), PaO2/FiO2 (ratio between partial pressure of oxygen in arterial blood and fraction of inspired oxygen), ARDS (acute respiratory distress syndrome).

[a]Results are presented as the mean difference in HADS-depression, HADS-anxiety, and IES-R scores, calculated by linear regression models using generalized estimating equations (GEE), an exchangeable correlation structure, and an indicator for time (12- vs 6-month follow-up).

[b]Variables included in multivariable analyses are those from bivariable analyses that were associated (at $p < 0.20$) with each outcome measure of psychiatric symptom score.

[c]All the significant associations ($p<0.05$) in multivariable models are highlighted in bold.

[d]Age quartiles in years: 18–39 (quartile 1), 40–49 (quartile 2), 50–59 (quartile 3), 60–89 (quartile 4). Quartile 4 (60–89) was used as the reference group.

[e]Represents the difference in mean outcome scores, between 12- vs. 6-month follow-up, after adjusting for the other variables.