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General anxiety symptoms after acute lung injury: Predictors and correlates

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Abstract

Objective—Acute lung injury (ALI) is common in the intensive care unit (ICU), typically requiring life support ventilation. Survivors often experience anxiety after hospital discharge. We evaluated general anxiety symptoms 3 months after ALI for: (1) associations with patient characteristics and ICU variables, and (2) cross-sectional associations with physical function and quality of life (QOL).

Methods—General anxiety was assessed as part of a prospective cohort study recruiting patients from 13 ICUs at four hospitals in Baltimore, MD using the Hospital Anxiety and Depression Scale — Anxiety Subscale (HAD-A), with associations evaluated using multivariable linear and logistic regression models.

Results—Of 152 patients, 38% had a positive screening test for general anxiety (HAD-A ≥ 8). Pre-ICU body mass index and psychiatric comorbidity were associated with general anxiety (OR, 95% confidence interval (CI): 1.06 (1.00, 1.13) and 3.59 (1.25, 10.30), respectively). No ICU-related variables were associated with general anxiety. General anxiety was associated with the number of instrumental ADL dependencies (Spearman's rho = 0.22; $p = 0.004$) and worse overall QOL as measured by EQ-5D visual analog scale (VAS) (rho = −0.34; $p < 0.001$) and utility score

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Conflict of interest statement

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(rho = −0.30; $p < 0.001$), and by the SF-36 mental health domain (rho = −0.70; $p < 0.001$) and Mental Component Summary score (rho = −0.73; $p < 0.001$).

Conclusion—Many patients have substantial general anxiety symptoms 3 months after ALI. General anxiety was associated with patient characteristics and impaired physical function and quality of life. Early identification and treatment of general anxiety may enhance physical and emotional function in patients surviving critical illnesses.

Keywords

Acute lung injury; adult; Anxiety; Critical care; Intensive care units; Physical function; Quality of life; Respiratory distress syndrome; adult

Introduction

Critical illnesses, requiring life support therapies such as mechanical ventilation in the intensive care unit (ICU) setting, can have a significant impact on psychological outcomes [1]. In particular, survivors of critical illnesses are at high risk for experiencing anxiety symptoms [2–4]. Up to 50% of ICU survivors experience clinically important general (or non-specific) anxiety symptoms one year after discharge [1,2], which is much higher than the US general population's 18% prevalence of any type of anxiety disorder [5]. Such anxiety symptoms are associated with somatization, as well as impaired psychological functioning and lower health-related quality of life (HRQOL) [3,6–11].

Within the ICU setting, acute lung injury (ALI), and its more severe subset, acute respiratory distress syndrome (ARDS), is an archetypal critical illness [12]. ALI is characterized by acute onset of severe hypoxemia caused by non-cardiogenic pulmonary edema evidenced by bilateral pulmonary infiltrates on chest x-ray [13,14]. A variety of pulmonary (e.g. pneumonia) and non-pulmonary (e.g. pancreatitis) risk factors are associated with onset of ALI [13,14]. Patients with ALI commonly experience severe dyspnea and require mechanical ventilation in the ICU. In-hospital mortality of ALI may be as high as 45% [15,16].

There have been few prior studies of general anxiety symptoms in survivors of critical illnesses, leaving substantial gaps in the extant literature on risk factors, as well as the association between general anxiety symptoms and HRQOL or physical function. Other studies have identified associations between depressive symptoms and physical functioning in ICU survivors [8,17,18]. We hypothesized a priori that several baseline patient characteristics and ICU variables would be associated with general anxiety symptoms, and that general anxiety symptoms would be associated cross-sectionally with HRQOL and physical function. As such, the objectives of this study were to evaluate survivors 3 months after ALI for general anxiety symptoms and associations with: (1) patient characteristics and ICU variables, and (2) physical function and health-related quality of life (HRQOL).

Methods

Study design and patient sample

This evaluation was conducted as part of amulti-site prospective cohort study. A total of 520 participants were recruited from 13 intensive care units (ICUs) in four hospitals in Baltimore, MD. Participants were consecutive, mechanically-ventilated adults with ALI [19] enrolled between October 2004 and October 2007. ICUs specializing in neurological conditions, and ALI patients with primary neurological disease and/or brain trauma were not eligible for enrollment. In addition, the following were key exclusion criteria: (1) >5 days of

mechanical ventilation during hospitalization prior to enrollment; (2) pre-existing ALI for >24 h before transfer to a study ICU; (3) pre-existing illness with a life expectancy <6 months; (4) a limitation in use of life support at time of enrollment; (5) prior lung resection; (6) pre-existing cognitive impairment or communication/language barriers, and (7) no fixed address for follow-up purposes. Informed consent for prospective follow-up was obtained in writing fromthe patients once they regained decision-making capacity or from a substitute decision-maker for patients who remained incapable of making medical decisions. Institutional review board approval was obtained from the Johns Hopkins University and all participating study sites.

Assessment of primary outcome: general anxiety symptoms

The primary outcome for this evaluation was the prevalence of general anxiety symptoms 3 months after ALI onset. Outcome assessment was performed by research assistants who were blinded to the exposure variables. General anxiety symptoms were measured with the 7-item anxiety subscale (range 0 to 21, with higher scores indicating worse symptoms) of the Hospital Anxiety and Depression Scale (HAD-A) [20]. The HAD-A is a validated measure commonly used in a wide variety of medical populations, with a score of ≥8 signifying a positive screening test for general anxiety symptoms (i.e., clinically significant symptoms of anxiety) [20–23].

Assessment of patient characteristics

Patient variables were evaluated based on prior studies of psychological outcomes of ICU patients [3,24,25] and a priori hypotheses for other potentially relevant characteristics. Baseline patient characteristics were collected from the medical record and interview with the patient or proxy, and included demographics, educational achievement, body mass index, and relevant comorbidities. Comorbidities were measured with the Charlson index,which is a standardized method of measuring comorbidity burden that assigns weights to the 19 categories of baseline comorbidity evaluated (e.g. a weight of 1 for diabetes, 2 for moderate to severe renal disease, 3 for moderate to severe liver disease) to derive a total comorbidity score [26]. Specific comorbidities were also examined in this study as follows: cardiovascular disease, chronic pulmonary disease, chronic fatigue, HIV/AIDS, psychiatric history (i.e., any record of psychiatric diagnosis and/or treatment), drug/alcohol abuse (i.e., current or prior illicit drug use or excess alcohol use), and at least moderate pain or discomfort.

Assessment of in-ICU variables

Critical illness and ICU hospitalization variables were evaluated based on prior studies of psychological outcomes of ICU patients [18,27–32]. These variables included ICU type (surgical vs. non-surgical); severity of illness at ICU admission (Acute Physiology and Chronic Health Evaluation [APACHE II] score) [33]; maximum daily organ failure in the ICU (Sequential Organ Failure Assessment (SOFA) score) [28–30]; proportion of ICU days with sepsis from microbiologically-proven infection [34]; hospital and ICU length of stay; low blood glucose (mean daily minimum glucose value) [31]; and the mean daily dose and duration of use of selected medications (benzodiazepines [in midazolam-equivalents], opiates [in morphine-equivalents] and systemic corticosteroids [in prednisone-equivalents]).

Correlates of general anxiety symptoms

General anxiety symptoms were evaluated for their cross-sectional association with physical function and HRQOL 3 months after ALI onset. Physical function was evaluated by the number of dependencies in activities of daily living, measured by the Katz Index of Independence in Activities of Daily Living (ADLs) (range 0 to 6, with a higher score

indicating more ADL dependencies) and instrumental activities of daily living, measured by the Lawton Instrumental Activities of Daily Living scale (IADLs) (range 0 to 8, with a higher score indicating more IADL dependencies), using validated instruments [35,36]. HRQOL was measured using the EQ-5D [37] and Medical Outcomes Study Short Form-36 version 2 (SF-36) [38] instruments. The EQ-5D provided 2 measures of overall HRQOL used in this evaluation: a visual analog scale (VAS) (range: 0 to 100, with a higher score indicating better HRQOL) and a utility score based on patient responses to 5 items each evaluating a different domain of HRQOL (range: −0.11 to 1.0, with a higher score indicating better HRQOL). The SF-36 has 8 separate domains (4 mental and 4 physical) with 2 overall summary measures of mental and physical health known as the Mental and Physical Component Summary measures. From the SF-36, the Mental and Physical Component Summary measures (norm-based scores, with range 0 to 100, mean = 50, standard deviation = 10, and higher scores indicating better HRQOL) were evaluated in addition to the mental health and physical function domains (not norm-based scores, with range 0 to 100, and higher scores indicating better HRQOL).

Statistical methods

Summary statistics were calculated for the 3-month HAD-A score modeled as both a binary variable (i.e., a positive screening test for general anxiety symptoms (i.e., HAD-A ≥ 8)) and as a continuous variable. Participants were classified according to the binary HAD-A threshold, and the patient- and ICU-related variables were summarized using percentages or median (first quartile, third quartile) within each group. The bivariable association between the continuous and binary measures of general anxiety symptoms and the patient and ICU-related variables was estimated using simple linear and logistic regression models. All patient and ICU-related variables with $p < 0.10$ in the bivariable analyses, plus all comorbidities regardless of bivariable association, were then analyzed in multivariable linear and logistic regression models. Standard model checking procedures were used for multivariable models, including evaluation of residuals (including normal probability plots for linear regression, DFBeta, and DFFit plots) [39]. Scatterplots and loess curves [40]were generated to visualize the cross-sectional association between the 3-month general anxiety symptoms and physical function and quality of life measures, and Spearman rank correlation coefficients were calculated. All analyses were completed on the available data. Exploratory analyses were conducted to compare the patient and ICU-exposures for participants with and without HAD-A data, revealing no statistically significant or clinically relevant differences between the two groups. All *p*-values were two-sided with statistical significance defined as $p < 0.05$. All analyses were performed using R statistical software [41].

Results

Of the 520 patients with ALI enrolled in the study, 284 (55%) survived to hospital discharge. Among those 284 hospital survivors, prior to 3 month follow-up, an additional 38 (13%) died, 37 (13%) declined consent, and 13 (<5%)were lost to follow-up. Of the eligible consenting survivors, 22 (8%) were unable to complete a 3-month follow-up visit, and 22 (8%) had a visit without completing the HAD-A survey, leaving 152 patients with complete HAD-A data at 3 months (Fig. 1). We compared the patient- and ICU-related variables among the 152 participants that completed the 3-month follow-up and the 44 who were eligible but did not complete either the 3-month follow-up or the HAD-A at their 3-month visit. With the exception of BMI, there were no statistically or clinically significant differences between the patient and ICU exposures in these two groups. Although BMI was statistically significantly different between groups ($p < .05$), the median BMI in the two groups was not clinically relevant. Of these 152 patients, the median (inter-quartile range (IQR)) age was 49 [40,57] with 59% male and 61% Caucasian (Table 1).

At 3-month follow-up, 38% (58/152) of patients had a positive screening test for general anxiety symptoms (HAD-A ≥ 8) with a median (IQR) HAD-A score of 6 (3, 9). In simple logistic regression analyses of all patient- and ICU-related variables with a positive screening test for general anxiety symptoms (HAD-A ≥ 8), the following were associated at $p < 0.10$: body mass index, and both medical (e.g. Charlson index, chronic pulmonary disease, HIV/AIDS, pain) and psychiatric comorbidities (e.g. psychiatric history, drug/alcohol abuse) (Table 2). Associations of patient- and ICU-related variables with general anxiety symptoms were similar when general anxiety symptoms were modeled as a continuous variable in simple linear regression models (Table 3).

Multivariable logistic regression models demonstrated that the following variables were independently associated (odds ratio (OR) (95% confidence interval (CI))) with a positive screening test for general anxiety symptoms (HAD-A ≥ 8) (Table 2): pre-ICU body mass index (1.06 (1.00, 1.13) per unit increase in BMI), Charlson index (1.28 (1.00, 1.64)), cardiovascular disease (0.26 (0.06, 1.10)), chronic pulmonary disease (3.41 (1.22, 9.57)), psychiatric comorbidity (3.59 (1.25, 10.30)), and pain (4.81 (0.89, 26.06)). Several of these variables also were associated with general anxiety symptoms measured as a continuous variable in multivariable linear regression models (Table 3) including: higher pre-ICU body mass index (0.15 (95% CI: 0.06, 0.25) increase in the HAD-A score for each 1 unit increase in body mass index); Charlson index (0.33 (−0.05, 0.70)); cardiovascular disease (−2.1 (−4.22, 0.02)); chronic pulmonary disease (1.89 (0.31, 3.47)); psychiatric history (2.33 (0.71, 3.95)); and pain (1.65 (−0.25, 3.54)). None of the other patient- and ICU-related variables was associated with a positive screening test for general anxiety symptoms (HAD-A ≥ 8) or the continuous HAD-A score in these multivariable regression analyses.

Greater general anxiety symptoms were significantly associated with worse overall HRQOL, as measured by the EQ-5D VAS (Spearman's rho = −0.34; $p < 0.001$) and utility score (rho = −0.30; $p < 0.001$), and by the SF-36 mental health domain (rho = −0.70; $p < 0.001$; Fig. 2) and Mental Component Summary score (rho = −0.73; $p < 0.001$). Associations were weaker, but statistically significant, for physical aspects of HRQOL as measured by the SF-36 physical function domain (rho = −0.26; $p < 0.001$) and Physical Component Summary score (rho = −0.18; $p = 0.009$). Greater general anxiety symptoms were cross-sectionally associated with impaired physical function, as measured by the number of IADL dependencies (rho = 0.22; $p = 0.004$). There was not a statistically significant association between general anxiety symptoms and number of ADL dependencies (r = 0.11; $p = 0.124$).

Discussion

This multi-site study of 152 survivors of ALI demonstrated that 38% had a positive screening test for general anxiety symptoms at 3-month follow-up. General anxiety symptoms were cross-sectionally associated with worse physical function and HRQOL. Bivariable analyses suggested that several patient variables were associated with increased general anxiety symptoms. Multivariable regression analyses demonstrated significant associations of general anxiety symptoms for higher body mass index, specific medical comorbidities, and psychiatric comorbidity. Of 10 potentially relevant ICU variables evaluated, none was independently associated with general anxiety symptoms.

The 38% prevalence of ALI survivors having a positive screening test for general anxiety symptoms at 3 month follow-up is much higher than the 18% 12-month prevalence of any anxiety disorder in the United States general population [5] and the 21% point prevalence of a HAD-A score ≥8 in a large non-clinical sample of adults [42]. Several other studies also have identified a high prevalence of general anxiety symptoms among survivors of critical illness [3,4,43,44]. Using the Beck Anxiety Inventory (BAI), Mikkelson and colleagues

identified a very high prevalence of moderate or severe general anxiety symptoms (62%) among 102 ALI survivors at 12-month follow-up [43]. In a prospective cohort of 62 ALI survivors that also used the BAI, 23% experienced moderate to severe symptoms of general anxiety (BAI ≥ 16) at two years after hospital discharge [3]. Authors of another study of 200 patients recruited from 35 academic, teaching, and community hospitals across the United States, found that approximately half of ALI survivors experienced substantial depression, general anxiety, or insomnia symptoms on a Quality of Well-Being subscale at 6 and 12 months after hospitalization [44]. Hence, the prevalence of general anxiety symptoms in our cohort is comparable with prior research.

Our prospective study revealed that greater general anxiety symptoms following ALI were cross-sectionally associated with impaired physical function and HRQOL. Other studies have revealed similar associations between ALI and HRQOL [4,7,8,11,45], but to our knowledge, none has investigated associations with activities of daily living as done in our study. However, other studies have identified associations between depressive symptoms and physical functioning in ICU survivors [17,18,46].

Several patient risk factors evaluated in this study have not been evaluated in prior studies including: body mass index, specific comorbidities, and pain/discomfort. Other patient risk factors we examined were based on previous studies of psychological outcomes of critically ill patients [3,24,25,47]. Our study was not able to evaluate three patient variables that previously have been associated with symptoms of general anxiety or PTSD: personality traits (e.g. neuroticism), dysfunctional coping strategies, and stressful life events [48–51]. Unlike a prior study of PTSD [52], we did not find that female sex was a risk factor for general anxiety. Our study identified several patient characteristics (body mass index, specific medical comorbidities, and psychiatric history) as independently associated with general anxiety symptoms. Other studies also have identified independent associations between anxiety symptoms and both body mass index [27,31] and psychiatric history [11,24,53] in ALI survivors.

The critical illness and ICU variables we evaluated were based on prior studies of psychological outcomes of ICU patients [18,27–32]. Our study included 10 in-ICU variables which we hypothesized as potentially related to general anxiety symptoms, including severity of illness, the mean daily dose and duration of use of selected medications (benzodiazepines, opioids, and steroids), and hospital and ICU length of stay. Our study did not reveal any significant association between these in-ICU variables and general anxiety symptoms. Conversely, other studies have identified associations between anxiety and benzodiazepine administration, ICU sedation duration, mechanical ventilation duration, dyspnea and ICU length of stay [2,27,54,55].

There may be several reasons our findings differ from prior literature. It is possible that other in-ICU contributors not evaluated in this study could be more closely associated with general anxiety symptoms including dysregulation of the hypothalamic–pituitary–adrenal (HPA) or sympathetic–adrenal–medullary (SAM) axis (i.e., stress response), hypoxia, or perceived level and/or type of social support provided during ICU hospitalization. It is also possible that patient characteristics (e.g. trait anxiety/personality, pre-existing psychopathology, dysfunctional coping strategies) may be more clearly associated with general anxiety symptoms than in-ICU variables. In addition, other ALI studies differed fromours in other important ways. First, the methods for measuring general anxiety symptoms differed. Specifically, other studies used selected questions from a larger general health survey or from a very brief measure (i.e., a visual analog scale) [54,55]. Second, in one study patients were evaluated while still in the ICU [55]. General anxiety symptoms may differ when measured in-hospital versus at 3-months following hospitalization given

variability in general anxiety symptoms over time [56] or treatment interventions provided after hospital discharge.

Clinical investigators have recently begun to assess whether early psychological intervention may prevent development of anxiety symptoms, including post-ICU posttraumatic stress disorder symptoms, among survivors of critical illness. A pre–post study of a non-pharmacological psychological intervention in an Italian trauma ICU suggested lower rates of general anxiety symptoms (8.9% vs 17.4%, $p = 0.087$) among the intervention vs control group at 12-month follow-up [57]. A randomized controlled trial of a music therapy intervention administered during the ICU stay also suggested decreased general anxiety symptoms in the intervention group ($p < 0.001$) [58].Other studies of music interventions in-ICU indicate that these interventions are anxiolytic [59–62]. Supportive interventions provided in-ICU (e.g. supportive nurse- and physician–patient interactions) [63] and relaxation strategies (e.g. guided imagery) also appear anxiolytic during an ICU stay, but post-hospital follow-up data are lacking from these studies [60,64,65]. Because in-ICU psychological distress may be a risk factor for later general anxiety symptoms, early intervention may be important for improving outcomes after critical illness [66]. Each of these studies suggests that a non-drug intervention in the ICU is feasible and may be effective in reducing general anxiety symptoms in the ICU [58–61].

Our study had several strengths. It is one of only a few studies evaluating general anxiety symptoms following ICU admission in survivors of critical illness [2–4]. We used a well-established measure that has been validated for assessment of general anxiety symptoms in medical patients. In addition, we identified cross-sectional associations between a positive screening test for general anxiety symptoms and important outcomes, including physical function and quality of life.

Our study also has potential limitations. First, we did not adjust for potentially confounding variables in the correlations described and given our cross-sectional design; we could not explore longitudinal relationships between general anxiety symptoms and physical function or quality of life. Hence, we are unable to determine the mechanisms underlying the relationships described nor the direction of association between general anxiety symptoms and these other outcomes (e.g. impaired physical function leading to general anxiety symptoms or vice versa). Additional research is needed to understand causal associations between general anxiety symptoms and impaired physical function and HRQOL. Second, we are unable to specify any specific psychiatric diagnosis associated with the general anxiety symptoms because a general screening instrument was used rather than a clinical diagnostic interview (e.g. the Structured Clinical Interview for DSM-IV Axis I Disorders). Given the anticipated added burden to participants when they were in the early phases of physically and emotionally recovering from ALI, we believed that a clinical diagnostic interview would not have been feasible and would have resulted in greater loss to follow-up and incomplete data collection. In addition, a clinical diagnostic interview administered in-person by a trained clinician would have been logistically challenging given that 48% of all 3-month follow-up assessments were done outside of the hospital's research clinic (e.g. in patients' homes or long-term care facilities). Third, we also obtained information on prior psychiatric illness and alcohol/drug use/abuse from medical records review rather than gathering this information directly from the patient or proxy. Therefore, we may have underestimated the true impact of these baseline conditions as potential risk factors for post-ALI general anxiety. Fourth, we did not account for possible treatment of anxiety between ALI onset and 3-month follow-up. Hence, our prevalence data may underestimate the true burden of general anxiety symptoms if patients experienced symptoms that resolved with treatment before 3-month follow-up. Lastly, in exploring patient- and ICU-related variables' associations with general anxiety symptoms, we were limited to those included in this

prospective cohort study. Additional variables (e.g. personality traits, dysfunctional coping strategies, and stressful life events) should be explored in future studies.

In conclusion, many patients surviving ALI experience substantial general anxiety symptoms at 3-month follow-up. General anxiety symptoms are cross-sectionally associated with impaired physical function and lower quality of life. Although we did find an association between specific patient variables (i.e., body mass index, specific medical comorbidities, and psychiatric history) and general anxiety symptoms, we did not find any association between in-ICU variables and general anxiety symptoms. Early identification of patients with general anxiety symptoms and providing appropriate interventions may be important to enhance ICU survivors' physical and emotional function, as well as quality of life.

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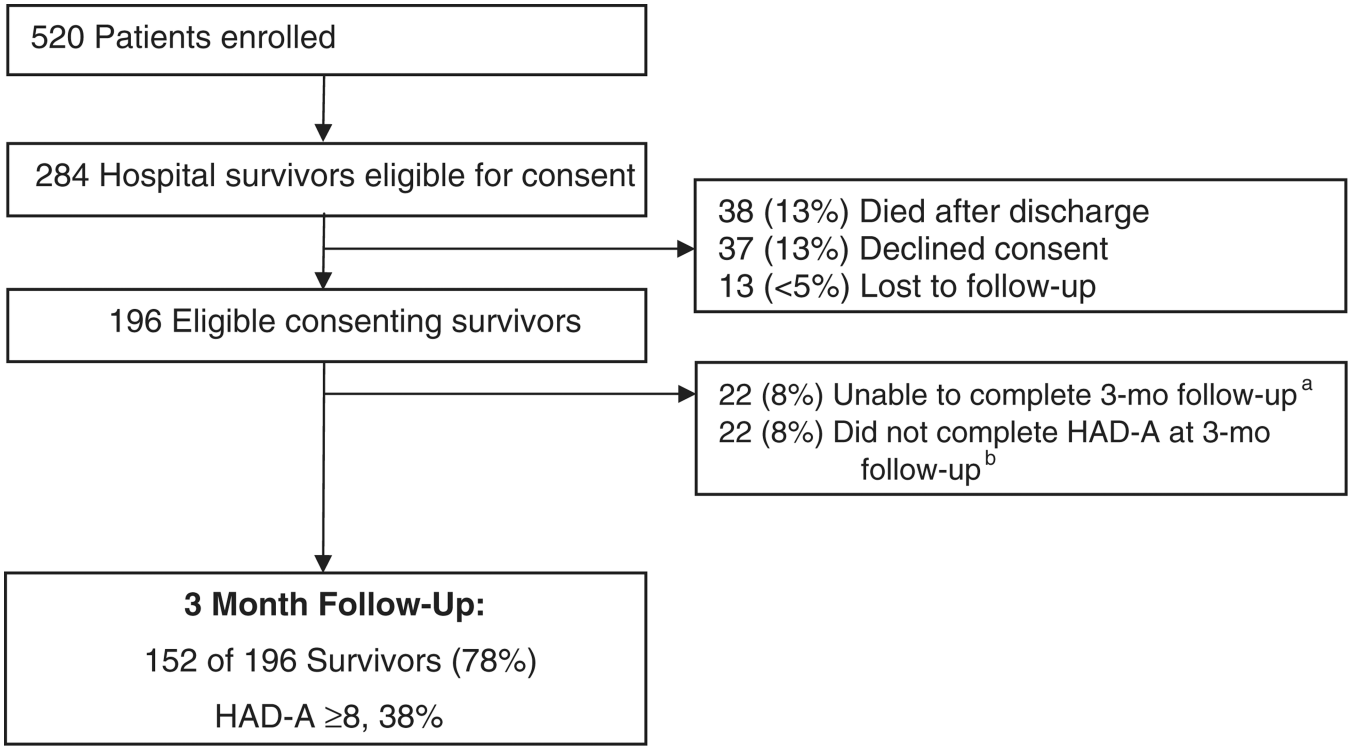

Fig. 1.

Flow diagram of study participants. Abbreviations: HAD-A, Hospital Anxiety and Depression Scale — Anxiety Subscale. [a] Patients were unable to complete a 3-month follow-up visit for the following reasons: unable to locate participant (n = 14), participant declined visit (n = 4), cognitively or physically incapable (n = 2), and other reasons (n = 2). [b] Some patients had a follow-up visit, but did not have complete HAD-A data for the following reasons: physically incapable (n = 9), cognitively incapable (n = 5) and other reasons (n = 8).

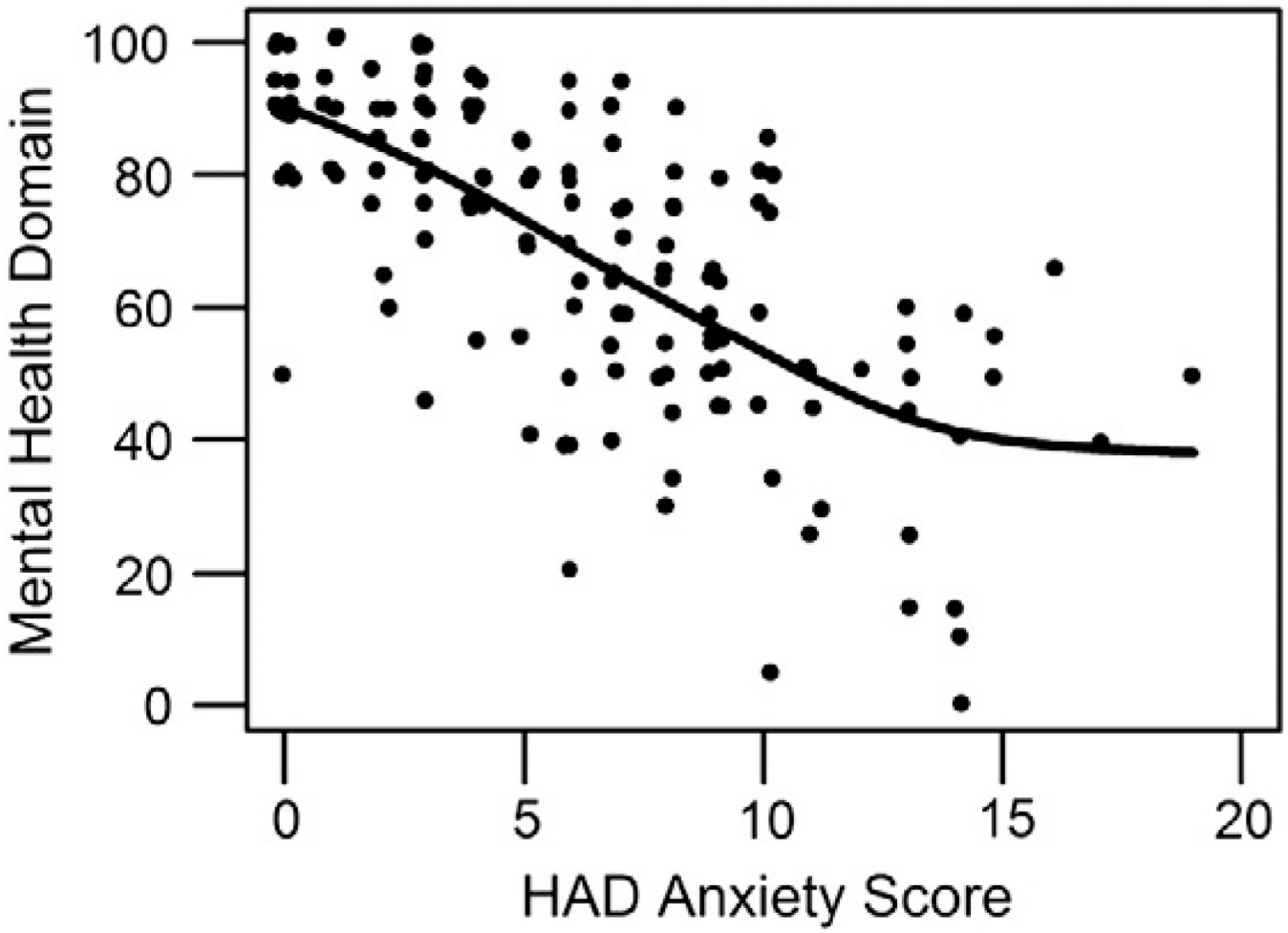

Fig. 2.
SF-36 mental health domain and anxiety symptoms at 3 months after acute lung injury. Mental health domain, SF36 Short-Form Health Survey Mental Health Domain; HAD anxiety score, Hospital Anxiety and Depression Scale – Anxiety Subscale.

Table 1

Patient characteristics, by HAD-A score at 3 months after acute lung injury

Variable	All patients[a] n = 152	HAD-A score[a]	
		Positive (HAD-A ≥ 8) n = 58	Negative (HAD-A < 8) n = 94
Patient variables			
Age	49 (40, 57)	51 (43, 57)	46 (38, 58)
Male	89 (59%)	35 (60%)	54 (57%)
Caucasian	92 (61%)	37 (64%)	55 (59%)
Surgical ICU	20 (13%)	10 (17%)	10 (11%)
BMI, kg/m^2	28 (23, 33)	29 (25, 34)	27 (23, 32)
More than high school education	57 (39%)	17 (32%)	40 (44%)
Employed	60 (39%)	20 (35%)	40 (43%)
Charlson comorbidity index	1 (0, 3)	2 (1,5)	1 (0, 2)
Specific comorbidities:			
Cardiovascular disease	26 (17%)	9 (16%)	17 (18%)
Chronic pulmonary disease	65 (43%)	32 (55%)	33 (35%)
Chronic fatigue	52 (34%)	19 (33%)	33 (36%)
HIV/AIDS	24 (16%)	13 (22%)	11 (12%)
Psychiatric history	38 (25%)	25 (43%)	13 (14%)
Drug/Alcohol abuse	68 (45%)	33 (57%)	35 (37%)
Pain	103 (82%)	42 (93%)	61 (76%)
ICU-related variables			
APACHE II severity of illness	23 (19, 28)	24 (19, 28)	23 (19, 28)
Maximum daily SOFA organ failure score	9 (7, 11)	9 (7, 11)	9 (7, 11)
Proportion of ICU days with sepsis	75 (6, 96)	78 (33, 96)	68 (0, 96)
Length of hospital stay, days	26 (16, 36)	29 (17, 38)	25 (16, 34)
Length of ICU stay, days	15 (9, 23)	16 (10, 25)	14 (9, 21)
Mean daily minimum glucose < 100 mg/dL	59 (39%)	20 (35%)	39 (42%)
Mean daily benzodiazepine dose (midazolam-equivalent), mg	24 (3, 71)	23 (3, 71)	24 (3, 73)
Total days of benzodiazepine in ICU	9 (4, 13)	8 (4, 13)	9 (4, 12)
Mean daily corticosteroid dose (prednisone-equivalent), mg	5 (0, 31)	6 (0, 20)	4 (0, 33)
Total days of steroids in ICU	1 (0, 7)	1 (0, 8)	1 (0, 7)
Mean daily opiate dose (morphine-equivalent), mg	104 (44, 204)	105 (36, 186)	103 (50, 209)
Total days of opiate in ICU	10 (6, 15)	10 (6, 17)	10 (6, 14)

HAD-A, Hospital Anxiety and Depression Scale — Anxiety Subscale; ICU, intensive care unit; BMI, body mass index; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment.

[a]Data presented as number (proportion) or median (inter-quartile range). Proportions may not add to 100% due to rounding.

Table 2

Associations with positive anxiety screening test at 3 months after acute lung injury

Variable	Odds ratio (95% CI) for positive anxiety screening test (HAD-A ≥ 8)			
	Bivariable	*p* value[a]	Multivariable	*p* value[a]
Patient variables				
Age	1.01 (0.99, 1.04)	0.249		
Male	1.13 (0.57, 2.22)	0.725		
Caucasian	1.25 (0.63, 2.49)	0.518		
Surgical ICU	1.75 (0.67, 4.59)	0.246		
BMI, kg/m^2	1.06 (1.01, 1.11)	0.018	1.06 (1.00, 1.13)	0.052
More than high school education	0.59 (0.28, 1.21)	0.139		
Employed	0.71 (0.36, 1.42)	0.324		
Charlson comorbidity index	1.15 (1.00, 1.32)	0.040	1.28 (1.00, 1.64)	0.048
Specific comorbidities				
Cardiovascular disease	0.83 (0.34, 2.05)	0.683	0.26 (0.06, 1.10)	0.061
Chronic pulmonary disease	2.28 (1.15, 4.50)	0.016	3.41 (1.22, 9.57)	0.017
Chronic fatigue	0.89 (0.44, 1.82)	0.752	0.50 (0.18, 1.38)	0.171
HIV/AIDS	2.18 (0.89, 5.36)	0.083	1.43 (0.30, 6.75)	0.643
Psychiatric history	4.72 (2.12, 10.49)	<0.001	3.59 (1.25, 10.30)	0.015
Drug/Alcohol abuse	2.23 (1.13, 4.40)	0.019	1.87 (0.71, 4.92)	0.198
Pain	4.36 (1.18, 16.09)	0.024	4.81 (0.89, 26.06)	0.063
ICU-related variables				
APACHE II severity of illness	1.01 (0.97, 1.05)	0.670		
Maximum daily SOFA organ failure score	1.01 (0.91, 1.12)	0.825		
Maximum daily SOFA > 10	0.98 (0.47, 2.03)	0.950		
% of ICU days with sepsis per 10% increase	1.05 (0.97, 1.14)	0.240		
Length of ICU stay, days	1.01 (0.99, 1.03)	0.333		
Length of hospital stay, days	1.00 (0.99, 1.02)	0.590		
Mean daily minimum glucose, mg/dL	1.00 (0.98, 1.02)	0.768		
Mean daily minimum glucose < 100 mg/dL	0.74 (0.37, 1.48)	0.390		
Mean daily midazolam equivalent dose per 25 mg	1.01 (0.92, 1.10)	0.885		
Total days of benzodiazepine in ICU	1.01 (0.97, 1.05)	0.638		
Total dose of midazolam equivalent per 75 mg	1.00 (0.99, 1.01)	0.827		
Mean daily midazolam equivalent dose > 100 mg	1.06 (0.45, 2.50)	0.892		
Mean daily prednisone equivalent dose per 40 mg	0.83 (0.63, 1.09)	0.177		
Total days of steroids in ICU	0.99 (0.95, 1.03)	0.659		
Total dose of prednisone equivalent per 40 mg	0.99 (0.97, 1.01)	0.232		
Mean daily morphine equivalent dose per 10 mg	0.99 (0.98, 1.01)	0.507		
Mean daily morphine equivalent dose > 100 mg	0.98 (0.50, 1.92)	0.961		

CI, confidence interval; HAD-A, Hospital Anxiety and Depression Scale — Anxiety Subscale; ICU, intensive care unit; BMI, body mass index; Max., maximum.

[a] *p* values calculated using logistic regression. All variables from Table 1 were presented herein and those with a *p* value ≤ 0.10 in simple logistic regression analysis were analyzed in the multivariable logistic regression model.

Table 3

Associations with anxiety symptoms at 3 months after acute lung injury

Variable	Increase in mean HAD-A score (95% CI)			
	Bivariable	*p* value[a]	Multivariable	*p* value[a]
Patient variables				
Age	0.01 (−0.04, 0.06)	0.790		
Male	−0.19 (−1.60, 1.23)	0.792		
Caucasian	1.09 (−0.33, 2.50)	0.127		
Surgical ICU	0.20 (−1.86, 2.27)	0.844		
BMI, kg/m^2	0.12 (0.04, 0.21)	0.006	0.15 (0.06, 0.25)	0.002
More than high school education	−1.08 (−2.54, 0.38)	0.140		
Employed	−1.28 (−2.69, 0.13)	0.072	−0.64 (−2.14, 0.85)	0.392
Charlson comorbidity index	0.33 (0.06, 0.61)	0.015	0.33 (−0.05, 0.70)	0.082
Specific comorbidities:				
Cardiovascular disease	−0.22 (−2.08, 1.63)	0.810	−2.1 (−4.22, 0.02)	0.050
Chronic pulmonary disease	1.71 (0.32, 3.09)	0.015	1.89 (0.31, 3.47)	0.018
Chronic fatigue	−0.21 (−1.70, 1.27)	0.774	−1.23 (−2.81, 0.35)	0.121
HIV/AIDS	1.86 (−0.03, 3.75)	0.050	1.33 (−1.15, 3.81)	0.285
Psychiatric history	3.42 (1.91, 4.93)	<0.001	2.33 (0.71, 3.95)	0.005
Drug/Alcohol abuse	1.54 (0.16, 2.92)	0.027	1.01 (−0.52, 2.53)	0.189
Pain	2.90 (0.93, 4.88)	0.004	1.65 (−0.25, 3.54)	0.085
ICU-related variables				
APACHE II severity of illness	0.04 (−0.04, 0.13)	0.317		
Maximum daily SOFA organ failure score	−0.01 (−0.22, 0.20)	0.915		
Maximum daily SOFA > 10	0.44 (−1.09, 1.97)	0.565		
% of ICU days with sepsis, per 10% increase	0.13 (−0.04, 0.30)	0.137		
Length of ICU stay, days	0.05 (0.00, 0.09)	0.041	0.02 (−0.03, 0.07)	0.470
Length of hospital stay, days	0.02 (−0.01, 0.06)	0.210		
Mean daily minimum glucose, mg/dL	0.01 (−0.03, 0.06)	0.480		
Mean daily minimum glucose <100 mg/dL	−0.73 (−2.15, 0.70)	0.310		
Mean daily midazolam equivalent dose, per 25 mg	0.11 (−0.08, 0.30)	0.235		
Total days of benzodiazepine in ICU	0.05 (−0.02, 0.13)	0.175		
Total dose of midazolam equivalent, per 75 mg	0.01 (−0.01, 0.03)	0.225		
Mean daily midazolam equivalent dose > 100 mg	0.95 (−0.84, 2.74)	0.290		
Mean daily prednisone equivalent dose, per 40 mg	−0.29 (−0.64, 0.05)	0.094	−0.22 (−0.57, 0.12)	0.202
Total days of corticosteroids in ICU	−0.03 (−0.11, 0.05)	0.524		
Total dose of prednisone equivalent, per 40 mg	−0.02 (−0.04, 0.01)	0.122		
Maximum daily prednisone equivalent dose > 70 mg	−0.93 (−2.47, 0.61)	0.230		
Mean daily corticosteroid dose ≥ 40 mg	−1.40 (−3.14, 0.34)	0.109		
Mean daily morphine equivalent dose > 100 mg	−0.15 (−1.55, 1.25)	0.831		

CI, confidence interval; HAD-A, Hospital Anxiety and Depression Scale — Anxiety Subscale; ICU, intensive care unit; BMI, body mass index.

[a] *p* values calculated using linear regression. All variables from Table 1 were presented herein and those with a *p* value ≤ 0.10 in simple linear regression analysis were analyzed in the multivariable linear regression model.