

Depressive Symptoms and Impaired Physical Function after Acute Lung Injury

A 2-Year Longitudinal Study

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Rationale: Survivors of acute lung injury (ALI) frequently have substantial depressive symptoms and physical impairment, but the longitudinal epidemiology of these conditions remains unclear.

Objectives: To evaluate the 2-year incidence and duration of depressive symptoms and physical impairment after ALI, as well as risk factors for these conditions.

Methods: This prospective, longitudinal cohort study recruited patients from 13 intensive care units (ICUs) in four hospitals, with follow-up 3, 6, 12, and 24 months after ALI. The outcomes were Hospital Anxiety and Depression Scale depression score greater than or equal to 8 ("depressive symptoms") in patients without a history of depression before ALI, and two or more dependencies in instrumental activities of daily living ("impaired physical function") in patients without baseline impairment.

Measurements and Main Results: During 2-year follow-up of 186 ALI survivors, the cumulative incidences of depressive symptoms and impaired physical function were 40 and 66%, respectively, with greatest incidence by 3-month follow-up; modal durations were greater than 21 months for each outcome. Risk factors for incident depressive symptoms were education 12 years or less, baseline disability or unemployment, higher baseline medical comorbidity, and lower blood glucose in the ICU. Risk factors for incident impaired physical function were longer ICU stay and prior depressive symptoms.

Conclusions: Incident depressive symptoms and impaired physical function are common and long-lasting during the first 2 years after ALI. Interventions targeting potentially modifiable risk factors (e.g., substantial depressive symptoms in early recovery) should be evaluated to improve ALI survivors' long-term outcomes.

Keywords: depression; recovery of function; critical illness; critical care; acute lung injury

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AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Survivors of acute lung injury (ALI) frequently have substantial depressive symptoms and impaired physical function after hospital discharge, but the longitudinal epidemiology and risk factors for these conditions have not been fully evaluated.

What This Study Adds to the Field

This prospective, longitudinal cohort study shows that, in the first 2 years after ALI, new-onset depressive symptoms and new-onset physical impairment are common and long lasting (cumulative incidences were 40 and 66%, respectively, and modal durations were greater than 21 months for each outcome). Depressive symptoms were a significant and potentially modifiable risk factor for later-onset physical impairment.

Survivors of acute lung injury/acute respiratory distress syndrome (ALI) and other critical illnesses frequently have substantial depressive symptoms and impaired physical functioning, with associated decrements in quality of life (1–9). At present, there are gaps in knowledge regarding the incidence and duration of these conditions in ALI survivors, as well as their risk factors.

Our objective was to longitudinally examine the incidence and duration of depressive symptoms and impaired physical functioning in the first 2 years after ALI. We also sought to determine risk factors for each of these conditions, to help inform future prevention and treatment efforts. Some of the results of this study have been reported previously in the form of an abstract (10).

METHODS

Study Population

Mechanically ventilated patients with ALI (11) were enrolled consecutively in a prospective cohort study involving 13 intensive care units (ICUs) at four hospitals in Baltimore, Maryland, between October 2004 and October 2007 (12). To avoid inclusion of patients with primary neurologic disease or head trauma, neurologic specialty ICUs at the participating hospitals were excluded. Key exclusion criteria were (1) preexisting illness with a life expectancy of less than 6 months, (2) preexisting cognitive impairment or communication/language barriers, (3) no fixed address, (4) transfer to a study site ICU with preexisting ALI of greater than 24 hours' duration, (5) more than 5 days of mechanical

ventilation before ALI, and (6) a physician order for no escalation of ICU care (e.g., no vasopressors or hemodialysis) at the time of study eligibility.

Informed consent was obtained after patients regained capacity, typically around the time of hospital discharge (13). Follow-up occurred at 3, 6, 12, and 24 months after the onset of ALI. The institutional review boards of Johns Hopkins University and all participating study sites approved this research.

Definition of Depressive Symptoms Incidence, Remission, and Recurrence

To ascertain patients' baseline mood status, we reviewed the medical records related to the ALI hospitalization for evidence of any preexisting "depression" diagnosis. At each follow-up time point, depressive symptoms were measured using the depression subscale of the Hospital Anxiety and Depression (HAD) Scale (14, 15). "Incident depressive symptoms" were defined as having an HAD depression score greater than or equal to 8 at any follow-up, in the absence of baseline depression. The HAD depression subscale was designed to evaluate depressive states in patients with general medical illnesses, as it primarily measures anhedonia rather than neurovegetative symptoms (e.g., diminished energy) that could be symptomatic of general medical conditions rather than depressive states. The HAD depression subscale has been validated as a screening tool for depressive states in many medical and general population settings, with an optimal threshold of 8 or more in most studies, corresponding to a sensitivity and specificity of approximately 80% across studies (15); the criterion standards for these studies were depression-related psychiatric diagnoses—which varied by study but included major depressive disorder and/or dysthymia or adjustment disorder—measured using structured or semistructured (clinical) diagnostic interviews (15).

We were also interested in the course of incident depressive symptoms after ALI. We defined remission as having an HAD depression score less than 8 at any follow-up time point after incident depressive symptoms, along with a statistically reliable decrease in score using the Reliable Change Index (RCI) (16). To calculate the RCI, we used standard deviation (SD) and test–retest reliability estimates from previous studies (17, 18). To have a statistically significant change, patients had to have a difference in scores of greater than or equal to 4; this threshold is substantially larger than the minimal clinically important difference (1.5 points) established for this measure (19). We defined recurrence as having an HAD depression score greater than or equal to 8 at any follow-up after remission, along with an increase in scores of greater than or equal to 4.

Definition of Impaired Physical Function Incidence, Remission, and Recurrence

We chose dependencies in instrumental activities of daily living (IADLs) (20) as our measure of physical impairment, as IADL dependencies are reflective of more subtle dysfunction than ADL dependencies (20), and the former are less prone to ceiling effects in predicting the ability to live independently (21). IADL dependencies (i.e., difficulty with using the telephone, shopping, preparing meals, doing housework, laundering clothes, transportation, taking medications, and managing money) are strongly associated with other physical performance measures, such as gait velocity, balance function, grip strength, and chair stand time (22). In the current study, numbers of IADL dependencies were strongly related to 36-item Short-Form health survey (SF-36v2) (23) Physical Component scores at each follow-up, with Spearman rank correlations ranging between -0.64 and -0.71 . We chose a threshold of two or more IADL dependencies, as used elsewhere (24, 25), to help ensure that the measured dysfunction would be meaningful to patients and caregivers. Patients were considered to have "incident impaired physical function" if they did not have baseline (pre-ALI) impairment (assessed retrospectively around hospital discharge, using the IADL instrument) but had two or more dependencies at any follow-up. Patients self-reported their IADL dependencies in 86% of the baseline assessments and in 96% of the follow-up assessments; their closest available proxies reported on the remainder.

We were also interested in the course of incident impaired physical function after ALI. We defined remission as having fewer than two IADL dependencies at any follow-up time point after incident impaired physical function, along with a statistically reliable decrease in number of dependencies. To calculate the RCI, we used SD and test–retest

reliability estimates from previous studies (26, 27). To have a statistically significant change, patients had to have a difference in number of dependencies of two or more. We defined recurrence as having two or more IADL dependencies at any follow-up after remission, along with an increase in number of dependencies of two or more.

Risk Factors for Incident Depressive Symptoms and Incident Impaired Physical Function

We conducted separate analyses of risk factors for new-onset depressive symptoms and new-onset physical impairment after ALI. Potential risk factors were selected in part based on findings from previous studies of ALI survivors (28, 29); some predictors of depressive symptoms at 3- and 6-month follow-ups were reported previously (30, 31).

Baseline characteristics included age, sex, race, education, employment status (disabled or unemployed vs. employed), body mass index, and the Charlson Comorbidity Index (32). Critical illness/ICU variables included organ failure (maximum Sequential Organ Failure Assessment [SOFA] [33] score), low blood glucose (operationalized using the mean daily minimum value), medication doses (mean daily benzodiazepine [midazolam-equivalent] and corticosteroid [prednisone-equivalent] doses), surgical (vs. medical) ICU admission, length of stay, delirium (proportion of ICU study days with a positive Confusion Assessment Method for the ICU [34] assessment), and deep sedation (proportion of ICU study days with Richmond Agitation-Sedation Scale [35] score of -4 or -5). We also examined prior depressive symptoms as a risk factor for new-onset physical impairment and prior impaired physical function as a risk factor for new-onset depressive symptoms.

Statistical Methods

Cumulative incidence functions for depressive symptoms and impaired physical function were generated separately using the Kaplan-Meier estimator. These discrete-time survival data were analyzed using logistic regression models, which allowed for a flexible baseline hazard function (with indicator variables for the 6-, 12-, and 24-mo follow-ups) to examine associations with potential risk factors (36). Multivariable models included all potential risk factors that had a bivariate association ($P \leq 0.10$) with the outcome variable.

Our primary analyses involved assumptions about depressive symptoms or impaired physical function status when data were missing. When HAD depression scores were missing, but SF-36v2 (23) Mental Health domain scores were available, depressive symptoms were deemed present if the Mental Health domain score was less than or equal to 69. This threshold was derived from a receiver operating characteristic analysis with the HAD depression score threshold (≥ 8) as the criterion variable, using data from the current study (area under the curve = 0.84). Using this procedure, we replaced 4, 3, 4, and 1 missing HAD depression scores at 3-, 6-, 12-, and 24-mo follow-ups, respectively. Otherwise, when patients had missing values for particular follow-ups, we assumed that their prior depressive symptoms or physical function status remained constant. Thus, our incidence estimates may be conservative, because we assume that subjects remain free of depressive symptoms or impaired physical function for longer than may be the case. To evaluate the potential for bias with this missing data strategy, we performed complete case analyses (i.e., only analyzing data from patients with complete data at all follow-ups) as sensitivity analyses. Results of the complete case analyses were similar to those of the primary analyses; hence, we only present results of the primary analyses. Statistical significance was defined as $P < 0.05$ (two-sided). All analyses were performed using R statistical software (37).

RESULTS

Of 520 eligible patients with ALI, 274 (53%) survived their acute hospitalization and were eligible for consent. Additional patients died, declined, or could not be contacted for consent, leaving 196 consenting survivors at 3 months after ALI (Figure 1). Of these 196 participants, 186 (95%) had at least one follow-up visit with complete HAD and IADL data. Thirty-nine of these patients (21%) had baseline (pre-ALI) depression, and 74 (40%) had baseline impaired physical function. The point prevalences of

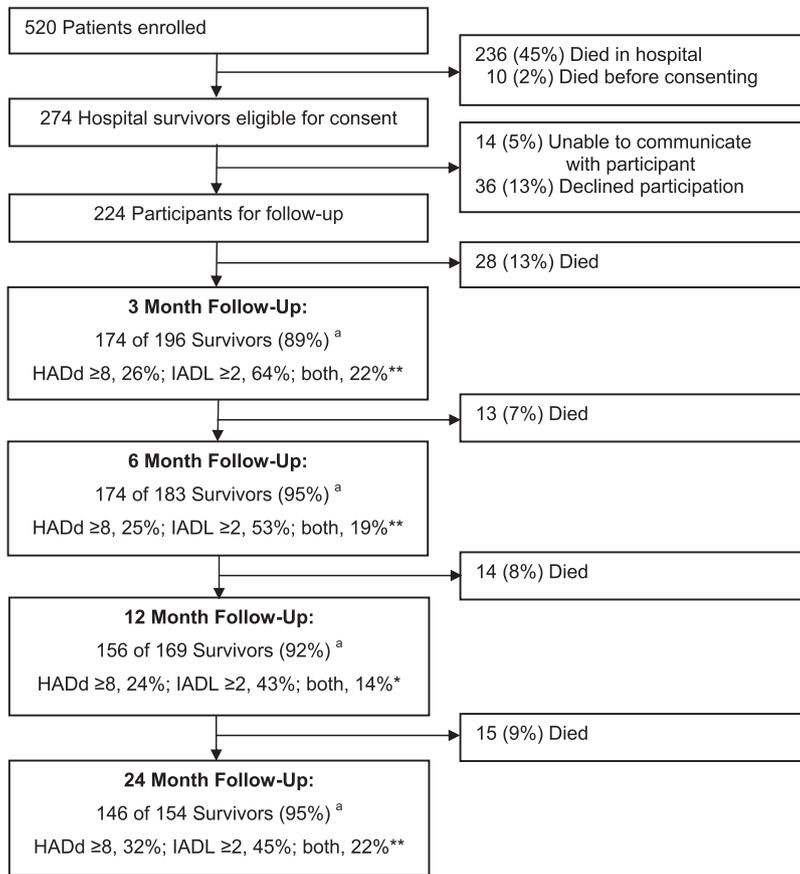


Figure 1. Flow diagram of study participants. ^aSome patients had a follow-up visit but did not have complete Hospital Anxiety and Depression Scale depression score (HADd) or number of dependencies in instrumental activities of daily living (IADL) data for the following reasons, respectively (cognitively incapable/physically incapable/other): At 3 months, 22 did not have complete HADd data (9/5/8), and 13 did not have complete IADL data (4/4/5). At 6 months, 13 did not have complete HADd data (5/2/6), and 5 did not have complete IADL data (0/2/3). At 12 months, 14 did not have complete HADd data (5/4/5), and 4 did not have complete IADL data (1/3/0). At 24 months, 10 did not have complete HADd data (0/6/4), and 4 did not have complete IADL data (0/2/2). The proportions with HADd ≥ 8 or IADL ≥ 2 reflect point prevalences, not incidences. Cross-sectionally, depressive symptoms and impaired physical function were related, **P* < 0.05 or ***P* < 0.001.

depressive symptoms and impaired physical function at the four follow-up time points ranged from 24 to 32% and 43 to 64%, respectively (Figure 1). At each follow-up, depressive symptoms and impaired physical function were significantly related to each other cross-sectionally (Figure 1).

Onset and Duration of Incident Depressive Symptoms and Incident Impaired Physical Function

During 2-year follow-up after ALI, the cumulative incidence of depressive symptoms in the 147 patients at risk was 40%, and the cumulative incidence of impaired physical function in the 112 patients at risk was 66% (Figure 2). Incidence was highest by the 3-month follow-up and declined thereafter.

The modal durations of incident depressive symptoms and incident impaired physical function were each more than 21 months (the maximum duration possible), with remissions during the follow-up period in 39 and 54%, respectively, of those eligible for remission (i.e., those with incidence before 24-month follow-up) and recurrences in 20 and 14%, respectively, of those with remissions. Of those with incident depressive symptoms, 69% had depressive symptoms at 24-month follow-up; of those with incident impaired physical function, 58% were impaired at 24-month follow-up.

Figure 3 illustrates individual and mean symptom levels for patients whose incident conditions remitted or did not remit during 2-year follow-up after ALI. In patients whose incident depressive symptoms remitted, the mean HAD depression score remained approximately 5 throughout the follow-up period; this score corresponds to the 75th percentile in a large nonclinical sample of adults (17). In patients whose depressive symptoms did not remit, the mean HAD depression score remained greater than or equal to 10; this score corresponds to the 96th percentile

in a large nonclinical sample of adults (17). In patients whose incident impaired physical function remitted, the mean number of IADL dependencies remained approximately 1 throughout the follow-up period. In patients whose impaired physical function did not remit, the mean number of IADL dependencies remained greater than or equal to four.

Risk Factors for Incident Depressive Symptoms and Incident Impaired Physical Function

Table 1 shows the distribution of potential risk factors in the entire sample (n = 186) and in those without baseline depression (n = 147, 79%) or baseline impaired physical function (n = 112, 60%) who were at risk for these incident conditions.

Potential risk factors that had a bivariate association (*P* ≤ 0.05) with incident depressive symptoms after ALI were education 12 or fewer years, baseline disability or unemployment, higher baseline medical comorbidity, and lower blood glucose in the ICU (Table 2). In a multivariable model, only education 12 or fewer years was significantly associated with incident depressive symptoms (odds ratio [OR] = 3.1; 95% confidence interval [CI], 1.5–6.6).

Potential risk factors that had a bivariate association (*P* ≤ 0.05) with incident impaired physical function were longer ICU length of stay and depressive symptoms at last follow-up (Table 2). In a multivariable model (Table 2), only depressive symptoms at last follow-up were significantly associated with incident impaired physical function (OR = 2.7; 95% CI, 1.2–6.0).

In addition to reflecting impaired physical function, IADL dependencies could reflect impaired cognitive function. For example, taking medications and managing money are sometimes referred to as “nonphysical” IADLs (22). To determine whether depression-related cognitive dysfunction could underlie the relationship

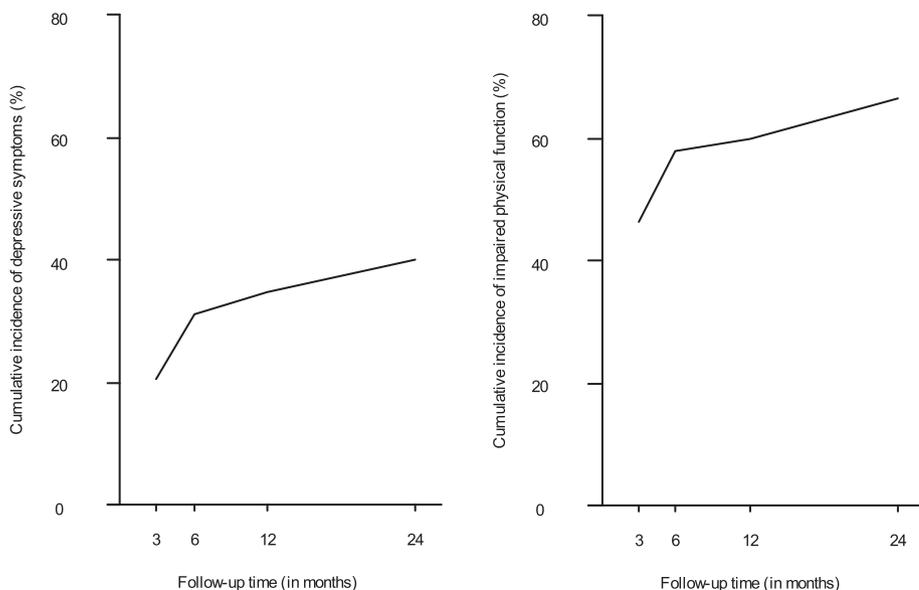


Figure 2. Cumulative incidence of depressive symptoms or impaired physical function in the first 2 years after acute lung injury. During 2-year follow-up after acute lung injury, the cumulative incidence of depressive symptoms was 40%, and the cumulative incidence of impaired physical function was 66%. Incidence was highest by the 3-month follow-up and declined thereafter.

Num. at risk	147	117	98	85	Num. at risk	112	60	45	43
Cases	30	16	5	7	Cases	52	13	2	7
Incidence (%)	20	14	5	8	Incidence (%)	46	22	4	16

between depressive symptoms at last follow-up and incident impaired physical function, we repeated the prior analyses to evaluate if depressive symptoms at last follow-up were only associated with individual nonphysical incident IADL dependencies. The

number of patients with incident IADL dependencies/number at risk were: using the telephone, 34/175; shopping, 80/133; preparing food, 57/132; housekeeping, 85/121; doing laundry, 67/136; traveling, 73/143; taking medications, 48/159; and managing

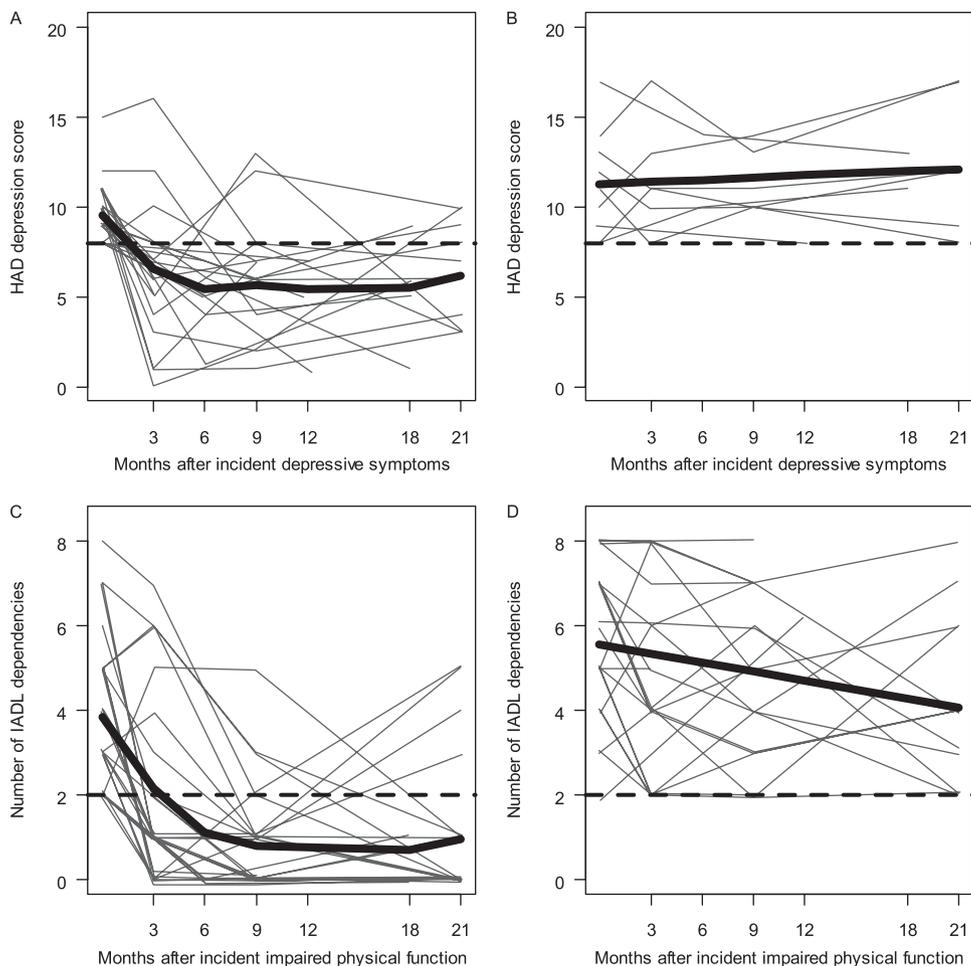


Figure 3. Recovery from incident depressive symptoms or impaired physical function in the first 2 years after acute lung injury. *Thin lines and thick lines* indicate individual and mean trajectories, respectively, for patients whose conditions remitted (A and C) and did not remit (B and D) during 2-year follow-up after acute lung injury. *Horizontal dashed lines* indicate thresholds for depressive symptoms (A and B) and impaired physical function (C and D). HAD = Hospital Anxiety and Depression Scale; IADL = instrumental activities of daily living.

TABLE 1. POTENTIAL RISK FACTORS FOR INCIDENT DEPRESSIVE SYMPTOMS OR INCIDENT IMPAIRED PHYSICAL FUNCTION IN ACUTE LUNG INJURY SURVIVORS

Potential Risk Factors	All (n = 186)	Incident Depressive Symptoms		Incident Impaired Physical Function	
		Case (n = 58)	Noncase (n = 89)	Case (n = 74)	Noncase (n = 38)
Baseline factors					
Age, yr, mean (SD)	49 (14)	50 (13)	48 (16)	49 (13)	46 (12)
Male	105 (56%)	30 (52%)	56 (63%)	41 (55%)	20 (53%)
Nonwhite	75 (40%)	32 (55%)	41 (46%)	30 (40%)	21 (55%)*
Education ≤ 12 yr [†]	112 (63%)	43 (80%)	41 (48%) [‡]	42 (59%)	21 (55%)
Disability or unemployment	108 (58%)	40 (69%)	39 (44%) [§]	39 (53%)	13 (34%)
BMI > 30 [†]	58 (32%)	17 (29%)	26 (30%)	19 (26%)	14 (38%)
Charlson Comorbidity Index, mean (SD)	2.2 (2.7)	2.9 (3.0)	1.8 (2.4) [§]	2.0 (2.5)	1.6 (2.3)
Critical illness/ICU factors					
Maximum daily SOFA score > 10	56 (30%)	20 (34%)	24 (27%)	26 (35%)	7 (18%)*
Mean daily minimum glucose < 100 mg/dl	72 (39%)	31 (53%)	31 (35%)	30 (40%)	10 (26%)*
Mean daily midazolam equivalent dose > 75 mg	39 (21%)	13 (22%)	16 (18%)	11 (15%)	11 (29%)*
Mean daily prednisone equivalent dose ≥ 50 mg [†]	53 (29%)	15 (26%)	27 (31%)	23 (31%)	8 (21%)
Surgical ICU admission	26 (14%)	11 (19%)	10 (11%)	12 (16%)	2 (5%)*
Length of stay, d, mean (SD)	19 (17)	17 (12)	19.6 (18.6)	21.2 (19.6)	15.8 (11.5)
Delirium, proportion of d, mean (SD)	64% (33%)	61% (35%)	60% (33%)	60% (34%)	68% (34%)
Deep sedation, proportion of d, mean (SD)	32% (25%)	31% (27%)	30% (24%)	32% (24%)	36% (25%)
Longitudinal					
Impaired physical function at last follow-up [†]		30 (52%)	30 (35%)*		
Depressive symptoms at last follow-up				19 (26%)	4 (10%)

Definition of abbreviations: BMI = body mass index; ICU = intensive care unit; SD = standard deviation; SOFA = Sequential Organ Failure Assessment.

Those at risk for incident depression or incident impaired physical function were those without baseline depression (n = 147) or baseline impaired physical function (n = 112), respectively, before acute lung injury.

* 0.05 < P ≤ 0.1, derived from discrete time survival logistic regression models.

[†] n = 9 with missing education data; n = 2 with missing BMI data; n = 1 with missing prednisone equivalent data; n = 3 with missing baseline physical function data.

[‡] P < 0.001, derived from discrete time survival logistic regression models.

[§] P < 0.01, derived from discrete time survival logistic regression models.

^{||} P < 0.05, derived from discrete time survival logistic regression models.

money, 62/149. Adjusted ORs and 95% CIs relating depressive symptoms at last follow-up to incident IADL dependencies were: using the telephone, 1.7 (0.7–4.1); shopping, 2.1 (1.0–4.2); preparing food, 3.2 (1.5–6.6); housekeeping, 2.0 (1.0–4.0); doing laundry, 2.0 (1.0–3.9); traveling, 1.8 (0.9–3.8); taking medications, 2.2 (1.0–4.7); and managing money, 1.5 (0.8–3.1). Thus, the results did not support the hypothesis that depressive symptoms only precede nonphysical IADL dependencies (taking medications and managing money), because preceding depressive symptoms were significantly associated with incident dependencies in shopping, preparing food, housekeeping, and doing laundry, as well as taking medications; the weakest association was with managing money.

DISCUSSION

This multisite, prospective longitudinal study of 186 ALI survivors demonstrates that incident depressive symptoms and incident impaired physical function are common and long-lasting during the first 2 years after ALI. Our analyses indicate that depressive symptoms are not only relatively persistent in ALI survivors but also an independent risk factor for subsequent impairment in physical function. Hence, early identification and treatment of depressive states should be evaluated as a potential intervention to minimize the suffering and impairment that affect so many of these patients.

The cumulative 2-year incidences of depressive symptoms and impaired physical function after ALI were high at 40 and 66%, respectively. Incidence was highest by 3-month follow-up, as might be expected after a severe critical illness. However, the presence of additional incident cases throughout the 2-year follow-up period suggests that events after the ALI hospitalization (e.g., further illness and hospitalization, and financial and other stressors [38, 39]) contribute to ongoing morbidity for ALI survivors. Importantly, most survivors with post-ALI incidence of depressive symptoms

or impaired physical functioning were affected at the last follow-up. The most common pattern was to have incidence by 3-month follow-up and persistence through the last follow-up. Given that depressive symptoms and impaired physical function are common and persistent/recurrent in ALI survivors, comprehensive and ongoing evaluation, treatment, and rehabilitation of these patients are necessary (40).

The point prevalences of substantial depressive symptoms in the current report (24–32% during the first 2 yr post-ALI) are comparable to those in previous studies of ALI survivors (range 17–43%, median 28% during the first 2 yr post-ALI) (1). These point prevalences are substantially higher than the 8% point prevalence of an HAD depression score greater than or equal to 8 in a large nonclinical sample of adults (17).

We identified several risk factors for incident depressive symptoms in ALI survivors: lower education, baseline disability or unemployment, baseline comorbid medical conditions, and lower blood glucose in the ICU. We previously reported that lower in-ICU blood glucose appeared particularly relevant to depressive symptoms early in the follow-up period (i.e., at 3-mo follow-up) (30, 31). Having 12 or fewer years of education was a particularly strong and independent risk factor for incident depressive symptoms in this study. Lower education and other indicators of low socioeconomic status are well-established risk factors for depressive illness (41).

We also identified two risk factors for incident physical impairment in ALI survivors: longer ICU length of stay and prior depressive symptoms. Having prior depressive symptoms was a particularly strong and independent risk factor for incident physical impairment in this study. Importantly, although a history of depression is often noted in patients admitted to an ICU, antidepressants are often stopped in this setting; starting or restarting antidepressants and/or psychotherapy early during patient recovery might improve long-term physical and psychiatric outcomes in ALI survivors (42).

TABLE 2. ESTIMATED ODDS RATIOS FOR INCIDENT DEPRESSIVE SYMPTOMS OR INCIDENT IMPAIRED PHYSICAL FUNCTION GIVEN POTENTIAL RISK FACTORS

Potential Risk Factors	Incident Depressive Symptoms				Incident Impaired Physical Function			
	Bivariate		Multivariable		Bivariate		Multivariable	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
Baseline factors								
Age (per 10 yr)	1.13 (0.93–1.36)	0.21			1.09 (0.86–1.38)	0.45		
Male	0.70 (0.39–1.24)	0.21			1.11 (0.61–2.00)	0.73		
Nonwhite	1.43 (0.81–2.54)	0.21			0.56 (0.31–1.02)	0.05	0.65 (0.34–1.23)	0.18
Education ≤ 12 yr	3.52 (1.73–7.18)	<0.001	3.14 (1.49–6.58)	0.002	1.11 (0.60–2.04)	0.74		
Disability or unemployment	2.47 (1.34–4.56)	0.003	1.78 (0.86–3.69)	0.11	1.62 (0.90–2.94)	0.10		
BMI > 30	1.05 (0.56–1.96)	0.89			0.69 (0.36–1.34)	0.26		
Charlson Comorbidity Index (per point)	1.13 (1.03–1.24)	0.008	1.10 (0.98–1.23)	0.10	1.07 (0.95–1.22)	0.25		
Critical illness/ICU factors								
Maximum daily SOFA score > 10	1.28 (0.70–2.36)	0.41			1.82 (0.95–3.50)	0.06	1.12 (0.53–2.37)	0.76
Mean daily minimum glucose < 100 mg/dl	1.91 (1.07–3.40)	0.02	1.42 (0.74–2.70)	0.28	1.71 (0.92–3.19)	0.08	1.59 (0.81–3.12)	0.17
Mean daily midazolam equivalent dose > 75 mg	1.29 (0.64–2.58)	0.47			0.51 (0.23–1.10)	0.08	0.52 (0.23–1.19)	0.11
Mean daily prednisone equivalent dose ≥ 50 mg	0.81 (0.42–1.55)	0.51			1.48 (0.76–2.86)	0.24		
Surgical ICU admission	1.53 (0.72–3.23)	0.26			2.51 (0.96–6.51)	0.05	1.63 (0.59–4.54)	0.34
Length of stay (per d)	0.99 (0.98–1.01)	0.57			1.03 (1.00–1.05)	0.03	1.02 (0.99–1.05)	0.13
Delirium, proportion of days (per 10%)	1.00 (0.92–1.10)	0.91			0.95 (0.87–1.04)	0.24		
Deep sedation, proportion of days (per 10%)	1.02 (0.91–1.14)	0.76			0.96 (0.85–1.09)	0.54		
Longitudinal								
Impaired physical function at last follow-up	1.68 (0.94–3.00)	0.08	1.29 (0.67–2.47)	0.44				
Depressive symptoms at last follow-up					2.40 (1.11–5.17)	0.02	2.66 (1.17–6.01)	0.02

Definition of abbreviations: BMI = body mass index; CI = confidence interval; ICU = intensive care unit; OR = odds ratio; SOFA = Sequential Organ Failure Assessment. ORs derived from discrete time survival logistic regression models.

Several possible mechanisms may explain why depressive symptoms are a risk factor for impaired physical function in ALI survivors. First, depressive symptoms may decrease motivation for, and reward from, physical activities necessary for recovery or maintenance of functioning (43). This is consistent with our clinical experience that depressed patients are more difficult to engage in physical therapy, which is often crucial for recovery of function (28). Second, depressive symptoms can amplify symptoms of general medical illnesses (44, 45), and an increased physical symptom load could negatively affect functioning. Third, depressive symptoms can affect adherence to medication regimens (46), which could worsen the course of general medical illnesses. Fourth, depressive symptoms could affect functioning through direct neurobiologic pathways, including neuroendocrine and inflammatory mechanisms (47). Finally, it is possible that depressive symptoms negatively influence patients' perceptions of what they are able to do; nevertheless, like others (48), we do not doubt that depression-associated impairments in functioning are real, based on our clinical experience with these patients.

Limitations

There are several potential limitations of this study. First, we measured depressive symptoms using a well-validated self-report questionnaire (15), rather than psychiatric diagnoses using expert clinicians with specialized training to perform semi-structured interviews and incorporate informant and medical record data (49). We believe that, given the added burden for participants, the latter method would have pushed the limits of feasibility and resulted in substantially higher losses to follow-up and incomplete data, especially during the first 12 months when patients were still in early recovery and required three follow-up assessments. Obtaining psychiatric diagnoses also would have been logistically difficult, given the need for expert

clinicians to be physically present in patients' homes or long-term care facilities (58% of participants required at least one such visit during 2-yr follow-up).

Second, we used medical records to identify baseline (pre-ALI) depression, likely a relatively specific, but insensitive, method that could lead to an overestimate of the incidence of post-ALI depressive symptoms due to nondetection of baseline depression. On the other hand, chart review may have detected depression that had remitted well before ALI, thus potentially underestimating the incidence of post-ALI depressive symptoms. Such potential biases are generally unavoidable, given the infeasibility of directly assessing patients' mood status immediately before ALI onset. To examine the validity of our method, we compared retrospectively ascertained pre-ALI SF-36v2 Mental Health domain scores in patients with and without baseline depression identified via their medical records. Pre-ALI Mental Health domain scores were substantially lower in patients with baseline depression (mean = 52, SD = 23) than in patients without baseline depression (mean = 72, SD = 23) ($P < 0.001$).

Third, we did not account for possible effects of treatment of depression or impaired physical function. Thus, we may have missed instances of depressive symptoms or impaired physical function that occurred and resolved before the first follow-up or in between follow-ups.

Fourth, although we statistically controlled for several potential confounders in our analyses of risk factors, residual confounding could have influenced the associations detected in this study. However, because it is not possible to randomize patients to depressive symptoms, physical impairment, or indeed many of the potential risk factors we examined, observational studies provide essential information regarding likely relationships. Given the findings of the current study, it is important to evaluate interventions for early identification and treatment

of depressive states as part of a comprehensive post-ICU rehabilitation program (40), to determine if such an intervention would improve patients' mood states and physical functioning, as demonstrated previously in populations of elderly depressed persons (48, 50).

Conclusions

Incident depressive symptoms and incident impaired physical function are common and long-lasting during the first 2 years after ALI. Depressive symptoms are an independent risk factor for impaired physical function in this population. Hence, early identification and treatment of depressive states should be evaluated as a potential intervention to improve ALI survivors' long-term outcomes.

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