Neurologic Critical Care

Depressive Symptoms After Critical Illness: A Systematic Review and Meta-Analysis

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Objectives: To synthesize data on prevalence, natural history, risk factors, and post-ICU interventions for depressive symptoms in ICU survivors.

Data Sources: PubMed, EMBASE, Cumulative Index of Nursing and Allied Health Literature, PsycINFO, and Cochrane Controlled Trials Registry (1970–2015).

Study Selection: Studies measuring depression after hospital discharge using a validated instrument in more than 20 adults from non-specialty ICUs.

Data Extraction: Duplicate independent review and data abstraction.

Data Synthesis: The search identified 27,334 titles, with 42 eligible articles on 38 unique studies ($n = 4,113$). The Hospital Anxiety and Depression Scale-Depression subscale was used most commonly (58%). The pooled Hospital Anxiety and Depression Scale-Depression subscale prevalence (95% CI) of depressive symptoms at a threshold score greater than or equal to 8 was 29% (22–36%) at 2–3 months (12 studies; $n = 1,078$), 34% (24–43%) at 6 months (seven studies; $n = 760$), and 29% (23–34%) at 12–14 months (six studies; $n = 1,041$). The prevalence of suprathreshold depressive symptoms (compatible with Hospital Anxiety and Depression Scale-Depression subscale, ≥ 8) across all studies, using all instruments, was between 29% and 30% at all three time points. The pooled change in prevalence (95% CI) from 2–3 to 6 months (four studies; $n = 387$) was 5% (−1% to +12%), and from 6 to 12 months (three studies; $n = 412$) was 1% (−6% to +7%). Risk factors included pre-ICU psychologic morbidity and presence of in-ICU psychologic distress symptoms. We did not identify any post-ICU intervention with strong evidence of improvement in depressive symptoms.

Conclusions: Clinically important depressive symptoms occurred in approximately one-third of ICU survivors and were persistent through 12-month follow-up. Greater research into treatment is needed for this common and persistent post-ICU morbidity. (*Crit Care Med* 2016; 44:1744–1753)

Key Words: critical care; critical illness; depression; meta-analysis; review

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Increasing numbers of patients are surviving critical illness (1, 2). These survivors often experience long-term physical, cognitive, and mental health impairments (3–7). Within the mental health sequelae of critical illness, depressive symptoms are an important issue. Depressive symptoms can negatively impact survivors' quality of life (6, 8). Furthermore, such symptoms can prevent survivors from returning to work, participating in social roles, and coping with physical limitations during recovery (6).

Recognition of depressive symptoms in ICU survivors is growing, with the number of studies published on this topic

nearly doubling in the last 5 years. Therefore, our objectives were to synthesize existing data to: 1) estimate the prevalence of depressive symptoms after critical illness; 2) describe longitudinal changes in depressive symptoms after critical illness; 3) identify risk factors associated with depressive symptoms; and 4) identify post-ICU interventions that prevent or treat depressive symptoms.

MATERIALS AND METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (9) to report our systematic review and meta-analysis. No publicly accessible protocol was registered for this systematic review.

Search Strategy

We searched five electronic databases (PubMed, EMBASE, Cumulative Index of Nursing and Allied Health Literature, PsycINFO, and the Cochrane Controlled Trials Registry) from 1970 through March 13, 2015, to identify eligible studies. Because articles may have included evaluation of depressive symptoms in combination with other outcomes, our search strategy focused on articles with any outcome assessments after hospital discharge in survivors of critical illness, using a combination of keywords and controlled vocabulary for the concepts of "intensive care" combined with "outcome assessment" and "follow-up" (**Table S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B896). The search strategy was not limited by language of publication. We also performed a manual search of reference lists from relevant review articles and all articles eligible for this systematic review.

Study Selection

We used the following inclusion criteria: 1) study population consisted of adult survivors (> 16 yr old) of critical illness; and 2) depressive symptoms assessed using a validated measure after hospital discharge. We excluded studies meeting any of the following criteria: 1) less than 50% ICU patients in study population; 2) primary focus on patients from a specialty ICU (e.g., trauma or neurologic ICU) or with a specific disease (e.g., cardiac disease, acute respiratory distress syndrome); 3) less than or equal to 20 patients at follow-up; or 4) primary focus on evaluating psychometric properties of a questionnaire. We excluded abstracts and dissertations not published in a peer-reviewed journal.

Trained reviewers screened titles/abstracts and then full-text articles, in duplicate, using DistillerSR (2014 Evidence Partners, Ottawa, Canada). Disagreement regarding eligibility was resolved by consensus.

Data Abstraction

Data were abstracted by two independent reviewers from each eligible article, with any conflicts resolved by consensus in consultation with an independent coauthor (D.M.N.) or (A.E.T.). We collected the following data from each eligible article: study design, patient population, baseline patient characteristics, proportion of patients with preexisting psychiatric illness, timing and sample size at each depression assessment, depressive symptom assessment instrument and scoring method, point prevalence of depressive symptoms (indicated by having a score above a predefined threshold), potential risk factors for depressive symptoms, and any post-ICU interventions to prevent or treat depressive symptoms. We contacted authors for additional data when necessary. When risk factors were assessed in more than one study, we categorized them as pre-ICU, ICU, or post-ICU. We used analyses from the first follow-up assessment after hospital discharge for studies with longitudinal evaluations of risk factors and recorded risk factor associations from multivariable regressions, when available.

Risk of Bias Assessment

We conducted risk of bias assessment using the Cochrane Risk of Bias methodology (10) for randomized controlled trials (RCTs) and an adaptation of Newcastle Ottawa Scale (11) for observational studies (**Table S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/B896).

Statistical Analysis

First, the pooled prevalence of depressive symptoms was estimated by pooling data from all studies that assessed depressive symptoms using the most common measurement instrument in this systematic review (i.e., the depression subscale of the Hospital Anxiety and Depression Scale [HADS-D]). These data were used to estimate: 1) mean (SD) HADS-D score, and 2) point prevalence of depressive symptoms, defined as a HADS-D score greater than or equal to 8 and greater than or equal to 11. Both thresholds have been recommended for the HADS-D (12), with the optimal balance between sensitivity and specificity occurring at greater than or equal to 8 (13).Data were pooled for the three most commonly reported follow-up time points in eligible studies: 2–3, 6, and 12–14 months.

Second, we combined studies using different instruments for depressive symptoms to create a pooled prevalence, using similar thresholds across instruments as previously described (14).

Third, in studies assessing depressive symptoms in the exact same patient cohort at two different time points, we also calculated the change in mean HADS-D scores and depressive symptom prevalence between 2–3 to 6 months and 6 to 12 months.

Pooled mean HADS-D scores and depressive symptom prevalences were estimated using linear and binominal random effects models, respectively, with a random intercept for the study. The I^2 statistic was used to evaluate between-study statistical heterogeneity, with a value greater than 50% interpreted as substantial heterogeneity (15). Two separate sensitivity analyses were conducted. First, we removed patient groups undergoing post-ICU interventions to limit the potential effects that any intervention may have had on depressive symptoms prevalence. Second, we removed studies with high risk of bias based on either not reporting or having known high loss to follow-up. We did not assess publication bias due to an insufficient number of studies (16). STATA 13.1 (Stata Corporation, College Station, TX) was used to conduct all analyses.

RESULTS

Description of Search and Study Characteristics

We identified 27,334 citations and reviewed 18,693 unique titles and abstracts (after removing duplicates across databases), and 1,579 full text articles, with 42 publications on 38 unique studies meeting eligibility criteria (**Fig. S1**, Supplemental Digital Content 1, http://links.lww.com/CCM/B896). The 38 unique studies, included nine RCTs (17–25), 24 cohort studies (26–49), four cross-sectional studies (50–53) and one case-series (54) (**Table S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/B896). A total of 4,113 patients were included in the eligible studies, with most assessments occurring between 1 and 12 months after discharge (**Table 1**). A total of 18 of 38 studies (47%) included assessments of depressive symptoms at greater than one time point after discharge. Fourteen studies (37%; $n = 1,188$) were conducted in the United Kingdom (17–20, 24, 28, 29, 33, 36, 37, 40, 44, 50, 53), and 10 (26%; $n = 1,162$) were conducted in the United States (22, 26, 27, 30, 32, 34, 45, 47–49).

Only six studies collected data on the use of antidepressants, with only one study collecting data both before and after ICU admission. This study showed that 24% of patients were taking antidepressant in the week before ICU treatment, and 49% received an antidepressant medication within the first 2 months after critical illness (34). The same study revealed that suicidal ideation was endorsed by 23% of depressed patients after critical illness. No other study assessed for suicidal ideation. No study assessed the association between use of antidepressant in the ICU and depression at follow-up.

Risk of Bias Assessment

Among the nine RCTs, randomization and allocation concealment were adequate in most studies (**Table S4**, Supplemental Digital Content 1, http://links.lww.com/CCM/B896). Double-blinding was feasible in one RCT (17). Among the observational studies, 13 (45%) had adequate follow-up (Table S2, Supplemental Digital Content 1, http://links.lww.com/CCM/B896).

Measures and Prevalence of Depressive Symptom

The most common measurement instrument was the HADS-D in 22 studies (58%), followed by the Center for Epidemiological Studies Depression scale (CES-D) in six studies (16%) and Beck Depression Inventory-II in four studies (11%) (Table 1). Assessments were conducted in-person, by mail, and by phone in 15 (39%), 12 (32%), and 10 (26%) of the 38 studies, respectively, with some using more than one method and seven studies (18%) not clearly reporting the method. Patients with prior psychiatric history were excluded in four studies, with 15 studies reporting the prevalence of prior psychiatric problems before hospital admission (range, 10–54% between studies) (Table 1).

The prevalence of depressive symptoms across all included studies, using seven distinct instruments with different cut-offs, ranged from 4% to 64%. The pooled mean (95% CI) HADS-D score was 5.5 (4.8–6.1; $I^2 = 82\%$) at 2–3 months, 5.6 (5.1–6.1; $I^2 = 66\%$) at 6 months, and 5.2 (4.5–5.8; $I^2 = 81\%$) at 12–14 months. For studies using the HADS-D instrument, the pooled depressive symptoms prevalence (95% CI) at greater than or equal to eight threshold was 29% (22–36%; $I^2 = 84\%$), 34% (24–43%; $I^2 = 88\%$), and 29% (23–34%; $I^2 = 76\%$), respectively. Across studies using any instrument, the prevalence of suprathreshold depressive symptoms (compatible with HADS-D ≥ 8) was between 29% and 30% at all three time points. At greater than or equal to 11 threshold, the pooled prevalence (95% CI) was 17% (12–21%; $I^2 = 77\%$) at 2–3 months, 17% (10–23%; $I^2 = 83\%$) at 6 months, and 13% (10–16%; $I^2 = 52\%$) at 12–14 months (**Table 2**). Sensitivity analyses did not materially change these results or decrease heterogeneity.

In 387 patients (four studies) (17, 18, 25, 40), with HADS-D data on identical patient cohorts at 2 or 3 months and 6 months, the pooled difference in mean score (95% CI), comparing the latter time point to the early time point, was 0.1 (–0.2 to 0.3; $I^2 = 42\%$), and the pooled difference (95% CI) in depressive symptom prevalence at greater than or equal to 8 and greater than or equal to 11 thresholds was 5% (–1% to +12%; $I^2 = 0\%$) and –1% (–8% to +5%; $I^2 = 38\%$), respectively. In 412 patients (three studies) (18, 25, 33), with HADS-D data at both 6 and 12 months, the pooled mean difference in HADS-D score was 0 (–0.2 to +0.1; $I^2 = 0\%$), and the pooled difference in depressive symptoms prevalence was 1% (–6% to +7%; $I^2 = 0\%$) and 1% (–4% to +6%; $I^2 = 0\%$) for greater than or equal to 8 and greater than or equal to 11, respectively.

Risk Factors Associated With Depressive Symptoms

Among studies that estimated the association between age, sex, and depressive symptoms, age was not associated with depressive symptoms in nine of 11 (26, 33, 34, 36, 44, 45, 47, 53, 56) and sex was not associated in eight of eight (28, 34, 44, 45, 51–53, 56) studies (**Table 3**). Pre-ICU psychologic morbidities were strongly associated with depressive symptoms in four of five studies (34, 44, 45, 52). Severity of illness and ICU or hospital length of stay were not associated with depressive symptoms in six of six (29, 33, 36, 45, 51, 53) and five of five (33, 36, 44, 50, 53) studies, respectively. Benzodiazepine use and duration of sedation were not associated with depressive symptoms in three of three studies (29, 44, 45). Sedation minimization strategies, such as daily sedation interruption (22, 49), light sedation (21), and a no sedation protocol (23) were not associated with depressive symptoms in four of four studies.

The presence of psychologic distress symptoms in the ICU or hospital had a significant association with depressive symptoms at follow-up, with such symptoms evaluated in a variety of ways, including ICU mood symptoms (anger and nervousness) (44), acute stress symptoms (45), stressful experiences of ICU stay (35), and depressive symptoms in the hospital (33). "Delusional memories" and lack of factual memories were associated with more depressive symptoms at follow-up in two of two (29, 56) and three of five (29, 33, 44) studies, respectively. The association between delirium and depressive symptoms were assessed in three studies. One showed a positive unadjusted association (44), the second showed a positive association at 1-year follow-up (not at 3 mo) (47), and the third showed no association (45).

Depressive symptoms were concurrently correlated with greater anxiety and posttraumatic stress disorder (PTSD)

TABLE 1. Measurement of Depressive Symptoms Using Standardized Instruments

Study	Past Psychiatric Illness (%)	Instrument	Follow-Up (Mo)	No. at Follow-Up	Mean (SD) or Median (IQR)	Cut-Off Score	Point Prevalence (%)
Chelluri et al (26)	–	CES-D	1	12; 12	10 (5.02)[a]; 10 (5.99)[b]	–	–
			6	12; 12	8 (3.01)[a]; 9 (5.4)[b]		
			12	12; 12	6 (3.01)[a]; 6 (1)[b]		
Broslawski et al (27)	–	GDS-SF	6	27	–	≥ 6	4
Eddleston et al (28)	–	HADS-D	3	143	–	≥ 8; ≥ 11	9.8; 2.8
Kress et al (49)	38[c]; 11[d]	BDI-II	14 (5)[c]; 12 (7)[d]	13[c]; 19[d]	13.7 (9.7)[c]; 17.2 (10.6)[d]	≥ 17	38[c]; 53[d]
Jones et al (29)	16	HADS-D	2	30	5.28 (4.42)	≥ 8; ≥ 11	20; 13.3
Scragg et al (50)	–	HADS-D	13 (6)	80	–	≥ 8	30
Jackson et al (30)	Excluded	GDS-SF	6	34	6.4 (4.3)[e], 3 (3.4)[f]	≥ 6	24
Jones et al (17)	Excluded	HADS-D	2	114	5.9 (4.4)	≥ 8; ≥ 11	39; 31
			6	102	5.6 (3.9)		56; 36
Boyle et al (31)	–	CES-D	1	55	19.22 (10.42)	–	–
			6	51	13.79 (10.37)		
Chelluri et al (32, 55)	–	CES-D	2	129	14.1 (9.6)	≥ 16	35
			12	154	12.16 (11.02)		32
Rattray et al (33)	–	HADS-D	6	80	5.13 (3.56)	≥ 8; ≥ 11	26; 7
			12	80	5.16 (4.28)		27; 11
Weinert et al (34)	27[g]	CES-D	2	153	11, 8	≥ 16	27
			6	90	11, 6	–	33
		Structured Clinical Interview for DSM-IV	2	134	–	–	33
Samuelson et al (35)	–	HADS-D	2	226	1	≥ 11	7.5
Sukantarat et al (36)	–	HADS-D	3	51	6.6 (4.5)	≥ 8; ≥ 11	35; 23.53
			9	45	6.7 (4.8)		47; 31.11
McWilliams et al (37)	–	HADS-D	1 wk	38	7.2 (4.1)	≥ 8; ≥ 11	42; 13
			2	38	4.4 (3.6)		10.5; 8
Cuthbertson et al (18)	–	HADS-D	6	105[c], 115[d]	5.3 (4.3)[c], 5.3 (4.0)[d]	≥ 8; ≥ 11	27[c]; 12[c]/28[d]; 13[d]
			12	93[c], 100[d]	4.8 (4.5)[c], 4.8 (4.2)[d]		27[c]; 13[c]/28[d]; 11[d]
Knowles et al (19)	22.2[c]; 27.8[d]	HADS-D	1	18[c]; 18[d]	6.72 (4.64)[c]; 8.89 (5.12)[d]	≥ 8	38.9[c], 55.6[d]
			2	18[c]; 18[d]	4.17 (2.98)[c]; 8.29 (5.13)[d]		16.7[c], 44.4[d]
Myhren et al (39, 56)	–	HADS-D	1	252	4.76 (4.15)	≥ 8; ≥ 11	23; 12
			3	191	4.16 (3.92)		20; 8
			12	192	4.71 (4.23)		27; 11
Peek et al (20)	–	HADS-D	6	50[c], 32[d]	4.4 (0.6)[c], 5.8 (0.7)[d]	≥ 8; ≥ 11	16; 8[c]/25; 12.5[d]
Treggiari et al (21)	–	HADS-D	1	52[c], 50[d]	3.4 (3.7)[c], 3.1 (3.7)[d]	≥ 8; ≥ 11	15; 8[c]/12; 4[d]
Van der Schaaf et al (38)	–	HADS-D	12	247	4.4 (4.25)	≥ 8; ≥ 11	22; 11
Jackson et al (22)	–	BDI-II	3	47[c]; 32[d]	13 (7–20)[c]; 11 (7–17)[d]	> 10	64[c], 58[d]
			12	35[c]; 25[d]	12 (5–20)[c]; 14 (6–20)[d]		59[c], 62[d]

(*Continued*)

TABLE 1. (*Continued*). Measurement of Depressive Symptoms Using Standardized Instruments

Study	Past Psychiatric Illness (%)	Instrument	Follow-Up (Mo)	No. at Follow-Up	Mean (SD) or Median (IQR)	Cut-Off Score	Point Prevalence (%)
Rattray et al (40)	–	HADS-D	2 6	63 50	6.98 (5.381) 6.22 (4.586)	≥ 8; ≥ 11	42.9; 25.4 32; 18
Strøm et al (23)	8[c]; 23[d]	BDI-II	24	13[c], 13[d]	3 (1–7)[c]; 3 (1–11)[d]	> 10	8[c], 31[d]
Garrouste-Orgeas et al (14)	18.7[h]; 6.1[i]; 19.5[j]	HADS-D	3	21[h] 19[i] 12[j]	6.3 (6.9)[h] 3.7 (5.1)[i] 6.5 (4.7)[j]	≥ 8; ≥ 11	38.1; 28.6[h] 15.8; 15.8[i] 41.7; 25[j]
McKinley et al (42)	Excluded	Depression, Anxiety and Stress Scales-21-D	1 wk 2 6.5	156 156 156	8 (2–12) 4 (0–10) 4 (0.5–10)	≥ 14; ≥ 20	26.9; 13.7 16.6; 8.9 21.3; 9.4
Schandl et al (43)	18[c]; 15[d]	HADS-D	3[c] 6[c] 12[c] 14[c,d]	100[c] 68[c] 50[c] 98[c]; 73[d]	5.47 (4.15)[c] 5.02 (3.85)[c] 4.4 (3.12)[c] 4.78 (4.50)[c]; 5.76 (4.54)[d]	≥ 8; ≥ 11	28; 13[c] 25; 12[c] 24; 2[c] 21; 11[c]/33; 19[d]
Wade et al (44)	16[k]	CES-D	3	100	–	≥ 19	46.30
Davydow et al (45)	29[k]	PHQ-9	3 12	131 120	–	≥ 10	31 17
Kowalczyk et al (51)	–	HADS-D	34	186	7.82 (4.82)	≥8; ≥11	50; 27.4
Raveau et al (46)	42[k]	GDS-4 items	3	30	0 (0–10)	≥1	43
Risnes et al (54)	54	HADS-D	60	27	3.81 (3.3)	–	–
Jackson et al (47)	34[k]	BDI-II	3 12	407 347	10 (5–17) 10 (4.6–16.5)	≥ 14; ≥ 20	37; 20.4 33; 21
Paparrigopoulos et al (52)	42	CES-D	21 (3)	48	13.3 (2)	≥ 16	31
Battle et al (53)	10[k]	HADS-D	3	63	6.8 (5.3)	≥ 8; ≥ 11	46; 25.4
Jones et al (24)[o]	Excluded	HADS-D	3	14[l], 18[m], 19[n], 16[o]	4.93 (4.2)[l]; 2.74 (2.5)[m]; 6.37 (4.6)[n]; 4.81 (3.8)[o]	≥ 8; ≥ 11	29; 7[l]/5; 0 [m]/37; 21[n]/19; 12[o]
Parsons et al (48)	24; 18[k]	PHQ-9	12	120	–	≥ 10	18
Walsh et al (25)	–	HADS-D	3 6 12	98[c]; 87[d] 86[c]; 80[d] 81[c]; 77[d]	6.45 (3.89)[c]; 6.91 (4.27)[d] 7.17 (4.62)[c]; 6.71 (4.81)[d] 6.87 (4.82)[c]; 6.66 (4.14)[d]	≥ 8; ≥ 11	36.7; 15.3[c]/44.8; 22.9[d] 50; 24.4[c]/43.7; 20[d] 45.6; 24.6[c]/40; 19.4[d]

IQR = interquartile range, CES–D = Center for Epidemiological Studies Depression scale, GDS-SF = Geriatric Depression Scale Short Form, HADS-D = Hospital Anxiety and Depression Scale-Depression Subscale, BDI = Beck Depression Inventory, PHQ = Patient Health Questionnaire.

[a]Age < 75 yr old.

[b]Age ≥ 75 yr old.

[c]Intervention.

[d]Control.

[e]Cognitively impaired based on neuropsychologic battery.

[f]Cognitively non-impaired.

[g]Depressed in last month (per proxy).

[h]Pre-diary.

[i]Dairy.

[j]Post diary.

[k]History of depression.

[l]Control supplement, no Program of Enhanced Physiotherapy and Structured Exercise (PEPSE) (outpatient physiotherapy class),

[m]Control supplement, PEPSE.

[n]Essential amino acid (EAA) supplement, no PEPSE.

[o]EAA supplement, PEPSE.

Dashes indicate data not reported.

TABLE 2. Meta-Analysis of Depression Prevalence in ICU Survivors

Instruments to Assess Depressive Symptoms	2, 3 Mo	6 Mo	12, 14 Mo
Using HADS-D ≥ 8			
No. of studies	12[a]	7[b]	6[c]
No. of patients	1,078	760	1,041
Prevalence, % (95% CI)	29 (22–36)	34 (24–43)	29 (23–34)
I^2, %	84	88	76
Using multiple instruments compatible with HADS-D ≥ 8 (including HADS-D ≥ 8; Beck Depression Inventory-II ≥ 14 and 16; CES-D ≥ 16; Geriatric Depression Subscale-Short Form ≥ 6)			
No. of studies	15[d]	10[e]	8[f]
No. of patients	1,767	911	1,542
Prevalence, % (95% CI)	30 (24–35)	29 (20–39)	30 (25–34)
I^2, %	84	91	72
Using HADS-D ≥ 11			
No. of studies	12[a]	7[b]	6[c]
No. of patients	1,078	760	1,041
Prevalence, % (95% CI)	17 (12–21)	17 (10–23)	13 (10–16)
I^2, %	77	83	52
Using multiple instruments compatible with HADS-D ≥ 11 (including HADS-D ≥ 11; Patient Health Questionnaire-9 ≥ 10; Depression, Anxiety and Stress Scale 21-D ≥ 14; CES-D ≥ 19)			
No. of studies	16[g]	8[h]	9[i]
No. of patients	1,812	916	1,628
Prevalence, % (95% CI)	20 (15–24)	17 (12–23)	15 (12–18)
I^2, %	86	82	66

HADS-D = Hospital Anxiety and Depression Scale-Depression Subscale, CES-D = Center for Epidemiological Studies Depression scale.
[a]Relevant references: (17, 18, 24, 25, 36, 37, 39–41, 43, 50, 53).
[b]Relevant references: (17, 18, 20, 25, 33, 40, 43).
[c]Relevant references: (18, 25, 33, 38, 39, 43).
[d]Relevant references: (17, 18, 24, 25, 34, 36, 37, 39–41, 43, 47, 50, 53, 55).
[e]Relevant references: (17, 18, 20, 25, 27, 30, 33, 34, 40, 43).
[f]Relevant references: (18, 25, 32, 33, 38, 39, 43, 47).
[g]Relevant references: (17, 18, 24, 25, 36, 37, 39–45, 47, 50, 53).
[h]Relevant references: (17, 18, 20, 25, 33, 40, 42, 43).
[i]Relevant references: (18, 25, 33, 38, 39, 43, 47, 48, 58).

symptoms in five of five studies (19, 36, 50–52) and with worse quality of life in two of two studies (36, 52).

Interventions to Reduce Depressive Symptoms

No study specifically assessed pharmacologic intervention in this population. However, physical rehabilitation after ICU discharge was assessed in three studies, with significant benefit reported in one cohort study (37) and in one RCT when combined with oral supplementation with essential amino acids (24) (**Table 4**). In-hospital rehabilitation after ICU discharge did not show significant benefit in one RCT (25).

Use of an ICU diary was not associated with significant reduction in depressive symptoms in one pre-post cohort study. In one RCT (41), the group receiving an ICU diary combined with counseling demonstrated a significant decrease in depressive symptoms over time, but the difference between treatment groups was not statistically significant (19). A nurse-led ICU follow-up clinic did not have significant benefit in one RCT (18) whereas a multidisciplinary follow-up clinic showed benefit for women (but not men) in one RCT on a combined outcome of depression, anxiety, and PTSD symptoms (43).

DISCUSSION

This systematic review and meta-analysis in non-specialty populations of ICU survivors demonstrates that clinically important depressive symptoms occur in approximately 30%

TABLE 3. Association of Depressive Symptoms With Pre-ICU, ICU, and Post-ICU Factors

Risk Factors	Total Number of Studies	Studies Without Any Association		Positive Association (Greater Depressive Symptoms)	
		n	%	*n*	%
Pre-ICU factors					
Older age	11	9	82	2	18
Sex	8	8	100	0	0
Ethnicity	2	2	100	0	0
Low income and socioeconomic status	3	0	0	3	100
Low employment status	2	0	0	2	100
Low educational status	4	3	75	1	25
Marital status	3	3	100	0	0
Pre-ICU psychologic morbidity[a]	5	1	20	4	80
History of traumatic event	2	1	50	1	50
Chronic physical health morbidities	4	4	100	0	0
ICU factors					
Benzodiazepines/days of sedation	3	3	100	0	0
Sedation minimization[b]	4	4	100	0	0
Duration of mechanical ventilation	4	3	75	1	25
Antipsychotics in ICU	2	2	100	0	0
Opioids in ICU	3	3	100	0	0
Delirium	3	2[c]	67	1	33
Severity of illness[d]	6	6	100	0	0
Therapeutic Intervention Scoring	2	2	100	0	0
ICU LOS, hospital LOS	5	5	100	0	0
Admission diagnosis	6	5	83	1	17
ICU experience[e]	2	2	100	0	0
Psychologic symptoms in ICU/hospital[f]	4	0	0	4	100
Post-ICU factors					
Time since hospital discharge[g]	8	6	75	2	25
Having delusional memories	2	0	0	2	100
No factual memories from ICU stay	5	2	40	3	60
Quality of life	2	0	0	2	100
Psychiatric problems post-ICU[h]	5	0	0	5	100

LOS = length of stay.

[a]Depression, psychologic history in general.

[b]Two daily sedative interruption protocols, one light sedation and one no sedation protocol.

[c]One study was unable to show association at first time point (3 mo) but found positive association at 12 mo.

[d]Acute Physiology and Chronic Health Evaluation II/Simplified Acute Physiology Score II.

[e]Awareness of surroundings; satisfaction with care; frightening experiences.

[f]ICU mood, acute stress, stressful experiences, and depressive symptoms.

[g]Change in depressive symptoms longitudinally comparing two time points "after" hospital discharge, only two studies showed decrease in depressive symptoms over time.

[h]Anxiety and posttraumatic stress disorder.

TABLE 4. Association of Post-ICU Interventions With Depressive Symptoms

Post-ICU Interventions	Total Number of Studies	Studies Without Any Association		Negative Association (Less Depressive Symptoms)	
		n	%	*n*	%
Rehabilitation during post-ICU hospitalization	1	1	100	0	0
Physical rehabilitation after discharge[a]	3	1	0	2	67
Antidepressant + self-help manual vs antidepressant alone[b]	1	0	0	1	100
ICU diary	2	2	100	0	0
Nurse-led ICU follow-up clinic	1	1	100	0	0

[a]In one randomized controlled trial, physical rehabilitation plus essential amino acid supplement was effective.
[b]Self-help manual (rehabilitation package) alone reduced the rate of depressive symptoms but did not reach statistical significance ($p = 0.066$).

of patients over the first 12 months after critical illness. Studies with longitudinal assessment of depressive symptoms in fixed cohorts of survivors showed no significant change in HADS-D scored or prevalence of depressive symptoms during the first 12 months after discharge.

The prevalence of depressive symptoms in this review is similar to the 31–45% prevalence of depressive symptoms in cardiac patients without critical illness (59) and markedly higher than studies in American and European general populations with a prevalence of 8–11% (60–62). Pooled data evaluating the longitudinal prevalence of post-ICU depressive symptoms showed no significant change during the first 12 months post-ICU. The reason for this concerning finding is not clear but is similar to that of cardiac patients (59).

The 38 unique studies in this systematic review used seven different instruments, with variability in scoring, timing of follow-up, and risk factors evaluated, making synthesis and comparisons across studies challenging. The HADS-D was clearly the most common instrument used in more than 50% of studies. Validation of an instrument to measure depressive symptoms in critical illness survivors after discharge, and consistent use of this instrument with standardized scoring methods, thresholds, and reporting would help advance the field (63). Given that it is the most commonly used instrument, the HADS would be a particularly relevant instrument for validation in a population of ICU survivors. Notably, the HADS subscales have been validated in general medical patients, and some preliminary validation has been done in subgroups of critical illness survivors (64, 65).

Important patient factors consistently not associated with depressive symptoms included age and sex. This finding differs from studies in the general population in which depressive symptoms are twice as common in females (66) and more common in 40–59 years age group (60). Future research is needed to help understand any unique attributes of patients with critical illness and relevant mechanisms that may contribute to this finding. Aspects unique to critical illness (e.g., neuro-inflammation) might be an etiologic factor that affects both sexes similarly.

Many ICU factors, such as admission diagnosis, severity of illness, sedation and analgesia, and length of stay, also were consistently not associated with depressive symptoms at follow-up similar to prior findings for other psychologic symptoms in ICU survivors (7, 67). Hence, screening efforts for post-ICU depressive symptoms among general ICU survivors should be quite broad, considering both sexes, all ages, and the full range of severity of illness and length of stay. Focusing only on patients with a high severity of illness or a long length of stay may overlook a large number of symptomatic ICU survivors. Rather, identifying patients with preexisting psychologic morbidity and psychologic distress symptoms in the hospital may help maximize prevention and early intervention efforts. Furthermore, given high comorbidity of depression with anxiety and PTSD symptoms after critical illness, as demonstrated in this systematic review, patients who screen positive for depression, should be evaluated for a full spectrum of psychologic sequelae.

There were inconsistent results across three studies regarding the potential association of ICU delirium with postdischarge depressive symptoms. More research is required in this area.

There was no strong evidence to support a post-ICU intervention to prevent or treat depressive symptoms. Nevertheless, some studies suggested that post-ICU out-patient physical rehabilitation interventions reduced depressive symptoms, consistent with data in cardiac patients (68). Hence, the potential mental and physical benefits of rehabilitation and exercise interventions in general ICU survivors merit continued research. No study assessed the effect of pharmacologic treatment options in this population as an intervention. Similar treatments in cardiac patients have shown to be effective (69). This is an important area for future research.

Among observational studies and randomized trials, there were high rates of loss to follow-up, suggesting potential selection bias (70, 71). Since depressive symptoms may influence patients' willingness to participate, loss to follow-up may bias results from both interventional and prevalence/risk factor studies (including the results of this systematic review) and potentially underestimate the prevalence of depressive symptoms.

There are potential limitations of this systematic review. First, with the exception of two studies (34, 54), depressive symptoms were assessed using questionnaires, most of which have not been rigorously evaluated for their psychometric

performance in ICU survivors. Ideally, studies would use a clinician-administered, semi-structured diagnostic interview. However, this approach is often not feasible due to the required expertise of the interviewer and the time required to complete the assessment, which may be particularly burdensome in studies with repeated longitudinal assessments and evaluation of other psychologic and physical outcome measures of interest. Furthermore, diagnostic semi-structured interviews do not provide a quantitative measure of symptom severity which is useful for research studies. Second, there was substantial statistical heterogeneity in this meta-analysis that did not improve with sensitivity analyses. Hence, caution is advised in interpreting the pooled results of depressive symptom means and prevalences. Third, the existing data do not clarify whether depressive symptoms are the result of critical illness, or if post-ICU depressive symptoms mainly reflect preadmission morbidity or are a result of hospitalization without any unique contribution of an ICU stay. Finally, although we attempted to identify all potentially relevant studies, it is possible that eligible studies were inadvertently omitted from this systematic review.

CONCLUSION

Depressive symptoms occurred in approximately 30% of general critical illness survivors with persistent severity over 12-month longitudinal follow-up. ICU survivors with comorbid psychopathology before and during their hospitalization have a higher prevalence of depressive symptoms after discharge. However, age, sex, severity of illness, and length of stay were consistently not associated with depressive symptoms; hence, a large pool of ICU survivors are at-risk for depressive symptoms. No post-ICU intervention for preventing or treating depressive symptoms was supported by strong evidence although physical rehabilitation after discharge merits further investigation.

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