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REVIEW

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Depression in general intensive care unit survivors: a systematic review

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Abstract *Purpose:* To critically review data on the prevalence of depressive symptoms in general intensive care unit (ICU) survivors, risk factors for these symptoms, and their impact on health-related quality of life (HRQOL). *Methods:* We conducted a systematic review using Medline, EMBASE, Cochrane Library, CINAHL, PsycINFO, and a hand-search of 13 journals. *Results:* Fourteen studies were eligible. The median point prevalence of "clinically significant" depressive symptoms was 28% (total $n = 1{,}213$). Neither sex nor age were consistent risk factors for post-ICU depression, and severity of illness at ICU admission was consistently not a risk factor. Early post-ICU depressive symptoms were a strong risk factor for subsequent depressive symptoms. Post-ICU depressive symptoms were associated with substantially lower HRQOL. *Conclusions:* Depressive symptoms are common in general ICU survivors and negatively impact HRQOL. Future studies should address how factors related to individual patients, critical illness and post-ICU recovery are associated with depression in ICU survivors.

Keywords Depression · Critical care · Risk factors · Quality of life · Outcome assessment (health care)

Abbreviation

ICU Intensive care unit

Introduction

With advances in critical care medicine, more patients are surviving intensive care unit (ICU) stays [1]. With this increase in survival, critical care research has begun focusing on long-term outcomes of ICU patients, including mental health, health-related quality of life (HRQOL), and cognitive outcomes [2–5].

Critical illness and requisite ICU therapies expose patients to enormous stressors including respiratory insufficiency, discomfort with endotracheal tube suctioning, activation of the inflammatory cascade, strain on the hypothalamic–pituitary–adrenal (HPA) axis, administration of exogenous catecholamines, and delirium with associated psychotic experiences, all within the context of a limited ability to communicate and reduced autonomy.

Moreover, ICU survivors may face significant physical limitations during recovery [1]. Thus, symptoms of depression are a potential concern in ICU survivors. The recognition of depressive symptoms following critical illness is important because depression carries a risk of suicide, negatively impacts HRQOL [6], and delays return to work [7]. We previously conducted a systematic review of psychiatric morbidity in survivors of acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) and found that the point prevalence of "clinically significant" depressive symptoms ranged from 17 to 43% [8]. We are unaware of any comparable systematic review of depression in a general population of ICU survivors. In this report, we present results of a systematic review of: (1) the prevalence of depression following general ICU treatment, (2) potential risk factors for post-ICU depressive symptoms, and (3) the relationship of post-ICU depressive symptoms to HRQOL.

Methods

Search strategy

We searched Medline (1966–2007), EMBASE (1974–2007), CINAHL (1982–2007), the Cochrane Library (2007, Issue 1), and PsycInfo (1967–2007) as of 26 October 2007. Our search strategy included the following terms mapped to the appropriate MeSH/EMTREE subject headings and "exploded": ("mental disorders" or "psychometrics") and ("respiratory distress syndrome, adult" or "critical care" or "critical illness" or "intensive care units" or "sepsis"). The following terms were also included as text words: ("depress*" or "stress" or "anxi*") and ("respiratory distress syndrome" or "ARDS" or "acute lung injury" or "ALI"). In addition, we manually searched the tables of contents of 13 general medicine, psychiatry, and critical care journals (see Appendix 1) from January 2000 to October 2007. The search was limited to English-language articles. Articles dealing with neonatal or pediatric intensive care were excluded.

Since we recently conducted a separate systematic review of posttraumatic stress disorder (PTSD) following ICU care [9], we did not include studies which focused exclusively on PTSD and/or non-specific anxiety outcomes. Moreover, we did not include studies focusing exclusively on ALI/ARDS survivors since psychopathology in ALI/ARDS survivors has been specifically addressed in another systematic review [8]. Our goal for this systematic review was to address areas which are not explored in these prior publications. However, related search terms from these prior systematic reviews were included to help identify several eligible, but otherwise unidentified, studies.

Study selection

Two authors (D.S.D. and S.V.D.) independently and sequentially reviewed citations, abstracts, and full-text articles to select eligible studies. All citations or abstracts selected by either author were included in the next step of the selection process. At each step, the authors calculated interobserver agreement using percent agreement and the kappa statistic. Disagreements regarding eligibility of full-text articles were resolved by consensus among all authors.

Articles were selected for review if they met the following criteria: (1) the study population was comprised of adult ICU survivors, and (2) depression assessments were conducted using validated measures at $\geq$1 month following ICU discharge. Abstracts, case reports, and review articles were excluded. Since we recently systematically reviewed studies focusing solely on survivors of ALI/ARDS [8], we excluded these studies from the current report. Studies focusing exclusively on survivors from specialty ICUs (i.e., coronary, trauma/surgical or neurological ICUs) were excluded in order to allow a primary focus on a more general ICU patient population and to reduce confounding from other potential risk factors for depression (e.g., myocardial infarction, head injury), recognizing that residual confounding would remain since general ICUs also care for patients with potentially confounding conditions.

Data abstraction and study quality

For each eligible study, two authors (D.S.D. and J.M.G.) independently abstracted information regarding characteristics of the study cohorts, study quality, depression measures, potential risk factors, and associations between depressive symptoms and HRQOL. The authors calculated interobserver agreement for data abstraction using percent agreement and the kappa statistic. Authors of eligible studies were contacted for additional study data (e.g., mean/median scores on depression measures), when necessary.

Study quality was assessed using five criteria adapted from the United States Preventative Task Force [10] and a previous systematic review of heterogeneous outcome data [3]: (1) enrollment of consecutive patients; (2) no loss to follow-up of >10% of study participants prior to first depressive symptoms assessment; (3) description of patients lost to follow-up; (4) at least one statistical comparison between patients lost to follow-up and those remaining in the study; and (5) adjustment for confounders by stratification, statistical adjustment, or comparison with a matched population. Quality criteria were not used in decisions regarding inclusion or exclusion of eligible studies.

Results

Search results, study characteristics and quality

The authors reviewed 16,301 citations, 1,908 abstracts and 193 full-text articles (Fig. 1). Fourteen articles were eligible for data abstraction [11–24] (Table 1). The percent agreement (kappa statistic) for each stage of the study selection and data abstraction process were: citation review, 91% ($\kappa = 0.54$); abstract review 98% ($\kappa = 0.84$); full-text review 99% ($\kappa = 0.89$); and data abstraction, 98.7% ($\kappa = 0.98$).

Table 1 shows baseline descriptive data for the 14 studies, ordered by timing of follow-up assessments. Follow-up periods ranged from 2 weeks to approximately 14 months. The studies enrolled 1,621 unique patients. Of the 14 studies reviewed, 8 were prospective cohort studies [11–15, 18, 20, 22], one was a retrospective cohort study [21], three were cross-sectional studies [16, 19, 24], one was a case–control study [23], and one was a randomized-controlled trial [17]. Seven of the studies were conducted in the UK [13, 14, 17, 19–21, 24], five in the US [11, 16, 18, 22, 23], one in Australia [15], and one in Sweden [12].

A majority of studies enrolled patients admitted consecutively to the ICU [11, 12, 14, 15, 17, 19, 21, 22], although only six of these studies lost <10% of patients prior to the first assessment of depressive symptoms [12, 13, 16, 17, 19, 20] (Table 2). Over half of the studies that reported loss to follow-up described the patients lost to follow-up [11, 12, 14–16, 21, 24]; however, only four of these included a statistical comparison between the patients lost to follow-up and those that completed the study [11, 12, 14, 15]. Only half of the 14 studies adjusted for potential confounders in analyses [11, 13, 14, 17–19, 24].

Prior psychiatric history

Five of the studies excluded patients with a pre-ICU history of psychiatric illness [11–13, 17, 19] (Table 1). In three of these, patients were excluded only if they had a pre-existing psychotic illness or were admitted after a suicide attempt [12, 13, 17]; in the other two, patients with any prior or ongoing psychiatric illness [19] or any major psychiatric illness [11] were excluded.

Three of the studies reported information regarding patients' psychiatric histories [13, 18, 23] (Table 3). In one of these, a recent history of depression was identified

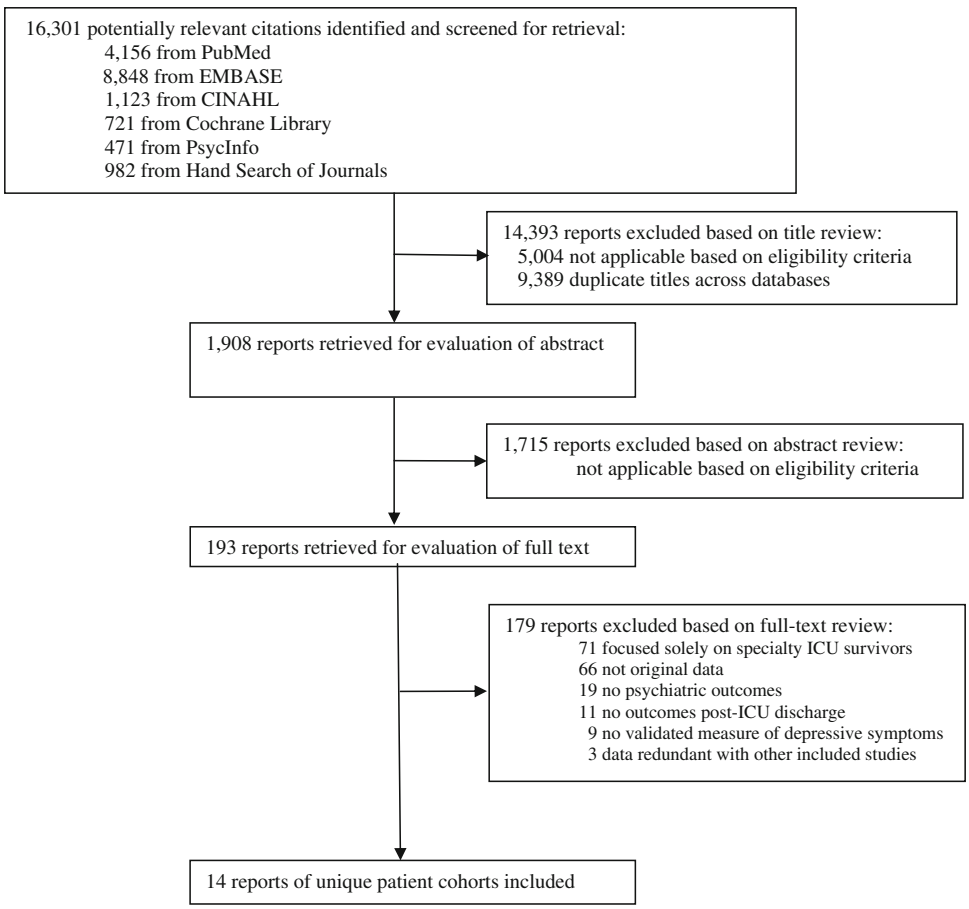

Fig. 1 Flow diagram of literature search results

Table 1 Study cohort characteristics, ordered by follow-up time

Study	Study type	No enrolled	Inclusion (I) and exclusion (E) criteria	Male (%)	Mean (standard deviation) or *median* (*interquartile range*) [absolute range]					
					Age in years	Days in hospital	Days in ICU	Days of mechanical ventilation	APACHE II score	Follow-up in months
Jackson et al. [11]	Prospective cohort	34	I: mechanically ventilated E: mental retardation, brain lesions, neurological disorder affecting cognitive function, major psychiatric illness, sensory or language deficits	53	53 (15)	–	–	–	25 (9)	0, 6
Samuelson et al. [12]	Prospective cohort	250	I: >18 years of age, mechanically ventilated, general ICU LOS at least 24 h E: head injury, psychotic illness, mental retardation, intoxication, admitted following suicide attempt, hearing/speech disability, non-Swedish speaking, transferred to another hospital, mechanically ventilated at d/c, mechanically ventilated >24 h pre-admission	52	63 (13)	–	6 (6), *4*	4 (5), *2*	*18*	0.16, 2
Jones et al. [13]	Prospective cohort	45	I: general medical and surgical ICU LOS at least 24 h, mechanically ventilated E: admitted following suicide attempt or head injury, ongoing or previous psychotic illness	44	*57* [17–82]	–	*8* [1–60]	–	*17* [4–28]	0.5, 2
Rattray et al. [14]	Prospective cohort	109	I: >18 years of age, general ICU LOS at least 24 h E: living >100 miles away	–	55 (18)	*28* (*15*, *57*)	*5* (*2*, *13*)	–	18 (5)	0.75, 6, 12
Boyle et al. [15]	Prospective cohort	66	I: >18 years of age, general ICU LOS at least 48 h E: non-English speaking, neurologic impairment, paraplegia or quadriplegia	63	59 (15)	26 (30)	7 (6)	2 (4)	16 (7)	1, 6
Guentner et al. [16]	Cross-sectional	30	I: >18 years of age, mechanically ventilated >7 days, tracheostomy E: MMSE < 24, non-English speaking	57	63 (18) [20–83]	*31* [7–205]	*30* [7–186]	*92*[a] [21–2,624][a]	–	[1.5–11]
Jones et al. [17]	Randomized controlled trial	69, 57[b], 126[c]	I: mechanically ventilated, mixed general ICU LOS at least 48 h E: burn injury, neurosurgical patient, preexisting psychotic illness, speech/reading difficulty, life expectancy <6 months	54 58[b]	57 (17) [17–77] 59 (16)[b] [17–84][b]	–	14 (20) [2–114] 13 (18)[b] [2–110][b]	–	17 (5) 16 (5)[b]	2, 6
Weinert et al. [18]	Prospective cohort	277	I: >18 years of age, mechanically ventilated >36 h E: coma >24 h, mental retardation, chronic cognitive dysfunction, craniotomy, plans to withdraw life support	52	*54* (*47–63*)	*22*	–	*6*	–	2, 6
Young et al. [19]	Cross-sectional	20	I: >18 years of age, ICU LOS at least 24 h E: head injury, living alone, psychiatric illness, admitted following suicide attempt	75	54 (17)	19 (17)	–	–	15 (5)	3

Table 1 continued

Study	Study type	No enrolled	Inclusion (I) and exclusion (E) criteria	Male (%)	Mean (standard deviation) or *median* (*interquartile range*) [absolute range]					
					Age in years	Days in hospital	Days in ICU	Days of mechanical ventilation	APACHE II score	Follow-up in months
Sukantarat et al. [20]	Prospective cohort	51	I: general ICU LOS at least 72 h E: major medical or surgical therapy following d/c, reluctance to undergo detailed testing, still in hospital at time of study, lived at a distance	43	57 (14) *60* (*49*, *66*) [27–82]	–	17 (17) *9* [3–78]	12 (17)	15 (6)	3, 9
Eddleston et al. [21]	Retrospective cohort	143	I: >17 years of age, ICU stay E: –	52	51 (19)	–	*4* (*1–11*)	–	15 (7)	3, 6, 12
Chelluri et al. [22]	Prospective cohort	296	I: >18 years of age, mechanically ventilated >48 h E: solid organ transplant, non-English speaking, prisoner, chronic ventilator dependence, social security number ending in 9	54	*65*	–	–	–	–	12
Kress et al. [23]	Case–control	13, 19[b], 32[c]	I: mechanically ventilated in medical ICU, received IV drip sedation E: –	31, 42[b]	50 (16), 47 (20)[b]	18 (13), 19 (10)[b]	7 (6), 13 (10)[b]	6 (6), 10 (7)[b]	16 (6), 18 (7)[b]	14 (7), 12 (5)[b]
Scragg et al. [24]	Cross-sectional	142	I: general ICU survivor between 1 October 1995 and 1 October 1997 E: head trauma, accidental or non-accidental injury, admitted for routine surgery w/o complications	53	*57* [19–90]	–	[1–33]	–	–	13 (6) [3–21]

d/c Discharge, *ICU* intensive care unit, *IV* intravenous, *LOS* length-of-stay, *MMSE* Mini-Mental Status Exam, *w/o* without, – not reported

[a] Many of the patients in this study were chronically ventilated following ICU discharge and thus had longer durations of ventilation than their ICU LOS

[b] Control group values (for randomized-controlled trial and case-control study)

[c] Entire sample

Table 2 Assessment of quality of studies reporting depressive symptoms in general ICU survivors

Study	Consecutive ICU admissions	Major losses to follow-up (% lost)[a]	Descriptions of patients lost to follow-up	Statistical comparison of patients lost to follow-up	Adjustment for confounding
Jackson et al. [11]	Y	Y (77)	Y	Y	Y
Samuelson et al. [12]	Y	N (6)	Y	Y	N
Jones et al. [13]	N	N (0)	N/A	N/A	Y
Rattray et al. [14]	Y	Y (17)	Y	Y	Y
Boyle et al. [15]	Y	Y (32)	Y	Y	N
Guentner et al. [16]	N	N (3)	Y	N	N
Jones et al. [17]	Y	N (10)	N	N/A	Y
Weinert et al. [18]	N	Y (12)	N	N/A	Y
Young et al. [19]	Y	N (0)	N/A	N/A	Y
Sukantarat et al. [20]	N	N (0)	N/A	N/A	N
Eddleston et al. [21]	Y	Y (37)	Y	N	N
Chelluri et al. [22]	Y	Y (18)	N	N/A	N
Kress et al. [23]	N	Y (59)	N	N/A	N
Scragg et al. [24]	N	Y (44)	Y	N	Y
Total/number of studies	8/14 (57%)	8/14 (57%)	7/11 (64%)	4/7 (57%)	7/14 (50%)

ICU intensive care unit, *N* no, *N/A* not applicable, *Y* yes

[a] Defined as loss of >10% of study participants at time of first depressive symptom assessment

via proxy report of depressed mood most of the day for 2 weeks in the month before ICU, or by determining if the patient had been prescribed an antidepressant medication in the 6 months immediately prior to ICU admission [18]; the other two studies apparently determined prior psychiatric history through chart review alone [13, 23]. The prevalence of pre-ICU psychiatric disorders was 18% [13] and 22% [23] in two of these studies; in the third, 27% of patients had a proxy-reported recent depressed mood, 34% had been seen for psychiatric problems in their lifetime, and 33% had recently been prescribed an antidepressant [18].

Prevalence of depressive symptoms/disorder

At least one measure of depressive symptoms was completed by 1,213 patients. Ten of the studies utilized in-person assessments [11, 13, 14, 16, 17, 19–23]; two, mailed questionnaires [15, 24]; and two, a combination of in-person and telephone assessments [12, 18]. One study employed a clinician to make diagnoses using the Structured Clinical Interview for DSM-IV (SCID), a semi-structured psychiatric diagnostic interview, in addition to a questionnaire [18] (Table 3); the remaining 13 studies only used questionnaires to assess depressive symptoms. Eight of these studies utilized the Hospital Anxiety and Depression Scale (HADS) [12–14, 17, 19–21, 24]; four, the Center for Epidemiologic Studies Depression Scale (CES-D) [15, 16, 18, 22]; one, the Geriatric Depression Rating Scale-Short Form (GDS-SF) [11]; and one, the Beck Depression Inventory-II (BDI-II) [23].

In determining the median point prevalence of questionnaire-ascertained "clinically significant" depressive symptoms post-ICU across studies, there were two important challenges. First, some studies collected depressive symptom data at more than one time point; in those instances, we used the median value from each study. Second, some studies had treatment or case groups versus control groups; in those instances, we used the prevalence for the entire sample, reasoning that the control groups in these studies are not necessarily more representative than the treatment or case groups. Notably, of the eight studies employing the HADS, two employed a more stringent threshold to define "clinically significant" depressive symptoms (i.e., a score >11, rather than the more common threshold of >8). The median point prevalence of "clinically significant" depressive symptoms post-ICU was 28% (range 8–57%) (14 studies, $n = 1{,}213$). The point prevalence of any clinician-diagnosed depressive disorder 2 months post-ICU was 33% (1 study, $n = 134$) [18]. In the five studies that explicitly tested for the effect of time on symptoms of depression [12, 14, 15, 18, 20], three found significant decreases in mean/median depression scores during the first 2–12 months post-ICU [12, 14, 15] (Table 3).

Potential risk factors for depressive symptoms/disorder

Patient-specific factors

Only one [14] of three studies [14, 18, 21] ($n = 80$–153) found a significant association between female sex and post-ICU depressive symptoms (measured at hospital

Table 3 Measurements of depressive symptoms, ordered by follow-up time

Study	Past psychiatric illness	Instrument	Follow-up in months	No. at follow-up	Mean (sd) or *median* (*IQR*) score	Cut-off score	Point prevalence (%)
Jackson et al. [11]	Excluded	GDS-SF	0 6	34	5 (3)	6	14 24
Samuelson et al. [12]	–	HADS	0.16 2	226	*4* *1*	11	8
Jones et al. [13]	18%	HADS	0.5 2	45 30	6 6 (5), *4*	– 8	– 24
Rattray et al. [14]	–	HADS	0.75 6 12	80 80 80	7 (4) 5 (4) 5 (4)	8	36 26 27
Boyle et al. [15]	–	CES-D	1 6	66 52	19 (10) 14 (10)	16	61 34
Guentner et al. [16]	–	CES-D	1.5–11[a]	30	–	16	57
Jones et al. [17]	–	HADS	2 6	63, 51[b], 114[c] 58, 44[b]. 102[c]	–	11	12, 25[b], 18[c] 10, 12[b], 11[c]
Weinert et al. [18]	27%[d], 34%[e], 33%[f]	CES-D	2 6	153 90	11, *8* 11, *6*	16	27 33
		SCID	2	134	N/A	N/A	33[g]
Young et al. [19]	Excluded	HADS	3	20	–	8	15
Sukantarat et al. [20]	–	HADS	3 9	51 45	7 (5) 7 (5)	8	35 47
Eddleston et al. [21]	–	HADS	3	143	–	8	10
Chelluri et al. [22]	–	CES-D	12	154	12 (11), *8*, (*4*, *20*)	16	32
Kress et al. [23]	38%, 11%[b], 22%[c]	BDI-II	14, 12[b]	13, 19[b], 32[c]	14 (10), 17 (11)[b]	17	38, 53[b], 47[c]
Scragg et al. [24]	–	HADS	13 (6), 3–21[a]	80	–	8	30

BDI-II Beck Depression Inventory-II, *CES-D* Center for Epidemiologic Studies Depression Scale, *GDS-SF* Geriatric Depression Rating Scale-Short Form, *HADS* Hospital Anxiety and Depression Scale, *IQR* interquartile range, N/A not applicable, *SCID* Structured Clinical Interview for DSM-IV, *sd* standard deviation, – not reported

[a] Range, [b]Control group values (for randomized-controlled trials and case–control studies), [c]Entire sample, [d]Percentage of patients who had a proxy identify them as depressed most of the day for 2 weeks in the month pre-ICU, [e]Percentage of patients who had been seen for psychiatric problems in their lifetime, [f]Percentage of patients who had been prescribed an antidepressant medication in the last 6 months pre-ICU, [g]Depressive diagnoses included depressive disorder not otherwise specified (21 patients), single major depressive episode (13 patients), recurrent major depression (3 patients), mood disorder due to a general medical condition (6 patients), and bipolar depression (1 patient)

discharge, Table 4). None of three studies found an association between age and depression [14, 18, 20] ($n = 51$–153).

Only one study examined premorbid psychopathology or physical functioning as a risk factor for post-ICU depressive symptoms [18]. Proxy-reported depressed mood in the month before ICU predicted depressive symptoms at 2 and 6 months post-ICU, though antidepressant prescription in the 6 months before ICU did not predict post-ICU depressive symptoms. Poor pre-ICU physical functioning also predicted post-ICU depressive symptoms [18].

ICU illness and treatment factors

Only one study examined ICU admission diagnosis as a risk factor for post-ICU depression; no association was evident [13]. ICU length of stay was not a significant predictor in any of the three studies [13, 14, 20]. Severity of illness at ICU admission, as measured by the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, was not a significant predictor in any of the three studies [13, 14, 20]. The in-ICU duration of sedation [13] and interruption of sedation [23] were not associated with post-ICU depressive symptoms.

Table 4 Potential risk factors for depressive symptoms

Study (n)	Measure of association	Potential risk factor	Outcome: depressive symptoms/disorder
Jackson et al. [11] ($n = 34$)	Wilcoxon rank sum test		GDS-SF scores
		(a) Cognitive impairment (+ vs. −) at hospital d/c	(a) Mean 6 versus 4 at hospital d/c, $P = 0.04$ 27% vs. 8% depressed)
		(b) Cognitive impairment (+ vs. −) at 6 months	(b) Mean 6 versus 3 at 6 months, $P = 0.02$ (36% vs. 17% depressed)
		(c) Degree of change in GDS-SF scores over 6 months, impaired versus non-impaired	(c) −0.2 versus 0.5, $P = 0.76$
Samuelson et al. [12] ($n = 226$)	Mann–Whitney U	(a) Time since hospital d/c (5 days vs. 2 months)	(a) Median HADS-D 4 versus 1, $P < 0.0001$
		(b) Recall of "extremely stressful" ICU nightmares 5 days post-ICU	(b) $r > 0.2$ (with HADS-D at 2 months), $P < 0.01$
	Spearman's correlation	(c) Recall of "extremely stressful" ICU fearfulness 5 days post-ICU	(c) $r > 0.2$ (with HADS-D at 2 months), $P < 0.01$
		(d) Type of ICU memory (e.g., factual vs. delusional) 5 days post-ICU	(d) NS
		(e) IES-R score at 2 months (PTSD symptoms)	(e) $r = 0.66$ (with HADS-D at 2 months), $P < 0.0001$
	Mann–Whitney U	(f) Recall of "extremely stressful" ICU nightmares (+ vs. −) 5 days post-ICU	(f) Median HADS-D 4 versus 1 at 2 months, $P = 0.001$
		(g) Recall of "extremely stressful" ICU fearfulness (+ vs. −) 5 days post-ICU	(g) Median HADS-D 5 versus 1 at 2 months, $P = 0.02$
Jones et al. [13] ($n = 30$–45)	χ^2	(a) ICU diagnostic group	(a) $P = 0.23$
	Univariate ANOVA	(b) No factual memories of ICU + "delusional memories" versus factual memories of ICU + "delusional memories" versus no "delusional memories" 2 weeks post-ICU	(b) Mean HADS-D 13 versus 4 versus 3 at 2 weeks, $P = 0.0001$
		(c) ICU LOS, APACHE II, days of sedation/opiates	(c) NS at 2 or 8 weeks
Rattray et al. [14] ($n = 80$)	Repeated measures ANOVA	(a)Time since hospital d/c (d/c vs. 6 vs. 12 months)	(a) Mean HADS-D 7 versus 5 versus 5, $P = 0.001$
	Pearson's correlation	(b) Female sex	(b) $r = 0.27$ with HADS-D at hospital d/c, $P < 0.02$
		(c) Age	(c) NS
		(d) APACHE II	(d) NS
		(e) ICU LOS	(e) NS
		(f) Hospital LOS	(f) NS
		(g) Recall of ICU experiences (hospital d/c)	(g) $r = -0.26$ with HADS-D at 6 months, $P = 0.01$
	Multivariable regression	(h1) HADS-D (hospital d/c)	(h1) $\beta_{st} = 0.44$ with HADS-D at 6 months, $P < 0.001$
		(h2) Frightening ICU memories(hospital d/c)	(h2) $\beta_{st} = 0.06$ with HADS-D at 6 months, $P = 0.54$
		(h3) Recall of ICU experiences (hospital d/c)	(h3) $\beta_{st} = -0.21$ with HADS-D at 6 months, $P = 0.05$
		(h4) Satisfaction with ICU care (hospital d/c)	(h4) $\beta_{st} = -0.05$ with HADS-D at 6 months, $P = 0.65$
		(i1) HADS-D (hospital d/c)	(i1) $\beta_{st} = 0.40$ with HADS-D at 12 months, $P < 0.001$
		(i2) Awareness of ICU surroundings (hospital d/c)	(i2) $\beta_{st} = -0.02$ with HADS-D at 12 months, $P = 0.88$
		(i3) Recall of ICU experiences (hospital d/c)	(i3) $\beta_{st} = -0.10$ with HADS-D at 12 months, $P = 0.37$
		(i4) Satisfaction with ICU care (hospital d/c)	(i4) $\beta_{st} = -0.09$ with HADS-D at 12 months, $P = 0.46$
Boyle et al. [15] ($n = 52$)	Student's paired t test	(a) Time since hospital d/c (1 vs. 6 months)	(a) Mean CES-D 19 versus 14, $P = 0.03$
		(b) Chronic pain + versus − at 6 months ($n = 47$)	(b) Mean CES-D 14 versus 10 at 6 months, $P = 0.67$

Table 4 continued

Study (*n*)	Measure of association	Potential risk factor	Outcome: depressive symptoms/disorder
Jones et al. [17] ($n = 114$)	Fisher's exact test	(a) No self-help rehabilitation manual ($n = 114$)	(a) 25 versus 12% (HADS-D > 11 at 2 months), $P = 0.07$
	One-way ANOVA	(b) Antidepressant + no self-help rehabilitation manual versus antidepressant + self-help manual ($n = 21$)	(b) Higher mean HADS-D at 2 months, $P = 0.004$
	Fisher's exact test	(c) No self-help rehabilitation manual ($n = 102$)	(c) 12 versus 10% (HADS-D > 11 at 6 months), NS
Weinert et al. [18] ($n = 90$–153)	Least squares regression		CES-D scores (square root) at 2 months
		(a) Age	(a) $\beta = -0.006$, $P = 0.46$
		(b) Male sex	(b) $\beta = -0.12$, $P = 0.66$
		(c) Pre-ICU physical functioning	(c) $\beta = -0.01$, $P = 0.01$
		(d) Antidepressant in 6 months before ICU	(d) $\beta = 0.53$, $P = 0.09$
		(e) Proxy report of depressed mood in the month before ICU	(e) $\beta = 1.07$, $P = 0.002$
			CES-D scores (square root) at 2 and 6 months
	Repeated-measures regression analysis	(f) Time since hospital d/c (2, 6 months)	(f) $\beta = -0.007$, $P = 0.97$
		(g) Age	(g) $\beta = -0.007$, $P = 0.45$
		(h) Male sex	(h) $\beta = 0.07$, $P = 0.78$
		(i) Pre-ICU physical functioning	(i) $\beta = -0.01$, $P = 0.03$
		(j) Antidepressant in 6 months before ICU	(j) $\beta = 0.54$, $P = 0.08$
		(k) Proxy report of depressed mood in the month before ICU	(k) $\beta = 0.95$, $P = 0.004$
	Relative risk (RR)	(l) Depression at 2 months post-ICU	(l) Depression at 6 months, RR = 4.2, 95% CI = 2–7.7
		(m) Change in physical functioning from pre-ICU baseline to 2 months post-ICU	(m) NS
	Spearman's correlation	(n) Improvement in physical functioning from 2 to 6 months post-ICU	(n) $r = -0.45$, $P < 0.001$
Sukantarat et al. [20] ($n = 51$)	Student's paired *t* test	(a) Time since hospital d/c (3 vs. 9 months)	(a) 35 versus 47% (HADS-D score ≥ 8), $P = 0.52$
	Spearman's correlation	(b) HADS anxiety score at 3 and 9 months	(b) HADS-D at same time points, $P < 0.0001$
		(c) IES intrusion and avoidance scores (PTSD symptoms) at 3 and 9 months	(c) HADS-D at same time points, $P < 0.002$
		(d) Physical symptom score at 3 and 9 months	(d) HADS-D at same time points, $P < 0.001$
		(e) Age, ICU LOS, APACHE II score, TISS points	(e) NS
Eddleston et al. [21] ($n = 143$)	Fisher's exact test	Female versus male sex	12 versus 8%, NS
Kress et al. [23] ($n = 32$)	Student's paired *t* test or Mann–Whitney *U*	Control versus daily sedative interruption	BDI-II mean score 17 versus 14, $P = 0.36$

ANOVA Analysis of variance, *APACHE II* Acute Physiology and Chronic Health Evaluation II, *BDI-II* Beck Depression Inventory-II, β regression coefficient, β_{st} standardized linear regression coefficient in multivariable model, *CES-D* center for Epidemiologic Studies Depression Scale, *CI* confidence interval, *d/c* discharge, *df* degrees of freedom, *GDS-SF* Geriatric Depression Scale-Short Form, *HADS* Hospital Anxiety and Depression Scale, *HADS-D* HADS depression subscale, *ICU* intensive care unit; *IES* Impact of Events Scale, *IES-R* Impact of Events Scale-Revised, *LOS* length of stay, *NS* not significant, *PTSD* posttraumatic stress disorder, *TISS* therapeutic Intervention Scoring System, – not reported

Early post-ICU memories of in-ICU experiences

Three studies examined early post-ICU memories of in-ICU experiences as predictors of depressive symptoms. Poor recall of the ICU at hospital discharge, but not memories of frightening experiences, predicted depressive symptoms 6 months post-ICU in one study [14]. Memories of "extremely stressful" in-ICU nightmares or fearfulness 5 days post-ICU predicted depressive symptoms 2 months post-ICU in another study [12]. Memories of in-ICU psychotic/nightmare experiences were cross-sectionally associated with more

Table 5 Associations of depressive symptoms/disorder and health-related quality of life

Study (*n*)	Measure of association	Follow-up in months	Depressive symptoms/disorder instrument	Health-related quality of life instrument(s)	Test value (*s*)
Weinert et al. [18] ($n = 153$)	*t* test	2	SCID incident major depressive episode or depressive disorder not otherwise specified versus no active psychiatric diagnosis	SF-36 PF	14 versus 43; $P < 0.001$
Sukantarat et al. [20] ($n = 51$)	Spearman's correlation	3	HADS depression subscale	EQ-5D VAS	$r = -0.63$, $P < 0.001$
				SF-36 PCS	$r = -0.44$, $P < 0.005$
				SF-36 MCS	$r = -0.48$, $P < 0.001$
		9		EQ-5D VAS	$r = -0.67$, $P < 0.001$
				SF-36 PCS	$r = -0.44$, $P < 0.005$
				SF-36 MCS	$r = -0.62$, $P < 0.001$

EQ-5D VAS EQ-5D quality of life instrument Visual Analogue Scale, *HADS* Hospital Anxiety and Depression Scale, *SCID* Structured Clinical Interview for DSM-IV, *SF-36 MCS* Short Form-36 Mental Component Summary, *SF-36 PCS* Short Form-36 Physical Component Summary, *SF-36 PF* Short-Form-36 Physical Functioning domain

depressive symptoms 14 days after ICU discharge in one study [13].

Post-ICU psychiatric symptoms

Psychiatric symptoms at hospital discharge and beyond were prospective predictors or cross-sectional correlates of post-ICU depressive symptoms in five of five studies [11, 12, 14, 18, 20]. Depressive symptoms at hospital discharge were a strong predictor of depressive symptoms at both 6 and 12 months post-ICU in one study [14], and depressive symptoms at 2 months post-ICU were a strong predictor of depressive symptoms at 6 months post-ICU in another study [18]. Post-ICU PTSD symptoms were strongly correlated cross-sectionally with post-ICU depressive symptoms in two studies [12, 20]; post-ICU non-specific anxiety symptoms were also strongly correlated cross-sectionally with post-ICU depressive symptoms in the one study that examined this issue [20]. Finally, cognitive impairment at 6 months was associated with more depressive symptoms in one study that examined this association [11].

Post-ICU physical functioning

Post-ICU physical functioning was examined as a correlate of post-ICU depressive symptoms in two studies [18, 20]. Although change in physical functioning from hospital discharge to 2 months post-ICU was not a significant predictor of post-ICU depressive symptoms, change in physical functioning from 2 to 6 months post-ICU was a significant predictor of depressive symptoms at 6 months in one study [18]. In the other study, increased physical symptoms, as measured by a non-validated symptom scale, were significant predictors of depressive symptoms at 3 and 9 months post-ICU [20].

Association of depressive symptoms/disorder and health-related quality of life

While eight studies evaluated HRQOL [11, 15, 16, 18–20, 22, 23], only two studies examined the relationships between depressive symptoms and HRQOL [18, 20] (Table 5). Symptoms of depression were associated with lower HRQOL, as measured with the Medical Outcomes Study Short Form-36 (SF-36) [25], in both studies. In one study [18], diagnoses of SCID incident major depressive episode or depressive disorder not otherwise specified were associated with a lower SF-36 physical functioning domain score. In the other study [20], symptoms of depression were more strongly associated with mental health HRQOL domains measured via the mental component summary score than with physical health HRQOL domains measured via the physical component summary score, although associations with the latter were also substantial.

Discussion

This systematic review of depressive symptoms in general ICU survivors highlights three important issues. First, the prevalence of substantial depressive symptoms is quite high in the year after ICU care. Across studies, the median point prevalence of questionnaire-ascertained "clinically significant" depressive symptoms was 28% (14 studies, $n = 1{,}213$), and the point prevalence of clinician-diagnosed depressive disorder was 33%. These

prevalences are substantially higher than the 7% 1-year prevalence of major depressive disorder in a recent study of US adults that utilized non-clinicians administering a structured interview [26], and are also considerably greater than the 8 and 4% prevalences of "clinically significant" depressive symptoms ascertained in non-clinical samples using two of the same questionnaires described in this study, the HADS and the GDS-SF, utilizing similar cutoffs for case definition [27, 28]. In addition, these figures are higher than the median point prevalence of substantial depressive symptoms in survivors of acute myocardial infarction (14% in hospital, lower thereafter) [29] in studies using the HADS with the lower threshold (score > 8) for case definition, and are also higher than the point prevalence of these symptoms in a recent systematic review of burn injury survivors (4–13% using the HADS with variable thresholds for case definition) [30]. The median point prevalence of "clinically significant" depressive symptoms reported here is similar to that in survivors of ALI/ARDS [8]. Notably, our median point prevalence estimate is likely an underestimate for the population of all general ICU survivors since several of the studies excluded patients with pre-ICU psychopathology.

Second, although ten studies examined potential risk factors for post-ICU depressive symptoms, many of the specific risk factors examined were unique to particular studies. Nevertheless, in cases where similar risk factors were considered across multiple studies, a few conclusions can be drawn: (1) neither sex nor age were consistent risk factors; (2) severity of illness at ICU admission was consistently not a risk factor; and (3) early post-ICU depressive symptoms were a strong risk factor for subsequent post-ICU depressive symptoms. Interestingly, although ICU treatment factors such as duration of sedation and ICU length of stay may be associated with increased depressive symptoms in ALI survivors [8], similar associations were not evident in the three studies that examined this issue in our review [13, 14, 20].

Third, post-ICU depressive symptoms may have substantial associations with both physical and mental health aspects of quality of life on HRQOL. Though only two studies addressed this issue, the results are consistent with findings in ALI/ARDS survivors [8], and with the general literature on the effect of depression on HRQOL [6, 31]. More detailed discussions of HRQOL after critical illness and measurement instruments can be found in prior publications [3, 4]; additional research is needed to understand the nature of these associations, as well as to understand other associations between depressive symptoms post-ICU and function. For instance, there is extensive research demonstrating that untreated depression is associated with worse outcomes for patients with chronic medical illnesses and with lower adherence to treatment regimens for these diseases [32]; similar research in patients surviving critical illnesses would be valuable.

The existing literature has several important limitations. First, only a modest percentage of patients eligible to participate in these studies did so, introducing the potential for selection bias. Also, 13 of the 14 studies relied exclusively on questionnaires (i.e., screening instruments) to estimate the burden of depressive symptoms in-ICU survivors. To our knowledge, only the CES-D has been validated against clinician diagnoses in the post-ICU setting [18]. Future studies of depressive symptoms in ICU survivors should utilize expert clinicians to conduct diagnostic interviews in larger cohorts, to more definitively estimate prevalence and incidence, and to evaluate the psychometric properties of other existing questionnaires (e.g., the HADS, which has been used most commonly) in this setting. In addition, the mental health domains of the SF-36 quality of life instrument may measure some of the same symptoms as the depression measures [33]. Hence, it may be difficult to know if an association between depressive symptoms and mental health aspects of quality of life reflect overlapping constructs; nevertheless, there are also associations between depressive symptoms and physical health aspects of quality of life, though the directionality of any cause–effect relationship is unclear.

Additional research is necessary to understand pre-ICU risk factors for post-ICU depression. Since prior anxiety and depressive disorders are potent risk factors for depression [34], it is striking that only one study examined survivors' pre-ICU psychopathology (specifically, depression shortly before ICU admission) as a risk factor for post-ICU depression [18]. Remarkably, no study evaluated personality traits as a predictor of post-ICU depressive symptoms. High neuroticism (a general tendency to experience negative emotions) is a strong predictor of depression in the setting of stress [35], and future studies should explicitly assess this variable as a potential risk factor.

Potential ICU-related risk factors for post-ICU depression also require further research. Weinert [36] hypothesized that post-ICU depression is due to neuronal changes in the context of critical illness. However, potential etiologic factors such as hypoxia, inflammatory cytokines, or stress on the hypothalamic–pituitary–adrenal axis have not been examined in this context. The finding that critical illness-induced cognitive impairment is associated with depressive symptoms [11] may support the hypothesis of direct neuronal involvement in post-ICU depression. Also consistent with this hypothesis, our group recently found that in-ICU hypoglycemia was a predictor of depressive symptoms at 3 months after ALI/ARDS [37]. In addition, delirium is very common in the ICU [38], and patients may be at greater risk for depression following episodes of delirium [39]. Factors related to physical health and function, such as ICU-

acquired weakness, may also play a role in mental health outcomes. Further research is essential in order to clarify the role that these and other ICU-related factors may play.

In addition, post-ICU factors should be considered in any comprehensive model of post-ICU depression. Based on the limited available research, post-ICU depression may be associated with post-ICU physical functioning [18, 20]. Also, PTSD, which is common following ICU stays [9], may affect the development of depressive symptoms; depression and PTSD can frequently co-occur following a traumatic event [40], and major depressive disorder is the most frequent concomitant psychiatric condition in patients with PTSD [41]. Other factors, such as chronic medical illnesses, family/financial strain, as well as feelings of loss due to post-ICU cognitive and physical deficits, could also add risk for post-ICU depression; such factors should be examined in future studies.

The number of studies examining psychiatric morbidity following ICU stays has steadily increased over the last decade. Given this trend and the findings in this systematic review, we make several recommendations for future studies of psychopathology after critical illness. First, where possible, studies assessing the prevalence of psychiatric disorders post-ICU should utilize expert clinicians administering semi-structured diagnostic interviews, and such studies should also attempt to validate existing questionnaires against interview results. Second, assessments should be carried out at more than one time point to evaluate the natural history of post-ICU psychopathology. Third, future studies should assess pre-ICU psychiatric illness and personality traits as risk factors for post-ICU psychopathology and incorporate these factors into a comprehensive model, including in-ICU factors (e.g., sedatives) and post-ICU factors (e.g., physical and cognitive deficits).

Several potential limitations of this systematic review are noteworthy. First, confidence regarding the precision and validity of our findings should be tempered given the methodological limitations of the original studies, as described above. Second, although we summarized evidence that depressive symptoms may decrease over time after ICU discharge [12, 14, 15], we did not feel we could draw strong conclusions regarding the effect of time on prevalence of substantial depressive symptoms given the small number and heterogeneity of the existing studies. Third, although we excluded studies that focused exclusively on survivors from trauma, neurological, coronary, or surgical specialty ICUs, some patients in the reviewed studies did have trauma, neurologic, cardiac and surgical problems which may be important independent risk factors for depression; thus, we cannot conclude that the reported high prevalences of depressive symptoms are specific to critical illness and ICU treatment alone. Fourth, many of the specific risk factors reviewed were unique to particular studies, without external replication, limiting their generalizability. Future research in this field will benefit from new, more comprehensive reviews and studies of risk factors for depression. Moreover, it may be advantageous to specifically review studies of survivors from specialty ICUs to obtain a more complete understanding of risk factors and to evaluate if risk factors vary substantially by type of critical illness. Finally, despite a comprehensive search of 16,301 citations, potentially eligible studies may have been inadvertently omitted due to inconsistent indexing of eligible studies in electronic databases.

In conclusion, depressive symptoms are common in general ICU survivors and may negatively impact HRQOL. Although further research is necessary to more fully define risk factors for post-ICU depression, we can preliminarily conclude that sex, age and severity of illness at ICU admission are not risk factors, and early post-ICU depressive symptoms are a strong risk factor for subsequent depressive symptoms. Clinicians should recognize that symptoms of depression are common following intensive care, requiring collaboration between intensivists, primary care physicians, and psychiatrists to ensure prompt, comprehensive evaluation and treatment in order to reduce post-ICU morbidity and improve ICU survivors' quality of life.

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Appendix 1: Manually searched journals from January 2000 to October 2007

American Journal of Critical Care
American Journal of Psychiatry
American Journal of Respiratory and Critical Care Medicine
Archives of General Psychiatry
Biological Psychiatry
Critical Care
Critical Care Medicine
General Hospital Psychiatry
Intensive Care Medicine
JAMA
New England Journal of Medicine
Psychosomatic Medicine
Psychosomatics

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