Outcome of delirium in critically ill patients: systematic review and meta-analysis

Jorge I F Salluh,[1] Han Wang,[2] Eric B Schneider,[2] Neeraja Nagaraja,[2] Gayane Yenokyan,[3] Abdulla Damluji,[4] Rodrigo B Serafim,[1, 5] Robert D Stevens[6]

[1]D'OR Institute for Research and Education, Rio de Janeiro, Brazil

[2]Department of Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA

[3]Department of Biostatistics, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA

[4]Elaine and Sydney Sussman Cardiac Catheterization Laboratories, Cardiovascular Division, University of Miami Miller School of Medicine, Miami, FL, USA

[5]Department of Internal Medicine, Federal University of Rio de Janeiro, Rio de Janeiro, Brazil

[6]Department of Anesthesiology and Critical Care Medicine, Neurology, Neurosurgery, and Radiology, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA

Correspondence to:
R D Stevens rstevens@jhmi.edu

ABSTRACT

OBJECTIVES
To determine the relation between delirium in critically ill patients and their outcomes in the short term (in the intensive care unit and in hospital) and after discharge from hospital.

DESIGN
Systematic review and meta-analysis of published studies.

DATA SOURCES
PubMed, Embase, CINAHL, Cochrane Library, and PsychINFO, with no language restrictions, up to 1 January 2015.

ELIGIBILITY CRITERIA FOR SELECTION STUDIES
Reports were eligible for inclusion if they were prospective observational cohorts or clinical trials of adults in intensive care units who were assessed with a validated delirium screening or rating system, and if the association was measured between delirium and at least one of four clinical endpoints (death during admission, length of stay, duration of mechanical ventilation, and any outcome after hospital discharge). Studies were excluded if they primarily enrolled patients with a neurological disorder or patients admitted to intensive care after cardiac surgery or organ/tissue transplantation, or centered on sedation management or alcohol or substance withdrawal. Data were extracted on characteristics of studies, populations sampled, identification of delirium, and outcomes. Random effects models and meta-regression analyses were used to pool data from individual studies.

RESULTS
Delirium was identified in 5280 of 16 595 (31.8%) critically ill patients reported in 42 studies. When compared with control patients without delirium, patients with delirium had significantly higher mortality during admission (risk ratio 2.19, 94% confidence interval 1.78 to 2.70; P<0.001) as well as longer durations of mechanical ventilation and lengths of stay in the intensive care unit and in hospital (standard mean differences 1.79 (95% confidence interval 0.31 to 3.27; P<0.001), 1.38 (0.99 to 1.77; P<0.001), and 0.97 (0.61 to 1.33; P<0.001), respectively). Available studies indicated an association between delirium and cognitive impairment after discharge.

CONCLUSIONS
Nearly a third of patients admitted to an intensive care unit develop delirium, and these patients are at increased risk of dying during admission, longer stays in hospital, and cognitive impairment after discharge.

Introduction

A high proportion of adults admitted to hospital experience delirium, a pathological alteration in cognition associated with inattention, a fluctuating course, and an underlying systemic illness, metabolic imbalance, or association with a drug (or withdrawal).[1 2] Delirium has been linked to adverse short term outcomes, including up to threefold increases hospital mortality and length of stay,[3-5] which place considerable burdens on caregivers[6 7] and healthcare services.[8 9] Delirium can also have long term consequences, with studies indicating an association between delirium and a higher likelihood of death,[10] functional disability,[11] admission to residential care, cognitive impairment,[12] and dementia after discharge.[13] The risk of delirium is particularly high in selected subsets of hospital patients such as elderly people and those with pre-existing cognitive impairments,[14] people with terminal illnesses,[15] patients undergoing major surgery,[16] and those who are admitted to an intensive care unit.[17]

The identification, prevention, and treatment of delirium are increasingly regarded as major public health priorities.[18] Delirium has been described as one of the most common types of organ dysfunction encountered in intensive care, though its prevalence is variable across studies.[3 19] Delirium can be overlooked, misdiagnosed, and its significance underestimated by healthcare providers working in intensive care.[20 21] Studies evaluating the relation between delirium and mortality have yielded inconsistent results, some reporting a significant association[4 22-24] and others not.[25-27]

Knowledge of the true magnitude of delirium and its associated burdens in critically ill patients would allow clinicians, researchers, and policymakers to allocate much needed resources towards reducing morbidity and mortality associated with delirium. We therefore conducted a systematic review of studies evaluating delirium in intensive care. We produced quantitative estimates of the prevalence of delirium in this setting and explored the association between delirium and

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Studies evaluating the relations between delirium in critically ill patients and mortality have yielded inconsistent results, some reporting a significant association and others not

WHAT THIS STUDY ADDS

Delirium is strongly associated with increased hospital mortality

Evidence also suggests a relation between delirium in the intensive care unit and long term cognitive impairment

short term clinical outcomes, specifically mortality in the intensive care unit and hospital, length of stay, and duration of mechanical ventilation. We also analyzed data on long term outcomes, including cognitive impairment after admission to intensive care.

Methods

Data sources and study selection

We carried out a systematic review and meta-analysis of prospective observational studies following the recommendations of the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group.[28] We searched PubMed (1966-2015), Embase (1974-2015), CINAHL (1982-2015), the Cochrane Library (2015), and PsychINFO (up to 2015). The most recent search was on 1 January 2015. We hand searched reference lists of retrieved articles, relevant review articles, and personal files. There was no language restriction. Search terms included delirium, acute confusional state, encephalopathy, organic brain syndrome, brain dysfunction, brain failure which were cross-referenced to the terms intensive care, intensive care unit, ICU, critical care, critical illness, critically ill, sepsis, acute respiratory distress, multiple organ system failure, and mechanical ventilation (see appendix 1 for details of search strategy). To be considered for inclusion, studies had to meet the following criteria:

- full length reports published in peer reviewed journals
- prospective observational cohorts or clinical trials of adult patients (aged >16) admitted to an intensive care unit
- patients were evaluated for delirium with a validated screening or diagnostic instrument: confusion assessment method (CAM)[29], confusion assessment method for the intensive care unit (CAM-ICU)[17], intensive care delirium screening checklist (ICDSC)[30], diagnostic and statistical manual of mental disorders 4th and 3th edition (DSM-IV and DSM-III)[2], and the Neelon and Champagne (NEECHAM) confusion scale[31]
- the relation between delirium and at least one of the following outcomes was reported: death in the intensive care unit or in hospital, length of stay in the intensive care unit or in hospital, duration of mechanical ventilation, or any outcome after hospital discharge.

We excluded articles if they did not have a control group of patients without delirium; if they were case studies or case series; if most enrolled patients (or the largest subgroup) had a primary central nervous system disorder (stroke, traumatic brain injury, central nervous system infections, brain tumors, recent intracranial surgery); if most enrolled patients were undergoing cardiac surgery or organ/tissue transplantation (patient subsets associated with pathophysiologically distinct forms of acute brain dysfunction); if most enrolled patients were experiencing alcohol or substance withdrawal; or if the primary study endpoint was the comparative efficacy or safety of different sedative drugs. RDS, JIFS, and AD screened citations identified by the initial search and selected potentially relevant titles for review of abstracts. From these, RDS, JIFS, and RBS then chose articles for review of full length reports. Figure 1 shows the study selection process.

Data extraction and study quality assessment

Three authors (RBS, JIFS, and AD) independently abstracted data from the selected articles. They recorded the following information (when available): study characteristics (study location, period of enrolment, type of intensive care unit, criteria for patient enrollment, number of patients enrolled, methods used to identify delirium, duration of follow-up); patients' characteristics (age, sex, premorbid cognitive and functional status, severity of illness scores, organ dysfunction scores, mechanical ventilation, renal replacement therapy); and outcomes (death in intensive care and in hospital, duration of mechanical ventilation, length of stay in intensive care, length of stay in hospital, and any reported endpoint after discharge). A fourth author (RDS) verified accuracy and reliability of the abstracted data by sampling 10% of the references selected at each stage the systematic search and evaluating extracted data against the original reference; any discrepancies were resolved by discussion among authors (RBS, JIFS, AD, RDS). If data were not reported, we planned to contact first or senior authors by email; this was not necessary as data points were readily available.

We used the Newcastle-Ottawa Scale to assess methodological quality of included studies. this scale has been validated for the assessment of observational
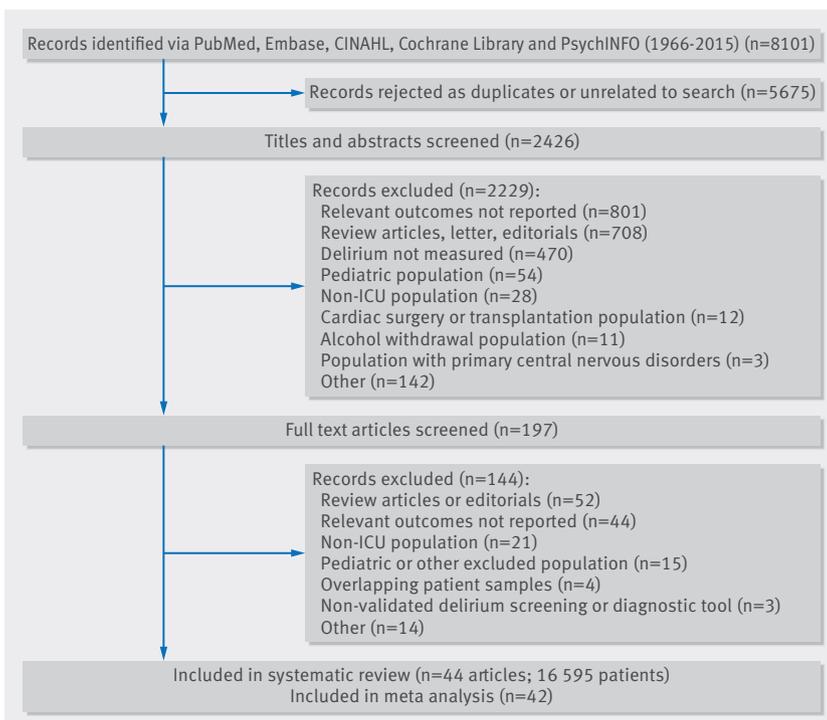

Fig 1 | Selection of studies on outcome of delirium in critically ill patients

studies in systematic reviews and meta-analyses.[32][33] The scale evaluates three aspects of study methods: the selection of study groups (range 0-4), the comparability of groups (range 0-1), and the quality of outcome ascertainment (range 0-3). The total score ranges from 0 to 8, and an acceptable methodological design is reflected by a score of >5. To rate the quality of randomized controlled trials we used the validated Cochrane Risk of Bias Tool.[34]

Patient involvement

There was no patient involvement in the design and development of this study.

Analytical approach

We estimated patients' characteristics and outcomes (mortality (in intensive care unit and hospital), length of stay (in intensive care unit and hospital), and duration of mechanical ventilation) in those with and without delirium. The principal outcome of interest was mortality (in intensive care unit and hospital). The strength of the relation between delirium and mortality was expressed as risk ratios with 95% confidence intervals. We selected risk ratio as a measure of effect for the binary outcome (death) as it is less prone to artificial inflation from heterogeneity than risk difference.[35] Studies with zero events were entered in the analysis to include all data and reduce bias.[36] To handle studies that reported zero outcomes for mortality, we performed a series of sensitivity analyses comparing Peto, Mantel-Haenszel, and inverse variance statistical methods with fixed and random effect with 0.5 continuity correction.[37][38] Inverse variance and Mantel-Haenszel methods yielded identical results; we have shown the Mantel-Haenszel data in the mortality forest plot. For continuous outcomes, we calculated weighted standard mean difference based on reported means or medians. Standard deviations were imputed as summarized by Thiessen Philbrook and colleagues.[39] Long term outcomes (mortality and cognitive impairment) were extracted from the selected studies; these results were summarized and crude data included in the systematic review.

We assessed heterogeneity by means of I² statistic, which reflects the amount of heterogeneity between studies over and above the sampling variation and is robust to the number of studies and choice of effect measure.[40] If the I² statistic indicated considerable heterogeneity (Cochrane Handbook, section 9.5.2, http://handbook.cochrane.org/), we combined the summary measures across the studies using a random effects model that assumed that the included studies represent a sample from a larger population of studies.[41] To explore heterogeneity between studies, we estimated the effect of study specific characteristics on outcome variables using meta-regression with the following predictors: age, proportion of women, and illness severity or organ failure score (either APACHE II or SOFA). The values of predictors were averaged across the groups with and without delirium. The outcome variable was the risk ratio of mortality, with age, sex, and severity as predictors. We assessed publication bias by inspecting funnel plots and using the modified Egger test for binary data.[42] Analyses were performed with STATA version 12 and RevMan version 5.0.

Results

The literature search produced 8101 citation titles, of which we screened 2426 potentially relevant abstracts, yielding 197 articles for detailed analysis; of the latter, 44 articles (16 595 patients) met our criteria and were included in the systematic review. In two instances (Ely and colleagues[3] and Milbrandt and colleagues,[8] and Marquis and colleagues[43] and Ouimet and colleagues[44]), a single study population was reported on in two separate articles. Hence, the final systematic review included 44 reports on 42 patient samples; only those 42 samples were included in the meta-analysis.

Study characteristics

Detailed characteristics of the included studies are shown in appendix 2. There were 40 prospective observational cohorts[3 4 10 12 19 21-27 43-67] and two randomized controlled trials.[47 68] Study populations ranged in size from 37 to 1824 (mean 384, median 185) patients. Twenty nine studies were conducted in mixed medical-surgical intensive care units, five studies evaluated only surgical intensive care units and two studies evaluated only medical intensive care units; seven studies evaluated only mechanically ventilated patients. Most studies (34) evaluated short term outcomes (recorded at hospital discharge or earlier). Seven studies extended follow-up to later time points, including 60 days,[4] 180 days,[3] 12 months,[45 46 59 69] and 18 months.[48] Twenty five studies used multivariable approaches to adjust for the association between delirium and mortality.[3 4 10 12 22 23 25 43-45 47 49 50 54 56 57 60 61 64 66-68 70 71] Details of methodological quality of included studies according to the Newcastle-Ottawa Scale are provided in appendix 3. The data originally from two randomized trials[47 68] were evaluated as low risk of bias on all five components of the Cochrane tool.[34] The funnel plot suggested moderate publication bias in studies reporting on mortality (fig 2).
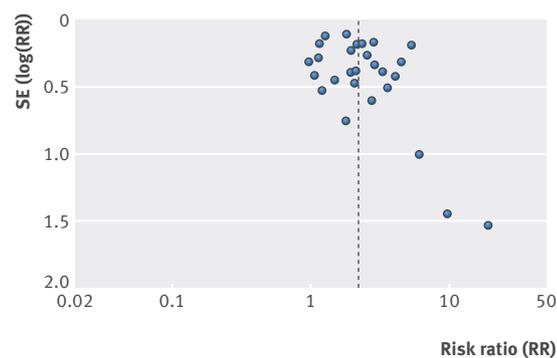

Fig 2 | Funnel plot of mortality in critically ill patients with delirium

Delirium identification and prevalence

The table shows delirium screening and prevalence data. Delirium was identified in 5280 of 16 595 patients (31.8%). Five studies reported on cognitive or psychological function before the index admission,[3 4 16 23 72] and three studies reported on pre-existing functional status.[3 16 23] The most common tool used for the diagnosis of delirium was the CAM-ICU, which was used in 28 studies,[3 4 9 10 12 16 21 24 26 45 47-50 53-58 60 63-67 69 71] while five studies used the ICDSC[25 27 43 68 70]. Other studies used CAM, DSM-IV, DSM-III, and the NEECHAM confusion scale.

Short term outcome

Figure 3 shows the association between delirium and mortality in the intensive care unit or in hospital. Twenty eight studies reported on mortality, and the

Delirium screening and prevalence data from studies of critically ill patients

Author	No of patients enrolled	Pre-existing cognitive or psychological function assessed (assessment method)?	Pre-ICU functional status assessed (assessment method)?	Delirium assessment tool	Physiologic scoring system	No of patients with delirium (%)
Kishi et al, 1995	238	No	No	DSM-III-R	NR	38 (15.97)
Aldemir et al, 2001	818	No	No	DSM-III-R	NR	90 (11.00)
Dubois et al, 2001	198	No	No	ICDSC	APACHE II	38 (19.19)
Ely et al, 2004; Milbrandt et al, 2004	224	Yes (mBDRS)	Yes (ADL)	CAM-ICU	APACHE II	183 (81.70)
Lin et al, 2004	102	No	No	CAM-ICU, DSM	APACHE III	22 (21.57)
Micek et al, 2005	93	No	No	CAM-ICU;	APACHE II	44 (47.31)
Roberts et al, 2005	185	No	No	ICDSC	APACHE II	84 (45.41)
Thomason et al, 2005	261	No	No	CAM-ICU	APACHE II	125 (47.89)
Ranhoff et al, 2006	401	Yes (MMSE)	Yes (ADL, APS)	CAM	APACHE II	117 (29.18)
Balas et al, 2007 a 2008	114	Yes (IQCODE, surrogate interview)	Yes (ADL, Katz)	CAM-ICU	APACHE II	34 (29.82)
Marquis et al, 2007; Ouimet et al, 2007a	537	No	No	ICDSC	APACHE II	189 (35.20)
Ouimet et al, 2007b	764	No	No	ICDSC	APACHE II	243 (31.81)
Plaschke et al, 2008	37	Yes	No	CAM-ICU	APACHE II	17 (45.95)
Angles et al, 2008	69	No	No	CAM-ICU	NR	41 (59.42)
Lin et al, 2008	151	Yes (BDRS)	No	CAM-ICU	APACHE III	31 (20.53)
Van Rompaey et al, 2008	172	No	No	CAM-ICU, NEECHAM	NR	34 (19.77)
Lat et al, 2009	134	No	No	CAM-ICU	APACHE II	84 (62.69)
Page et al, 2009	71	No	No	CAM-ICU	APACHE II	22 (30.99)
Spronk et al, 2009	46	Yes	No	CAM-ICU,	APACHE II	23 (50.00)
Van Rompaey et al, 2009	523	Yes (diagnosis of dementia)	No	NEECHAM	APACHE II	155 (29.64)
Van den Boogaard et al, 2010	1740	No	No	CAM-ICU	APACHE II	332 (19.08)
Tsuruta 2010	103	No	No	CAM-ICU	APACHE II	21 (20.39)
Shehabi 2010	354	No	No	CAM-ICU	NR	228 (64.41)
Salluh 2010	232	No	No	CAM-ICU	SAPS III	75 (32.33)
Heymann 2010	418	No	No	DDS	APACHE II	204 (48.80)
Girard 2010	77	No	No	CAM-ICU	APACHE II	65 (84.00)
Van den Boogaard et al, 2011	1613	No	No	CAM-ICU	APACHE II	411 (26.00)
Van den Boogaard et al, 2012 (CCM)	915	No	No	CAM-ICU	APACHE II	171 (18.60)
Sharma et al (2012)	140	No	No	DSM-IV	APACHE II	75 (54.00)
Tomasi et al (2011)	162	No	No	CAM-ICU, ICDSC	APACHE II	43 (26.50)
Serafim et al (2012)	467	No	No	CAM	APACHE II	43 (9.20)
Tsuruta et al, 2014	180	No	No	CAM-ICU	APACHE II	115 (64.00)
Almeida t al, 2014	170	No	No	CAM-ICU	SAPS II, SOFA,	161* (91.00)
Van den Boogaard et al, 2014	1824	No	No	CAM-ICU	APACHE II	410 (22.50)
Lahariya et al, 2014	309	No	No	CAM-ICU, DSM-IV-TR	APACHE II, SOFA	81 (18.77)
Pisani et al, 2009	309	Yes	Yes	CAM-ICU	APACHE II	N/A
Pandharipande et al, 2013	821	Yes	Yes	CAM-ICU	APACHE II, SOFA	606 (74.00)
Brummel et al, 2014	126	Yes	Yes	CAM-ICU	APACHE II	105 (84.00)
Wolters et al, 2013	1101	No	No	CAM-ICU	APACHE IV, SOFA	412 (37.00)
Mehta et al, 2014	420	No	No	ICDSC	APACHE II	226 (53.80)
Klein Klouwenberg et al, 2014	1112	No	No	CAM-ICU	APACHE II	558 (50.20)
Yamaguchi et al, 2014	126	No	No	ICDSC	NR	35 (27.80)

DSM=diagnostic and statistical manual of mental disorders; ICDSC=intensive care delirium screening checklist; BDRS=Blessed dementia rating scale; mBDRS=modified Blessed dementia rating scale; CAM=confusion assessment method; CAM-ICU=confusion assessment method for the intensive care unit; IQCOD=informant questionnaire on cognitive decline in the elderly; NEECHAM=Neelon and Champagne confusion scale; MMSE=mini-mental status examination; APACHE=acute physiology and chronic health evaluation score; SOFA=sequential organ failure assessment score; ADL=activity of daily living

	No of events/total				
Study or Subgroup	Patients with delirium	Patients without delirium	Mantel-Haenszel random risk ratio (95% CI)	Weight (%)	Mantel-Haenszel random risk ratio (95% CI)
Almeida 2014	110/161	3/9		3	2.05 (0.81 to 5.19)
Dubois 2001	6/38	24/160		3	1.05 (0.46 to 2.39)
Ely 2004; Milbrandt 2004	27/183	1/41		1	6.05 (0.85 to 43.25)
Kishi 1995	9/38	49/200		4	0.97 (0.52 to 1.80)
Klein 2014	94/558	40/554		6	2.33 (1.64 to 3.31)
Lat 2009	15/84	6/50		3	1.49 (0.62 to 3.59)
Lin 2004	14/22	26/80		5	1.96 (1.25 to 3.06)
Lin 2008	21/31	38/120		6	2.14 (1.50 to 3.06)
Marquis 2007; Ouimet 2007a	96/189	98/348		6	1.80 (1.45 to 2.24)
Mehta 2014	58/226	43/194		6	1.16 (0.82 to 1.63)
Micek 2005	14/44	8/49		4	1.95 (0.90 to 4.20)
Ouimet 2007b	76/243	128/521		6	1.27 (1.00 to 1.62)
Page 2009	8/22	5/49		3	3.56 (1.31 to 9.67)
Plaschke 2007	7/17	3/20		2	2.75 (0.84 to 9.00)
Ranhoff 2006	26/117	14/284		4	4.51 (2.44 to 8.32)
Roberts 2005	19/84	20/101		4	1.14 (0.65 to 1.99)
Salluh 2010	18/75	13/157		4	2.90 (1.50 to 5.60)
Serafim 2012	7/43	17/422		3	4.04 (1.78 to 9.20)
Sharma 2012	36/75	0/65		1	63.39 (3.97 to 1012.88)
Shehabi 2010	69/228	15/126		5	2.54 (1.52 to 4.25)
Spronk 2009	6/23	5/23		3	1.20 (0.43 to 3.38)
Thomason 2005	24/125	8/136		4	3.26 (1.52 to 7.00)
Tomasi 2011	10/43	13/119		4	2.13 (1.01 to 4.49)
Tsuruta 2010	2/21	0/82		1	18.86 (0.94 to 378.80)
Tsuruta 2014	8/115	0/65		1	9.67 (0.57 to 164.91)
Van den Boogaard 2010	54/332	80/1408		6	2.86 (2.07 to 3.96)
Van den Boogaard 2011	73/411	40/1202		5	5.34 (3.36 to 7.72)
Van Rompaey 2009	3/155	4/368		2	1.78 (0.40 to 7.86)
Total (95% CI)	910/3703	701/6953		100	2.19 (1.78 to 2.70)

Test for heterogeneity: τ^2=0.18, χ^2=96.96, df=27, P<0.001, I^2=72%
Test for overall effect: z=7.34, P<0.001

0.02 0.1 0 10 50

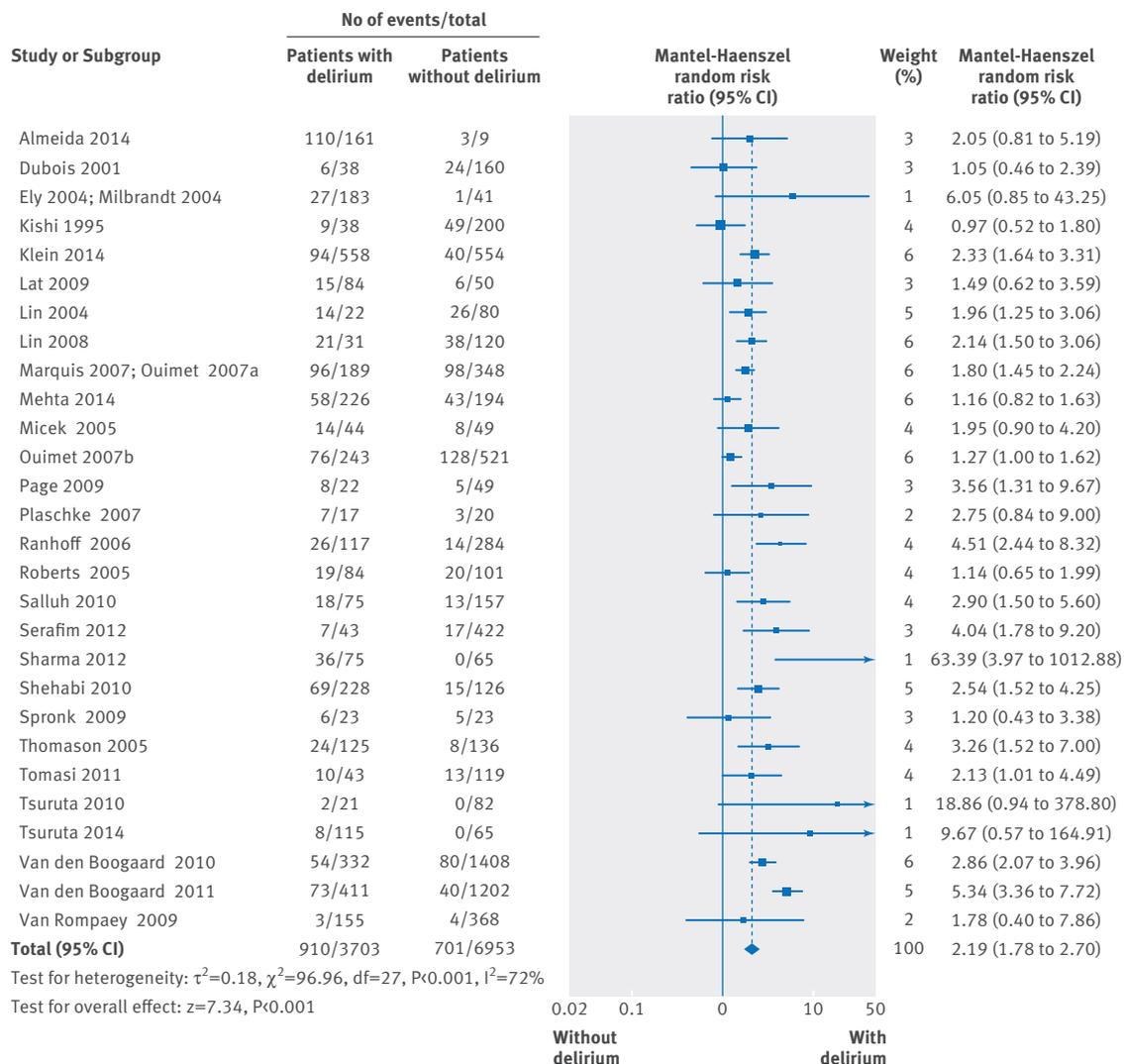Without delirium — With delirium

Fig 3 | Impact of delirium on hospital mortality in critically ill patients

overall risk ratio for death in patients with delirium was 2.19 (95% confidence interval 1.78 to 2.70; P<0.001). Severity of illness was rated with the APACHE II score in 31 studies and was higher in patients with delirium (mean 18.28 (SD 3.6) v 15.72 (SD 3.7); P=0.017). After adjustment for age, the proportion of female patients, and APACHE scores, the adjusted risk of mortality remained higher in the delirium group (effect size 2.72, 95% confidence interval 1.75 to 3.69).

Twenty eight studies reported length of stay in intensive care, which was significantly longer in patients with delirium (standardized mean difference 1.38, 95% confidence interval 0.99 to 1.77; P<0.001) compared with those without delirium (fig 4). This means that patients with delirium had a mean length of stay in intensive care that was 1 day and 9 hours longer than patients without delirium. Twenty two studies reported length of stay in hospital, which was significantly longer in patients with delirium (standardized mean difference 0.97, 0.61 to 1.33; fig 5).

Ten studies reported duration of mechanical ventilation, with point estimates indicating a longer duration

of mechanical ventilation in patients with delirium than in those without (1.79, 0.31 to 3.27; P<0.001; fig 6)—that is, the mean duration of mechanical ventilation was 1.79 days longer in patients with delirium.

Outcome after discharge

Eight studies reported follow-up after hospital discharge.[4 10 12 46 48 49 69 72] Two studies found increased mortality by six months in patients who had delirium when they were in intensive care (41.2% v 15.4%, P<0.001,[69] and 34% v 15%, P=0.03[3]), and one study showed that the number of days of delirium in intensive care was significantly associated with time to death within one year after admission to intensive care unit (hazard ratio 1.10, 95% confidence interval 1.02 to 1.18).[10] In a recent prospective cohort of 1101 people who survived a critical illness, no significant association was found between delirium in intensive care and mortality or quality of life at one year, after adjustment for sex, type of admission, APACHE IV score, and the cumulative SOFA score throughout the stay in intensive care.[49]

Study or Subgroup	Mean (SD)/total		Random standardized mean difference (95% CI)	Weight (%)	Random standardized mean difference (95% CI)
	Patients with delirium	Patients without delirium			
Aldemir 2001	10.7 (13.9)/90	5 (7)/728		4	0.71 (0.49 to 0.93)
Aldemir 2014	14 (7)/161	13 (10)/9		3	0.14 (-0.53 to 0.81)
Angles 2008	7.8 (1.1)/41	2.1 (0.2)/28		3	6.56 (5.33 to 7.78)
Balas 2007 and 2008	8.7 (11.8)/34	3 (1.8)/80		4	0.86 (0.44 to 1.28)
Dubois 2001	9.3 (12)/38	7 (7.9)/160		4	0.26 (-0.09 to 0.61)
Kishi 1995	15 (21.3)/38	5 (7)/200		4	0.94 (0.58 to 1.30)
Lat 2009	10 (7)/84	5 (3)/50		4	0.85 (0.49 to 1.22)
Lin 2008	13 (7)/31	8 (5)/120		4	0.91 (0.50 to 1.32)
Marquis 2007; Ouimet 2007a	10.8 (11.3)/189	3.9 (4)/348		4	0.93 (0.74 to 1.11)
Mehta 2014	12 (7)/226	8 (4)/194		4	0.69 (0.49 to 0.88)
Micek 2005	9.5 (5.8)/44	9.5 (5)/49		4	0.00 (-0.41 to 0.41)
Ouimet 2007b	11.5 (11.5)/243	4.4 (3.9)/521		4	0.98 (0.82 to 1.14)
Plaschke 2007	6.9 (6.6)/17	5 (3.6)/20		3	0.36 (-0.29 to 1.01)
Roberts 2005	10 (7.2)/84	6.8 (4.5)/101		4	0.54 (0.25 to 0.84)
Salluh 2010	22 (11)/75	7 (4)/157		4	2.12 (1.78 to 2.46)
Serafim 2012	6 (3)/43	2 (1)/422		4	3.04 (2.67 to 3.41)
Sharma 2012	7.9 (4.8)/75	4.5 (2.9)/65		4	0.84 (0.49 to 1.19)
Shehabi 2010	16 (7)/228	4 (3)/126		4	2.03 (1.77 to 2.29)
Spronk 2009	9 (6)/23	5 (3)/23		3	0.83 (022 to 1.43)
Thomason 2005	4 (3)/125	3 (2)/136		4	0.39 (0.15 to 0.64)
Tsuruta 2010	12 (6)/21	5 (3)/82		4	1.83 (1.29 to 2.38)
Van den Boogaard 2010	3 (1)/332	1 (1)/1408		4	2.00 (1.86 to 2.14)
Van den Boogaard 2011	6 (2)/411	1 (1)/1202		4	3.76 (3.59 to 3.94)
Van den Boogaard 2012	5 (2)/171	1 (1)/744		4	3.20 (2.98 to 3.42)
Van Rompaey 2008	17.5 (14.5)/34	5 (5.9)/138		4	1.50 (1.09 to 1.91)
Van Rompaey 2009	7.9 (11.5)/155	1.7 (2.3)/368		4	0.95 (0.75 to 1.14)
Wolters 2014	8 (5)/412	3 (2)/689		4	1.45 (1.31 to 1.59)
Yamaguchi 2014	7.1 (6)/35	3.4 (1.9)/91		4	1.04 (0.63 to 1.45)
Total (95% CI)	**3460**	**8259**		**100**	**1.38 (0.99 to 1.77)**

Test for heterogeneity: τ^2=1.04, χ^2=1636.83, df=27, P<0.001, I^2=98%
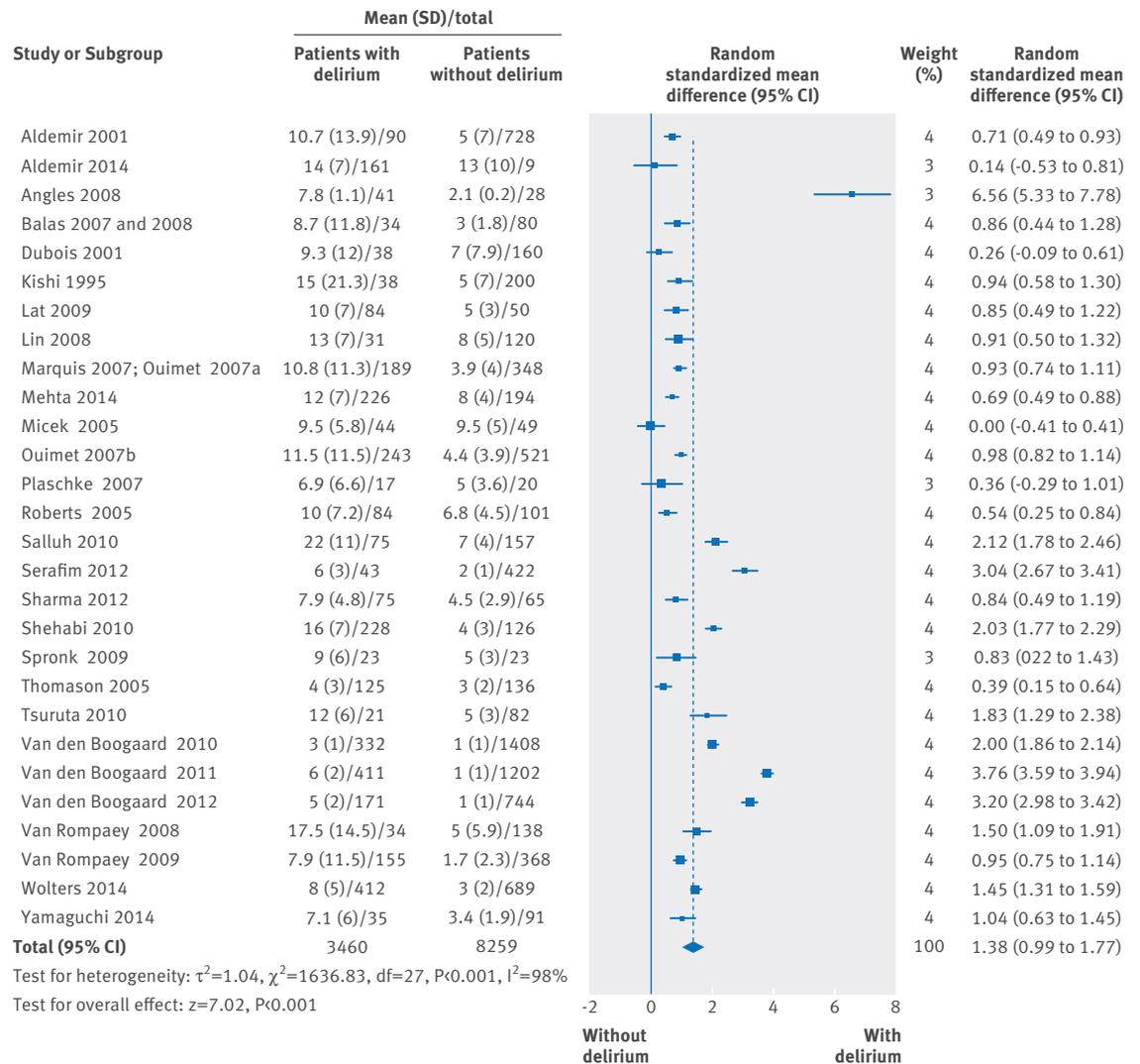Test for overall effect: z=7.02, P<0.001

Fig 4 | Impact of delirium on length of stay (days) in intensive care unit in critically ill patients

Regarding cognitive function after hospital discharge, Girard and colleagues reported that delirium was an independent predictor of worse scores on neuropsychological testing at follow-up at three months (P=0.02) and 12 months (P=0.03).[46] Pandharipande and colleagues found that longer duration of delirium was independently associated with worse global cognition at three and 12 months (P=0.001 and P=0.04, respectively) and worse executive function at three and 12 months (P=0.004 and P=0.007, respectively).[12] Van den Boogaard and colleagues found that duration of delirium was significantly correlated to memory and naming impairments 18 months after discharge.[48] Brummel and colleagues reported that in patients who survived after mechanical ventilation evaluated at 12 months, duration of delirium was associated with worse scores on activities of daily living and impaired perception of motor sensory function.[45]

Discussion

Principal findings

This systematic review and meta-analysis synthesized data on the prevalence of delirium in patients admitted to an intensive care unit and the association between delirium and outcomes of critically ill patients. We identified 42 studies enrolling a total of 16 595 patients. Delirium was detected in nearly a third of critically ill patients and was associated with increased hospital mortality, an association that persisted after adjustment for severity of illness. Delirium was also associated with longer length of stay and longer duration of mechanical ventilation. Despite the small number of studies that evaluated outcomes at more than one time point, available data suggest an association between delirium and cognitive impairment and mortality after discharge.

Strengths and limitation of study

Our study indicates that delirium identified in the intensive care unit is strongly associated with adverse outcomes, even after adjustment for illness severity. These findings are consistent with results of a previous systematic review[73] and expand them to include a much larger number of studies and patients (42 v 14 studies; 16 595 v 5891 patients). Our data, however, still do not clarify the nature of this association,
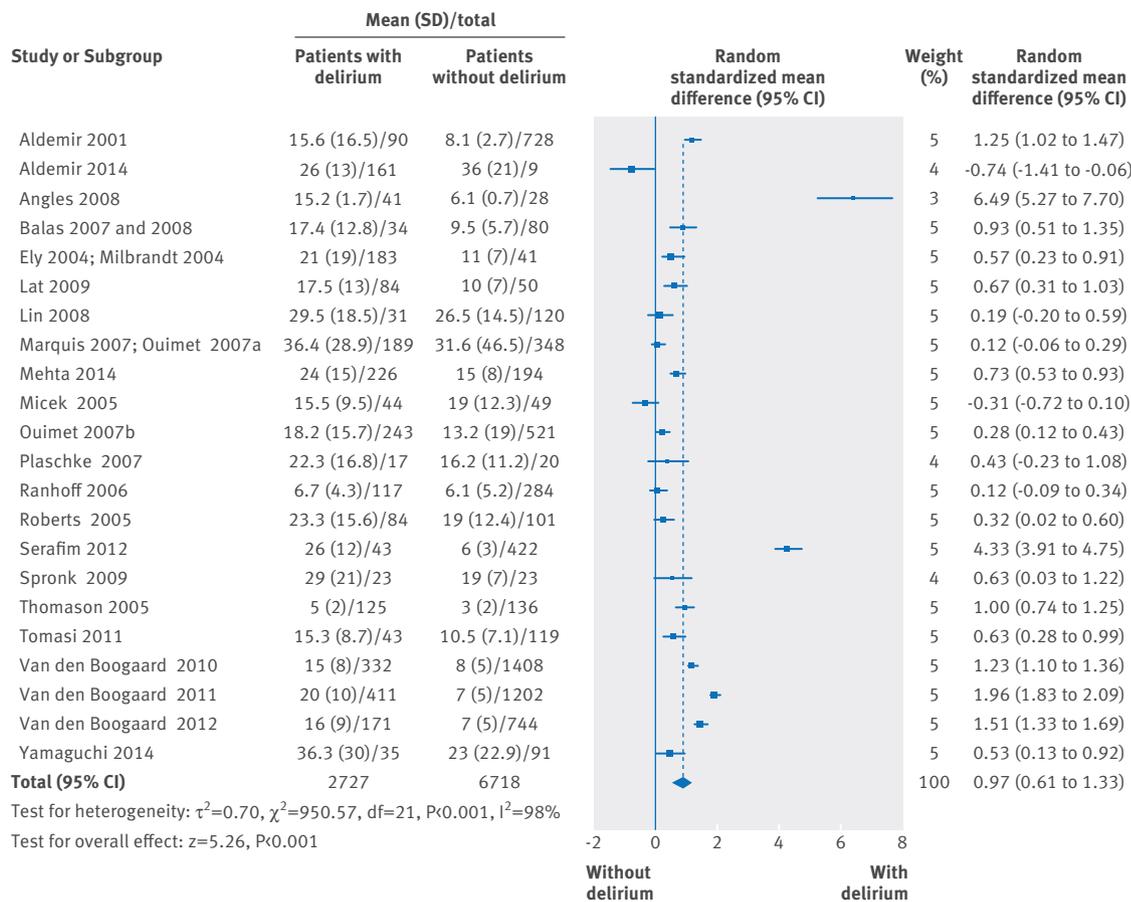
	Mean (SD)/total				
Study or Subgroup	Patients with delirium	Patients without delirium	Random standardized mean difference (95% CI)	Weight (%)	Random standardized mean difference (95% CI)
Aldemir 2001	15.6 (16.5)/90	8.1 (2.7)/728		5	1.25 (1.02 to 1.47)
Aldemir 2014	26 (13)/161	36 (21)/9		4	-0.74 (-1.41 to -0.06)
Angles 2008	15.2 (1.7)/41	6.1 (0.7)/28		3	6.49 (5.27 to 7.70)
Balas 2007 and 2008	17.4 (12.8)/34	9.5 (5.7)/80		5	0.93 (0.51 to 1.35)
Ely 2004; Milbrandt 2004	21 (19)/183	11 (7)/41		5	0.57 (0.23 to 0.91)
Lat 2009	17.5 (13)/84	10 (7)/50		5	0.67 (0.31 to 1.03)
Lin 2008	29.5 (18.5)/31	26.5 (14.5)/120		5	0.19 (-0.20 to 0.59)
Marquis 2007; Ouimet 2007a	36.4 (28.9)/189	31.6 (46.5)/348		5	0.12 (-0.06 to 0.29)
Mehta 2014	24 (15)/226	15 (8)/194		5	0.73 (0.53 to 0.93)
Micek 2005	15.5 (9.5)/44	19 (12.3)/49		5	-0.31 (-0.72 to 0.10)
Ouimet 2007b	18.2 (15.7)/243	13.2 (19)/521		5	0.28 (0.12 to 0.43)
Plaschke 2007	22.3 (16.8)/17	16.2 (11.2)/20		4	0.43 (-0.23 to 1.08)
Ranhoff 2006	6.7 (4.3)/117	6.1 (5.2)/284		5	0.12 (-0.09 to 0.34)
Roberts 2005	23.3 (15.6)/84	19 (12.4)/101		5	0.32 (0.02 to 0.60)
Serafim 2012	26 (12)/43	6 (3)/422		5	4.33 (3.91 to 4.75)
Spronk 2009	29 (21)/23	19 (7)/23		4	0.63 (0.03 to 1.22)
Thomason 2005	5 (2)/125	3 (2)/136		5	1.00 (0.74 to 1.25)
Tomasi 2011	15.3 (8.7)/43	10.5 (7.1)/119		5	0.63 (0.28 to 0.99)
Van den Boogaard 2010	15 (8)/332	8 (5)/1408		5	1.23 (1.10 to 1.36)
Van den Boogaard 2011	20 (10)/411	7 (5)/1202		5	1.96 (1.83 to 2.09)
Van den Boogaard 2012	16 (9)/171	7 (5)/744		5	1.51 (1.33 to 1.69)
Yamaguchi 2014	36.3 (30)/35	23 (22.9)/91		5	0.53 (0.13 to 0.92)
Total (95% CI)	2727	6718		100	0.97 (0.61 to 1.33)

Test for heterogeneity: τ^2=0.70, χ^2=950.57, df=21, P<0.001, I^2=98%

Test for overall effect: z=5.26, P<0.001

Fig 5 | Impact of delirium on length of stay (days) in hospital in critically ill patients

specifically whether delirium is a condition that is causatively linked to adverse outcome or whether it is a marker of severity of disease whose link to outcome is confounded by other measured or unmeasured variables. Despite this uncertainty, the results have major practical implications and provide an evidentiary basis for the recommendations of the PAD (pain, agitation, and delirium) guidelines recently put forward by the American College of Critical Care Medicine.[74] The burden of delirium could be reduced by a range of interventions such as rational titration of sedation and anesthesia,[75] reduced exposure to benzodiazepines,[76-78] promotion of sleep,[72] early implementation of mobility and occupational therapy in

	Mean (SD)/total				
Study or Subgroup	Patients with delirium	Patients without delirium	Random standardized mean difference (95% CI)	Weight (%)	Random standardized mean difference (95% CI)
Aldemir 2014	13 (6.5)/161	15 (5)/9		10	-0.31 (-0.98 to 0.36)
Lat 2009	7.5 (4)/84	3 (2)/50		10	1.32 (0.93 to 1.70)
Lin 2008	16 (6)/31	6 (3.5)/120		10	2.41 (1.93 to 2.89)
Mehta 2014	13 (8)/226	7 (4)/194		10	0.93 (0.72 to 1.13)
Micek 2005	6.8 (4.4)/44	3.9 (2.5)/49		10	0.82 (0.39 to 1.24)
Shehabi 2010	10.7 (5.8)/228	3.6 (1.8)/126		10	1.48 (1.24 to 1.73)
Spronk 2009	6 (4)/23	4 (1)/23		10	0.67 (0.08 to 1.27)
Tsuruta 2014	5 (3)/115	4 (3)/65		10	0.33 (0.03 to 0.64)
Van den Boogaard 2011	4.6 (0.9)/411	0.3 (0.2)/1202		10	8.85 (8.52 to 9.17)
Van den Boogaard 2012	7.15 (4.19)/171	3.75 (1.9)/744		10	1.36 (1.19 to 1.54)
Total (95% CI)	1494	2582		100	1.79 (0.31 to 3.27)

Test for heterogeneity: τ^2=5.62, χ^2=2074.39, df=9, P<0.001, I^2=100%

Test for overall effect: z=2.38, P=0.02

Fig 6 | Impact of delirium on duration (days) of mechanical ventilation in critically ill patients

7

the intensive care unit,[79] use of antipsychotic agents particularly in specific subgroups,[80-82] and bundled interventions.[83 84] Delirium is therefore a potentially modifiable risk factor for adverse outcomes in critically ill patients in hospital.

Given the prevalence and adverse consequences of delirium, our results underscore the need for prospective cohort studies with standardized methods to accurately and reliably detect and rate delirium and to characterize short and long term outcomes. Such studies need to be stringent in identifying all factors that could contribute to the onset, pathogenesis, and resolution of delirium associated with critical illness. Studies should be designed to allow discriminative analysis of subgroups of patients in intensive care who have different causes, severities, and durations of delirium.[71 85-87] Specific attention should be devoted to determining endpoint measures that are relevant from a biological, clinical, and process of care standpoints. The latter might include resource utilization, long term cognitive function, psychological status, functional status, and quality of life. Additionally, large and appropriately designed clinical trials are needed to evaluate the efficacy and safety of single and bundled interventions in reducing the incidence and burden of delirium in acutely ill populations.

The present study has some limitations. First, there was considerable heterogeneity in the meta-analysis, as reflected by the I^2 statistic. This is not unexpected as there were major differences between studies in the patient populations, the methods used to detect and rate delirium, and the timeframes for mortality—such differences could account for substantial differences in prevalence and mortality. Second, funnel plot asymmetry suggests the possibility of moderate publication bias in studies reporting on mortality, though this was observed in a small proportion of all patients (11%) and was not likely to have an important impact on the conclusions. Third, we did not conduct a grey literature search, which could lead to an overestimation of the effect size. Fourth, we excluded studies of patients after cardiac surgery and organ transplantation. Phenotypes of brain dysfunction or encephalopathy in these settings are each highly distinctive in terms of epidemiology, genetic and biological determinants, pathophysiology, natural history, and outcomes; we therefore decided to remove these groups and plan to report on them separately.

Another constraint in this study is that there are potentially unmeasured confounders such as differences in the timing and frequency of assessment of delirium, in the use of sedatives, and in the medical management of critically ill patients. While advances have been made in identifying delirium in such patients, it is also apparent that the construct of delirium and the currently available assessment tools for delirium do not sufficiently characterize the range of central nervous system alterations that could be encountered in the intensive care unit.[88] Subtypes of delirium including hypoactive

delirium or subsyndromal delirium, for example, might not be accurately or reliably detected with available delirium instruments.[1 17 21] Criteria used in defining and scoring delirium differ between studies and could overlap with those used to describe other syndromes of impaired cognitive function or consciousness. In particular, patients whose level of consciousness is depressed or who are comatose might be misclassified as having delirium or alternatively might be excluded altogether from neurocognitive assessment.[79]

Recent work has shown that the impact of delirium on mortality in intensive care is reduced after adjustment for time varying confounders, with most of the negative impact on outcomes confined to the group with persistent delirium.[71 85] Although this does not diminish the overall importance of the present data, it certainly points in a new direction for clinical research. Future studies should focus on patients with persistent delirium and its impact on neurocognitive outcomes and survival. Notwithstanding these limitations, the results of this meta-analysis show a robust association between the occurrence of delirium in the intensive care unit and adverse short term outcomes.

Conclusion

Delirium is common in a broad sample of critically ill patients and is strongly associated with increased hospital mortality even after adjustment for severity of disease. Evidence also suggests a relation between delirium in the intensive care unit and long term cognitive impairment. Research is needed to unravel the biological mechanisms governing these relations and to discover strategies and treatments that will reduce the burden of acute and long term brain dysfunction in critically ill populations.

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Appendix 1: Search strategy

Appendix 2: Characteristics of included studied

Appendix 3: Newcastle-Ottawa Scale ratings of included observational studies