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

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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, 95% confidence interval 1.78 to 2.70; P < 0.001), 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). Delirium has been linked to adverse short term outcomes, including up to threefold increases hospital mortality and length of stay, which place considerable burdens on caregivers and healthcare services. Delirium can also have long term consequences, with studies indicating an association between delirium and a higher likelihood of death, functional disability, admission to residential care, cognitive impairment, and dementia after discharge. The risk of delirium is particularly high in selected subsets of hospital patients such as elderly people and those with pre-existing cognitive impairments, people with terminal illnesses, patients undergoing major surgery, and those who are admitted to an intensive care unit.

The identification, prevention, and treatment of delirium are increasingly regarded as major public health priorities. 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. Delirium can be overlooked, misdiagnosed, and its significance underestimated by healthcare providers working in intensive care. Studies evaluating the relation between delirium and mortality have yielded inconsistent results, some reporting a significant association and others not.

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...
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)37, intensive care delirium screening checklist (ICDSC)30, diagnostic and statistical manual of mental disorders 4th and 3rd edition (DSM-IV and DSM-III)2, and the Neelon and Champagne (NEECHAM) confusion scale31
- 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
studies in systematic reviews and meta-analyses.\textsuperscript{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.\textsuperscript{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.\textsuperscript{35} Studies with zero events were entered in the analysis to include all data and reduce bias.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 I\textsuperscript{2} 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.\textsuperscript{40} If the I\textsuperscript{2} 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.\textsuperscript{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.\textsuperscript{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\textsuperscript{3} and Milbrandt and colleagues,\textsuperscript{8} and Marquis and colleagues\textsuperscript{30} and Ouimet and colleagues\textsuperscript{34}), 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\textsuperscript{14,10,12,19,21-27,43-66} and two randomized controlled trials.\textsuperscript{67,68} 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,\textsuperscript{180} 180 days,\textsuperscript{3,12} months,\textsuperscript{65-67,69,69} and 18 months.\textsuperscript{48} Twenty five studies used multivariable approaches to adjust for the association between delirium and mortality.\textsuperscript{15,46-50,52,54-67} 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\textsuperscript{67,68} were evaluated as low risk of bias on all five components of the Cochrane tool.\textsuperscript{34} The funnel plot suggested moderate publication bias in studies reporting on mortality (fig 2).

![Funnel plot of mortality in critically ill patients with delirium](image-url)
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,3,16,23,27 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, 10,12,16,21,24,26-28,47-50,53-58,60-63,67,69,71 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

| 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                                                                             | DSM-III-R                                           | NR                       | APACHE II                  | 38 (15.97)                       |
| Aldemir et al, 2001           | 818                     | No                                                                             | DSM-III-R                                           | NR                       | APACHE II                  | 90 (11.00)                       |
| Dubois et al, 2001            | 198                     | No                                                                             | ICDSC                                               | NR                       | APACHE II                  | 38 (19.19)                       |
| Ely et al, 2004, Milbrandt et al, 2004 | 224   | Yes (mBDRS)                                                                    | Yes (DL)                                            | CAM-ICU                  | APACHE II                  | 183 (81.70)                      |
| Lin et al, 2004               | 102                     | No                                                                             | CAM-ICU, DSM                                        | APACHE III               | 22 (21.57)                 |
| Micek et al, 2005             | 93                      | No                                                                             | CAM-ICU                                             | APACHE II                | 44 (47.31)                 |
| Roberts et al, 2005           | 185                     | No                                                                             | ICDC                                                | APACHE II                | 84 (45.41)                 |
| Thomason et al, 2005          | 261                     | No                                                                             | CAM-ICU                                             | APACHE II                | 125 (67.89)                |
| 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                                                                             | ICDSC                                               | APACHE II                | 189 (35.20)                |
| Ouimet et al, 2007b           | 764                     | No                                                                             | ICDC                                                | APACHE II                | 243 (31.81)                |
| Plaschke et al, 2008          | 37                      | Yes                                                                            | CAM-ICU                                             | APACHE II                | 17 (45.95)                 |
| Angles et al, 2008            | 69                      | No                                                                             | CAM-ICU                                             | NR                       | 41 (59.42)                 |
| Lin et al, 2008               | 151                     | Yes (BDRS)                                                                     | CAM-ICU, NEECHAM                                    | APACHE III               | 31 (20.53)                 |
| Van Rompae et al, 2008        | 172                     | No                                                                             | CAM-ICU                                             | NR                       | 34 (19.77)                 |
| Lat et al, 2009               | 134                     | No                                                                             | CAM-ICU                                             | APACHE II                | 84 (62.69)                 |
| Page et al, 2009              | 71                      | No                                                                             | CAM-ICU                                             | APACHE II                | 22 (30.99)                 |
| Sprown et al, 2009            | 46                      | Yes                                                                            | CAM-ICU                                             | APACHE II                | 23 (50.00)                 |
| Van Rompae et al, 2009        | 523                     | Yes (diagnosis of dementia)                                                    | NEECHAM                                             | APACHE II                | 155 (29.64)                |
| Van den Boogard et al, 2010   | 1760                    | No                                                                             | CAM-ICU                                             | APACHE II                | 332 (19.08)                |
| Tsuruta 2010                  | 103                     | No                                                                             | CAM-ICU                                             | APACHE II                | 21 (20.39)                 |
| Shehabi 2010                  | 354                     | No                                                                             | CAM-ICU                                             | NR                       | 228 (64.41)                |
| Sailuh 2010                   | 232                     | No                                                                             | CAM-ICU                                             | SAPS III                 | 75 (32.33)                 |
| Heymann 2010                  | 418                     | No                                                                             | DDS                                                 | APACHE II                | 204 (46.80)                |
| Girard 2010                   | 77                      | No                                                                             | CAM-ICU                                             | APACHE II                | 65 (84.00)                 |
| Van den Boogard et al, 2011   | 1613                    | No                                                                             | CAM-ICU                                             | APACHE II                | 411 (26.00)                |
| Van den Boogard et al, 2012 (CCM) | 915 | No                                                                             | CAM-ICU                                             | APACHE II                | 171 (18.60)                |
| Sharma et al (2012)           | 140                     | No                                                                             | DSM-IV                                              | APACHE II                | 75 (54.00)                 |
| Tomasi et al (2011)           | 162                     | No                                                                             | CAM-ICU, ICDC                                       | APACHE II                | 43 (26.50)                 |
| Serafin et al (2012)          | 467                     | No                                                                             | CAM                                                  | APACHE II                | 43 (9.20)                  |
| Tsuruta et al, 2014           | 180                     | No                                                                             | CAM-ICU                                             | APACHE II                | 175 (64.00)                |
| Almeida et al, 2014           | 170                     | No                                                                             | CAM-ICU                                             | SAPS II, SOFA            | 161 (91.00)                |
| Van den Boogard et al, 2014   | 1824                    | No                                                                             | CAM-ICU                                             | APACHE II                | 410 (22.50)                |
| Lahariya et al, 2014          | 309                     | No                                                                             | CAM-ICU, DSM-IV-TR                                  | APACHE II, SOFA          | 81 (18.77)                 |
| Pisani et al, 2009            | 309                     | Yes                                                                            | CAM-ICU                                             | APACHE II                | N/A                       |
| Pandharipande et al, 2013     | 821                     | Yes                                                                            | CAM-ICU                                             | APACHE II, SOFA          | 606 (74.00)                |
| Brummel et al, 2014           | 126                     | Yes                                                                            | CAM-ICU                                             | APACHE II                | 105 (84.00)                |
| Wolters et al, 2013           | 1101                    | No                                                                             | CAM-ICU                                             | APACHE IV, SOFA          | 412 (37.00)                |
| Mehta et al, 2014             | 420                     | No                                                                             | ICDC                                                | APACHE II                | 226 (53.80)                |
| Klein Klouwenberg et al, 2014 | 1112                    | No                                                                             | CAM-ICU                                             | APACHE II                | 558 (50.20)                |
| Yamaguchi et al, 2014         | 126                     | No                                                                             | ICDC                                                | 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; IQCODE=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)                      |
| Klein 1995        | 9/38                   | 49/200                    |                                          | 4          | 0.97 (0.52 to 1.80)                       |
| Lat 2009          | 15/84                  | 6/50                      |                                          | 6          | 2.33 (1.64 to 3.31)                       |
| Lin 2004          | 14/22                  | 26/80                     |                                          | 3          | 1.49 (0.62 to 3.59)                       |
| Lin 2008          | 21/31                  | 38/120                    |                                          | 5          | 1.96 (1.25 to 3.06)                       |
| Marquis 2007; Oulmet 2007a | 96/189   | 98/348                    |                                          | 6          | 2.14 (1.50 to 3.06)                       |
| Mehta 2014        | 58/226                 | 43/194                    |                                          | 6          | 1.80 (1.45 to 2.24)                       |
| Micek 2005        | 14/44                  | 8/49                      |                                          | 4          | 1.95 (0.90 to 4.20)                       |
| Oulmet 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)                       |
| Serafin 2012      | 7/43                   | 17/422                    |                                          | 3          | 4.04 (1.78 to 9.20)                       |
| Sharma 2012       | 36/75                  | 0/65                      | 1.63 (3.97 to 1012.88)                   | 5          | 2.54 (1.52 to 4.25)                       |
| Shehabi 2010      | 69/228                 | 15/126                    | 3.04 (1.03 to 3.38)                      | 3          | 1.20 (0.43 to 3.38)                       |
| Spronk 2009       | 6/23                   | 5/23                      | 2.13 (1.01 to 4.49)                      | 4          | 3.26 (1.52 to 7.00)                       |
| Thomason 2005     | 24/125                 | 8/136                     | 1.86 (0.94 to 378.80)                    | 1          | 18.86 (0.57 to 164.91)                    |
| Tomasi 2011       | 10/43                  | 13/119                    | 6.26 (2.07 to 3.96)                      | 6          | 2.86 (1.36 to 7.27)                       |
| Tsuruta 2010      | 2/21                   | 0/82                      | 5.34 (3.36 to 7.72)                      | 5          | 1.78 (0.40 to 7.86)                       |
| Tsuruta 2014      | 8/115                  | 0/65                      | 100                                      | 2          | 2.19 (1.78 to 2.70)                       |

Test for heterogeneity: $\chi^2=0.18$, $P=96.96$, df=27, $P=0.001$, $I^2=72\%$

Test for overall effect: $z=7.34$, $P<0.001$

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**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) vs 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. Two studies found increased mortality by six months in patients who had delirium when they were in intensive care (41.2% vs 15.4%, $P<0.001$, and 34% vs 15%, $P=0.031$), 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). 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.
### 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).36 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).31 Van den Boogaard and colleagues found that duration of delirium was significantly correlated to memory and naming impairments 18 months after discharge.46 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 review37 and expand them to include a much larger number of studies and patients (42 versus 14 studies; 16,595 versus 5,891 patients). Our data, however, still do not clarify the nature of this association,
Impact of delirium on duration (days) of mechanical ventilation in critically ill patients

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

Specifically whether delirium is a condition that is causally 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 Academy 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,79 early implementation of mobility and occupational therapy in
The intensive care unit,\textsuperscript{79} use of antipsychotic agents particularly in specific subgroups,\textsuperscript{80,82} and bundled interventions.\textsuperscript{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.\textsuperscript{71,85,87} Specific attention should be devoted to determining endpoint measures that are relevant from a biological, clinical, and process of care standpoint. 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\textsuperscript{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.\textsuperscript{88} Subtypes of delirium including hypactive delirium or subsyndromal delirium, for example, might not be accurately or reliably detected with available delirium instruments.\textsuperscript{17,27} 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.\textsuperscript{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.\textsuperscript{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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Transparency: The lead author (the manuscript’s guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing: No additional data available.

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