**Supplemental Table 20. Characteristics and main findings of included studies.**

**A. Studies on predisposing and precipitating factors**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Article** | | **Study Design** | | | **Number of delirious / Total (%)** | | **Type IC** | | **Method Delirium Assessment** | | | | **Inclusion** | | **Exclusion** | | | **Risk Factor** | | | **Effect estimate Risk Factor** | | | | | | **Outcome**  **Model** | | | | | **Qualtiy** | |
| Abelha 2012  [1] | | Prospective Cohort | | | 26/173 (15%) | | PACU | | ICDSC 8 hrly  *??* | | | | Major elective surgery expected hospital stay >48hrs | | Neurological or cardiac surgery  CNS condition  Parkinson  Delirium  Antipsychotics use  Drug/alcohol/opioid abuse  No informed consent | | | Age ≥ 65 years  Emergency surgery  Congestive Heart failure | | | 9.3  59.7  6.2 | | | | (2.0 - 43.0)  (6.7 – 530.5)  (2.0 – 19.3) | | Delirium ICU incidence  Logistic Regression | | | | | ++ | |
| Comments: | | | * APOE4 allelle not associated with delirium (4% vs 17%, p=0.09) * Delirium only measured during PACU admission. LOS PACU non-delirious patients 19 (15-23) hrs and LOS PACU delirous patiets 46 (19-78) hrs.  Therefore risk of “immortal time bias”, the longer admitted (due to complications, severity of disease etc.) the higher the chance of becoming delirious * Adjusted for ASA physical status,hyperlipidemia, ischaemic heart disease, RCRI, previous Lawton scale, Dependency in P-ADL | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Agarwal 2010  [2] | | Prospective Cohort | | | 63/82 (77%) | | Burn ICU | | CAM-ICU  24 hrly  *??* | | | | >24 hrs MV  Burn injuries | | Neurological condition  Postanoxic encephalopathy  Moribund  Impaired hearing | | | Delirious previous day  Comatose previous day  Benzodiazepines dose <24 hr  Opiates dose <24 hr  Methadone dose <24 hr  Baseline Component | | | 26.5  44.9  6.8  0.5  0.7  0.6 | | | | (11.9-58.9)  (19-105.8)  (3.1-15.0)  (0.4-0.6)  (0.5-0.9)  (0.3-1.0) (ns) | | Daily transition towards delirium  Logistic Regression  (GEE + Markov) | | | | | ++ | |
| Comments | | | * OR presented using 25th and 75th percentile values as comparators (for continuous variables) * Benzodiazepines in mg midazolam equivalents and opiates in mg fentanyl equivalents * Principal component analysis was used to calculate a single value incorporating age, acute physiology component of the APACHE, history of alcohol/substance abuse, burn percentage and presence of an inhalation injury for use in Logistic Regression. | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Aldemir 2001 [3] | | Prospective Cohort | | | 90/818 (11%) | | Surgical  ICU | | | | | DSM-III 24hrly  *Research* | All patients | | None | | | Respiratory disease  Infection  Fever  Hypotension  Anemia  Hypocalcemia  Hyponatremia  Elevated serum urea nitrogen  Elevated hepatic enzymes  Hyperamylasemia  Hyperbilirubinemia  Metabolic acidosis | | | 30.6  18.0  14.3  19.8  5.4  30.9  8.2  4.6  6.3  43.4  8.7  4.5 | | | | (9.5-98.4)  (3.5-90.8)  (4.1-49.3)  (5.3-74.3)  (1.6-17.8)  (5.8-163.2)  (2.5-26.4)  (1.4-15.6)  (1.2-32.2)  (4.2-442.7)  (2.0-37.7)  (1.1-17.7) | | ICU Delirium Occurrence  Forward Stepwise  Logistic Regression | | | | | + | |
|  | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Q: Quality, PACU= Postanesthesia care unit, ICDSC: Intensive Care Delirium Screening Checklist, hrly: hourly, hrs: hours, CNS: Central Nervous System, ICU: Intensive Care, LOS: Length of Stay, CAM-ICU: Confusion Assessment Method for use in the ICU, MV: mechanical ventilation, GEE: Generelazid Estimated Equations, DSM-IV: Diagnostic Statistic Manual version IV, SICU: surgical ICU, ASA: American Society of Anesthesiologists, RCRI: revised cardiac risk index, P-ADL: Personal activities of daily living | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Article** | | **Study Design** | | | **Number of delirious / Total (%)** | | **Type IC** | | | | | **Method Delirium Assessment** | **Inclusion** | | **Exclusion** | | | **Risk Factor** | | | **Effect estimate**  **Risk Factor** | | | | | | **Outcome**  **Model** | | | | | **Quality** | |
| Angles 2008 [4] | | Prospective Cohort | | | 41/69 (59%) | | Trauma  ICU | | | | | CAM-ICU 24hrly *??*  +  chart review  <24hrs *R* | Trauma  ISS ≥ 8 | | Impaired vision/hearing No informed consent | | | Age  ISS  GCS at Emergency Department  Transfusion, units  Maximum MOF score | | | 1.03  1.1  0.6  1.4  8.8 | | | | (1.0-1.1)  (1.0-1.1)  (0.6-1.1) (ns) (1.0-1.9)  (1.7-45.1) | | Delirium ICU Occurrence  Logistic Regression | | | | | ++ | |
| Comments | | | * OR GCS at Emergency Department just not significant (p=0.08) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Bryczkowski 2014 [5] | | Prospective cohort | | | 70/115 (61%) | | Surgical ICU | | | | | CAM-ICU  12 hrly  *Research* | Trauma patients  Age > 50 years  Admission ≥ 24 hours | | Age ≤ 50 years  Died in SICU  History of dementia  Transferred from jail or in active police custody | | | Vent-free days  Chest injury (chest AIS score ≥ 3)  Age  Initial GCS score  Benzo-free days  TBI  Deep sedation, hours RASS low (≤ -3) | | | 0.79  0.28  1.1  0.85  0.84  0.65  0.99 | | | | (0.65-0.96)  (0.09-0.83)  (1.01-1.1)  (0.68-1.07) (ns)  (0.66-1.09) (ns)  (0.22-1.87) (ns)  (0.98-1.02) (ns) | | Delirium Incidence  Logistic Regression | | | | | + | |
| Colombo 2012 [6] | | B/A | | | 80/314 (26%) | | Mixed  ICU | | | | | CAM-ICU 12hrly  *Research* | All patients | | Cognitive disorders  Dementia  Psychosis  Disability after stroke  Moribund | | | Age  Midazolam + opiate infusion  Reorientation strategy | | | 1.03  2.1  0.5 | | | | (1.0-1.1)  (2.2-4.0)  (0.3-0.9) | | Time to delirium  Cox Regression  (Hazard Ratio) | | | | | + | |
| Comments | | | * Intervention: reorientation strategy * No blinding in different phases of the study | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Dubois 2001 [7] | | Prospective  Cohort | | | 40/198 (19%) | | Mixed ICU | | | | | DSM-IV screening  ICDSC  24hrly  *Bedside*  *Nurse* | >24hrs | | Moribund  No informed consent | | | Hypertension Smoking  Bilirubine (per 10% increase)  Epidural Morphine dose 0.01-7.1mg  Morphine dose 7.2-18.6mg  Morphine dose 18.6-331.6mg | | | 2.6  2.2  1.2  3.5  7.8  9.2  6.0 | | | | (1.1-5.7)  (0.9-4.9) (1.03-1.4)  (1.2-10.4)  (1.8-34.4)  (2.2-39.0) (1.4-25.4) | | Delirium Incidence first 5 days ICU  Logistic Regression | | | | | + | |
| Comments | | | * Laboratory data: proportion of days with abnormal values from admission to day delirium occurred * Opioids in parenteral morphine equivalents, benzodiazepines as lorazepam equivalents. * Delirious patients mean daily equivalent dosage during delirium phase. Non-delirious patients mean dose using all 5 days. | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ICU: intensive care, CAM-ICU: Confusion Assessment Method for use in ICU, hrly: hourly, hrs:hours, ISS: injury severity score, GCS: Glasgow Coma Scale, MOF: Multi Organ Failure, ns: non-significant, SICU: surgical intensive care unit, AIS: abbreviated injury scale, TBI: traumatic brain injury, RASS: Richmond Agitation-Sedation Scale, B/A: before after intervention study, MV: mechanically ventilated. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Article** | | **Study Design** | | | **Number of delirious / Total (%)** | | **Type IC** | | | | | **Method Delirium Assessment** | **Inclusion** | | **Exclusion** | | | **Risk Factor** | | | **Effect estimate**  **Risk Factor** | | | | | | **Outcome**  **Model** | | | | | **Quality** | |
| Ely 2007 [8] | | Prospective  Cohort | | | 47/53  (89%) | | Medical ICU | | | | | CAM-ICU 12hrly  *Research team* | MV  >24hrs | | None | | | APOE4 present  Age, years  APACHE II  Coma days, quintiles  Sepsis/ARDS/pneumonia  Total dose lorazepam, mg | | | 7.3  1.0  1.0  1.3  1.7  1.0 | | | | (1.8-29.5)  (0.98-1.1)(ns)  (0.9-1.1) (ns)  (1.1-1.6)  (0.6-5.3) (ns)  (1.0-1.0) (ns) | | ICU delirium days  Logistic Regression  (Proportional Odds) | | | | | ++ | |
| Girard 2012 [9] | | Prospective  Cohort | | | 107/138 (78%) | | Medical  ICU | | | | | CAM-ICU  24hrly  *Research team* | MV >12 hrs | | Moribund  After cardiac arrest  Neurological disease  MV ≥ 2 weeks | | | MMP-9 (ng/mL)  sTNFR1 (pg/mL)  Protein C (% control) | | | 0.4  2.1  0.4 | | | | (0.2-0.8)  (1.2-3.6)  (0.2-0.9) | | Delirium day after biomarker assessment  Logistic Regression  (GEE) | | | | | ++ | |
| Comments | | | * OR represents odds of being delirious day after biomarker measurement with increase in biomarker concentration from the 25th to the 75th percentile * Adjusted for age, APACHE II APS, admission with severe sepsis | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Guillamondegui 2011 [10] | | Prospective Cohort | | | 55/97  (57%) | | Trauma  ICU | | | | | CAM-ICU  12hrly *??* | ISS > 15 | | Intracranial hemorrhage  No continuous oxygen saturation data. | | | Ventilator days  Pulse (Emergency Department) | | | 1.2  1.02 | | | | (1.1-1.3)  (1.00-1.04) | | Delirium ICU Occurence  Logistic Regression | | | | | ++ | |
| Comments | | | * Adjusted for ISS, Saturation ≤90% for ≥ 5minutes, blood transfusions, blood pressure at emergency department | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Heyman 2007 [11] | | Retrospective Cohort | | | 55/196  (28%) | | ICU + IMCU | | | | | DDS 8hrly *Bedside nurse* | All patients | | Deep sedation (RASS≤-3)  Psychiatric diseases  Cognitive disorders  Severe braininjuries (GCS≤8) | | | Hyperglycemia  APACHE II  SOFA  HAP/VAP  Alcohol abuse  Polytrauma  TISS | | | 4.2  3.1  1.2  1.1  1.5  8.0  2.3  7.2  2.3  14.5  2.7  1.1 | | | | (1.4-12.1)  (1.6-6.1) (HR)  (1.1-1.3)  (1.0-1.1) (HR)  (1.2-1.7)  (2.7-24.1)  (1.3-4.1) (HR)  (1.7-29.6)  (1.2-4.7) (HR)  (3.3-64.9)  (1.4-5.5) (HR)  (1.0-1.1) (HR) | | ICU + IMCU Hyperactive Delirium Occurrence  Logistic Regression  Cox Regression  (Hazard Ratio) | | | | | + | |
| Comments | | | * DDS not validated against DSM-IV criteria (possibly detection bias) * Outcome of hyperactive delirium defined as DDS > 7 * Due to retrospective study (with prospective delirium assessment) missing data in 137/333 patients (leaving 196 patients) | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ICU: intensive care unit, CAM-ICU: Confusion Assessment Method for use in ICU, hrly= hourly, MV: mechanically ventilated, APACHE (APS): Acute Physiology and Chronic Health Evaluation (Acute Physiology Score), ARDS: acute respiratory distress syndrome, GEE: Generelazid Estimated Equations, ISS: Injury Severity Score, hrs: hours, IMCU: intermediate care unit, DDS: delirium detection score, RASS: Richmond Agitation and Sedation Score, GCS: Glasgow Coma Scale, H-/VAP: Hospital/Ventilator Associated Pneumonia, TISS:Therapeutic Intervention Scoring System, HR: hazard ratio, ns=non-significant, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Article** | | **Study Design** | | | **Number of delirious / Total (%)** | | | **Type IC** | | | | **Method Delirium Assessment** | **Inclusion** | | **Exclusion** | | **Risk Factor** | | | | | **Effect estimate**  **Risk Factor** | | | | | | | | **Outcome**  **Model** | | **Quality** | |
| Hsieh 2013 [12] | | Prospective Cohort  Multicenter | | | 244/564 (43%) | | | Mixed ICU | | | | CAM-ICU  24 hrly  *Research Team* | Adult patients | | Non-Englisch or non-Spanish language  Developmental delay  End-stage dementia | | ARDS status  Not Intubated, no ARDS  Intubated, no ARDS  Intubated, with ARDS  Age  Charlson Comorbidity Index  APACHE IV  Dementia  Non-English language  Alcohol abuse  Illicit drug use  Severe sepsis  Any benzodiazepine  Any opiate  Any propofol  Any steroid | | | | | Ref  1.98  6.55  1.00  1.21  1.22  6.76  2.20  2.42  1.97  1.11  1.93  1.14  4.16  1.06 | | | (1.16-3.40)  (1.56-27.54)  (0.99-1.02) (ns)  (0.78-1.89) (ns)  (1.08-1.37)  (2.57-17.75)  (1.26- 3.84)  (1.09-5.37)  (0.73-5.32) (ns)  (0.58-2.13) (ns)  (1.09-3.41)  (0.64-2.01) (ns)  (2.41-7.20)  (0.63-1.79) (ns) | | | | | Delirium Prevalence  Logistic Regression | | + | |
| ICU: intensive care unit, CAM-ICU: Confusion Assessment Method for use in ICU, hrly= hourly, ARDS: acute respiratory distress syndrome, APACHE (APS): Acute Physiology and Chronic Health Evaluation (Acute Physiology Score), ns=non-significant, IQCODE: Informant Questionnaire on Cognitive Decline in the Elderly. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Article** | | **Study Design** | | | **Number of delirious / Total (%)** | | | **Type IC** | | | | **Method Delirium Assessment** | **Inclusion** | | **Exclusion** | | **Risk Factor** | | | | | **Effect estimate**  **Risk Factor** | | | | | | | | **Outcome**  **Model** | | | | **Quality** | |
| Kamdar 2015 [13] | | Prospective cohort | | | 123/223 (55%) | | Medical ICU | | | | | CAM-ICU  12 hrly  *Bedside* | Admission to ICU | | - | | Age, per year  Race  White  Black  Other  Uses pharmacological sleep aids at home  Home sleep quality  Very good  Somewhat good  Somewhat/very bad  Unkown/not answered  Total quality on RCSQ  Receiving mechanical ventilation without sedation  Received sedative infusion while not mechanically ventilated  Received sedative infusion while mechanically ventilated | | | | | 1.01 (1.00-1.02) (ns)  Ref  0.76 (0.49-1.17) (ns)  1.63 (0.65-4.12) (ns)  0.40 (0.20-0.80) (ns)  Ref  1.01 (0.59-1.73) (ns)  1.31 (0.72-2.38) (ns)  1.91 (0.94-3.87) (ns)  1.00 (0.99-1.00) (ns)  1.27 (0.85-1.91) (ns)  0.45 (0.17-1.16) (ns)  4.02 (2.19-7.38) | | | | | |  | | Daily transition to delirium  Logistic Regression | | | | ++ | |
| Leite 2014 [14] | | Prospective cohort | | | 34/64  (53,1%) | | Mixed ICU | | | | | CAM-ICU  twice daily  *Research Team* | Age ≥ 18 years  Admission to ICU  MV > 24 hours  Being in the  process of weaning from MV | | Degenerative neurological disease  Prior known psychiatric conditions  Recent psychiatric events including suicide attempts  History of drug addiction or alcoholism  Compromised level of consciousness (GCS ≤ 8 or RASS < -3) at beginning of study  Presence of tracheostomy | | Age  SOFA score  APACHE II score  Neurological cause  Sex | | | | | p-value 0.01  p-value 0.03  p-value 0.01  p-value 0.01  p-value 0.93 (ns) | | | | | |  | | Incidence of delirium  Principal component analysis | | | | + | |
| Comments | | | * No odds ratio’s or confidence intervals provided | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Limpawattana 2016 [15] | | Prospective Cohort | | | 44/99 (44,4%) | | Medical ICU | | | | | CAM-ICU  24 hrly  *Research Team* | ≥65 years of age | | Readmission to ICU  No informed consent  Coma (RASS score < -3)  Severe aphasia  Severe hearing impairment | | | | Previous stroke  Bed change > 3  Physical restraints  Use of bladder catheter  On mechanical ventilators | | | 6.35  15.75  21.46  2.03  0.86 | | | (1.64-24.55)  (1.31-188.95)  (4.6-100.16)  (0.49-8.39) (ns)  (0.26-2.9) (ns) | | | | | Prevalence and incidence of delirium  Logistic Regression | | | | + | |
| Comments | | | * Not entirely suitable for multivariate analysis because of the small sample size | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ICU: intensive care unit, CAM-ICU: Confusion Assessment Method for use in ICU, hrly= hourly, ARDS: acute respiratory distress syndrome, RCSQ: Richards-Campbell Sleep Questionnaire, ns=non-significant, MV: mechanically ventilated, SOFA: Sequential Organ Failure Assessment, APACHE: Acute Physiology and Chronic Health Evaluation, RASS: Richmond Agitation and Sedation Score. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Article** | | **Study Design** | | | **Number of delirious / Total (%)** | | | **Type IC** | | | | **Method Delirium Assessment** | **Inclusion** | | **Exclusion** | | **Risk Factor** | | | | | **Effect estimate**  **Risk Factor** | | | | | | | | | **Outcome**  **Model** | | | **Quality** | |
| Lin 2008 [16] | | Prospective Cohort | | | 31/143  (22%) | | Medical  ICU | | | | | CAM-ICU  24hrly  *Research Team* | MV | | Neurological disease  Psychological disorders  High dose morphine  High dose midazolam  General anesthesia/neuro-muscular blocking agents  3/5 Consecutive days comatose  No informed consent | | | | Hypoalbuminemia  Diabetes Mellitus  Sepsis | | | 5.9  2.5  3.7 | | | (1.2-28.8)  (0.9-7.4) (ns)  (1.03-12.9) | | | | | | Delirium incidence first 5 days of ICU admission  Logistic Regression | | | ++ | |
| Lin 2015 [17] | | Prospective cohort | | | 68/90 (75,6%) | | Medical ICU | | | | | CAM-ICU  twice daily | ≥65 years of age  RASS score ≥ -3  Admission in  previous 24 hours | | Readmission to ICU | | | | No. of sedatives used  Age  Length of stay  APACHE II  RASS  COPD  Stroke  Days of ventilator use  No. of anesthetic analgesics used  Total no. of medications used  Duration of trachea use  Use of steroids before ICU admission  Duration of dehydration  Sensory impairment  Malnutrition | | | 0.78  0.98  1.01  0.92  1.06  15.87  2.16  1.10  0.05  3.53  0.93  0.01  2.10  0.36  NA | | | (0.45-1.33) (ns)  (0.89-1.08) (ns)  (0.99-1.03) (ns)  (0.80-1.05) (ns)  (0.62-1.82) (ns)  (0.90-278.61) (ns)  (0.34-12.76) (ns)  (0.84-1.44) (ns)  (0.00-0.54)  (1.12-11.15)  (0.60-1.43) (ns)  (0.00-0.32)  (1.15-3.84)  (0.06-2.10) (ns)  NA | | | | | | Delirium incidence  Logistic Regresiion | | | + | |
| McNicoll 2003 [18] | | Prospective  Cohort | | | 83/118  (70%) | | Medical ICU | | | | | CAM-ICU  24hrly  *Research team* | ≥65 years of age | | No informed consent  Transfer from another ICU  Aphasia/advanced dementia  Death before first interview | | | | Dementia | | | 1.3 | | | (1.1-1.6) | | | | | | Hospital Delirium Occurrence    Logistic Regression  (Risk Ratio) | | | ++ | |
| Comments | | | * Dementia was defined as MBDRS ≥3 and the IQCODE ≥3.31 or MBDRS ≥3.5 or IQCODE ≥3.5 * Outcome is occurrence of delirium during initial ICU stay plus up to 7 days after transfer from ICU * Adjusted for Charlson Comorbidity Index, APACHE II, impairment in ADLs, invasive procedures other than MV | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ICU: intensive care unit, CAM-ICU: Confusion Assessment Method for use in ICU, hrly= hourly, MV: mechanically ventilated, ns=non-significant, RASS: Richmond Agitation and Sedation Score, APACHE: Acute Physiology and Chronic Health Evaluation, COPD: chronic obstructive pulmonary disease, NA: not applicable, MBDRS:Modified Blessed Dementia Rating Scale, IQCODE: Informant Questionnaire on Cognitive Decline for the Elderly, ADL: Activity of Daily Living. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Article** | **Study Design** | | | **Number of delirious / Total (%)** | | | | **Type IC** | | **Method Delirium Assessment** | | | **Inclusion** | **Exclusion** | | **Risk Factor** | | | | | | **Effect estimate**  **Risk Factor** | | | | | | | | **Outcome**  **Model** | | | | **Quality** | | |
| Mehta 2015 [19] | Prospective Cohort  Nested in SLEAP trial  Multicenter | | | 226/420 (53,8%) | | Mixed ICU | | | | ICDSC  24 hrly  *Bedside nurse* | | | MV ≥ 48 hours  Continuous IV  opioid and/or benzodiazepine infusion | Cardiac arrest  Traumatic brain injury  Neuromuscular blockers  Enrolled in a related trial  Previously enrolled in SLEAP  Lacking commitment to maximal therapy | | Age  < 40  41-65  66-80  > 80  APACHE II  <19  19-24  24-29  >29  Tabacco  Alcohol (≥ 2 drinks/day)  Neurologic condition  Cardiac disease  Randomization group  Coma  Renal replacement  Physical restraint  Total midazolam (1mg increase)  Total fentanyl (0,1 mg increase)  Antipsychotic use in ICU | | | | Ref  0.92  0.91  0.85  Ref  0.94  0.98  0.64  1.40  1018  0.86  1.33  0.94  0.55  1.05  1.87  0.998  1.0  1.67 | | | | | Ref  (0.59-1.43) (ns)  (0.53-1.56) (ns)  (0.38-1.88) (ns)  Ref  (0.63-1.42) (ns)  (0.63-1.55) (ns)  (0.38-1.09) (ns)  (0.96-2.06) (ns)  (0.69-1.99) (ns)  (0.52-1.41) (ns)  (0.64-2.76) (ns)  (0.68-1.29) (ns)  (0.25-1.22) (ns)  (0.63-1.73) (ns)  (1.33-2.63)  (0.997-1.0)  (1.0-1.0) (ns)  (1.01-2.77) | | | | | | Delirium prevalence  Cox proportional hazards regression analysis | | | + | | |
| Morandi 2011 [20] | Prospective Cohort  Nested in ABC trial | | | 40/62 (64%) | | Medical  ICU | | | | CAM-ICU  12hrly  *Research Team* | | | MV > 12hrs | Cardiac arrest  Ventilated ≥ 2 weeks  Moribund  Neurological disease  No informed consent | | IGF-1 | | | | 1.0 | | | | | (0.6-1.8) (ns) | | | | | | Delirium day after IGF-1 measurement  Logistic Regression | | | ++ | | |
| Comments | | | * Blood for measurement of serum IGF-1 concentration collected within 48hrs of enrollment * Total sample 110 of whom 48 died or comatose day after IGF-1 measurement leaving 62 patients in final sample * Adjusted for age, APACHE II, severe sepsis | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Morandi 2013 [21] | Prospective Cohort  Nested in VALID study | | | ?/?  (?%) | | | Medical  ICU | | | | | CAM-ICU  24hrly  *Research Team* | All patients | | ICU LOS >3days  Cardiac arrest  Severe chronic lung disease  Elective cardiothoracic surgery  Uncomplicated overdose  Died/discharged ≤48hrs | | | | 25-OHD, nmol/L  Age  APACHE II | | 1.0  1.0  1.1 | | | | (0.99-1.0) (ns)  (0.95-1.0) (ns)  (1.03-1.2) | | Delirium day after 25-OHD measurement  Logistic Regression | | | | | | | ++ | | |
| Comments | | | * Blood for measurement of serum 25-OHD concentration collected within 24hrs of ICU admission * Total sample 120 patients of whom unknown percentage died/comatose day after 25-OHD measurement, so unknown sample in presented analysis | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Ouimet 2007 [22] | Prospective Cohort | | | 243/764  (32%) | | | Mixed  ICU | | | | | ICDSC  1-8hrly  *Bedside* | All patients | | Moribund  Comatose >5 days/until death | | | | Hypertension (History)  Alcoholism (History)  APACHE II  Iatrogenic Coma  Pain (assessed by NRS)  Anxiety | | 1.9  2.0  1.05  3.7  0.9  1.8 | | | | (1.3-2.6)  (1.3-3.3)  (1.03-1.1)  (2.3-5.9)  (0.8-0.97)  (1.04-3.4) | | ICU Delirium Occurrence  Logistic Regression | | | | | | | ++ | | |
| ICU: intensive care unit, ICDSC: Intensive Care Delirium Screening Checklist, hrly: hourly, MV: Mechanical ventilated, IV: intravenous, APACHE: Acute Physiology and Chronic Health Evaluation, ns=non-significant, CAM-ICU: Confusion Assessment Method for use in the ICU, IGF-1: insulin growth factor-1, hrs: hours, LOS: Length of stay, 25-OHD:25-OH Vitamin D, ICDSC: Intensive Care Delirium Screening Checklist, NRS: Numeric Rating Scale (for pain assessment). | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Article** | | **Study Design** | | | **Number of delirious / Total (%)** | | **Type IC** | | | | | **Method Delirium Assessment** | **Inclusion** | | **Exclusion** | | | | **Risk Factor** | | **Effect estimate**  **Risk Factor** | | | | | | **Outcome**  **Model** | | | | | | | **Quality** | |
| Pandharipande 2006 [23] | | Prospective Cohort | | | ?/198  (?%) | | Medical or Coronary ICU | | | | | CAM-ICU  24hrly  *Research Team* | MV | | Neurological disease  Persistent coma  Lack of 2 consecutive cognitive assessments | | | | Lorazepam  Midazolam  Fentanyl  Morphine  Propofol  APACHE II  Age  Antipsychotics  Anticholinergic drugs  Cross products | | 1.2  1.7  1.2  1.1  1.2  1.06  1.02  ns  ns  ns | | | | (1.1-1.4)  (0.9-3.2) (ns)  (1.0-1.5) (ns)  (0.9-1.2) (ns)  (0.9-1.7) (ns)  (1.02-1.1)  (1.00-1.03) | | Daily transition towards delirium  Logistic Regression  (GEE + Markov) | | | | | | | ++ | |
| Comments | | | * Total of 696 observations from 198 patients were included in analysis * Anticholinergic drugs: atropine, diphenhydramine, bupropion hydrochloride, metoclopramide, prochlorperazine, promethazine) * Odds Ratio for medication intpereted as: every unit dose of lorazepam in log*e* milligrams previous day increases risk with 20% for transition towards delirium * Adjusted for mental status previous day, age, sex, visual and hearing deficits, history of dementia, depression (assessed by Geriatric Depression Scale short form, modified APACHE II (minus GCS), sepsis, history of neurologic disease, hematocrit at baseline, daily serum glucose * Cross-product sedative drug and mental status previous day to assess if previous cognitive status modifies the risk of the medication * Cross-product lorazepam and each of the other sedative and analgesic drugs to assess if combined use of the two drugs increases risk | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pandharipande 2008 [24] | | Prospective Cohort | | | 68/97  (70%) | | Surgical or Trauma ICU | | | | | CAM-ICU  24hrly  *Bedside* | MV > 24hrs | | Neurological disease  Hearing loss  Moribund  Persistent coma | | | | Anesthetics  H2 Blockers  Lorazepam  Midazolam  Fentanyl  Morphine | | 0.5  1.5  0.5  2.8  1.9  0.4 | | | | (0.2-1.2) (ns)  (0.8-2.6) (ns)  (0.2-1.3) (ns)  (1.4-5.3)  (0.99-3.6)(ns)  (0.2-0.8) | | Daily transition towards delirium  Logistic Regression  (GEE + Markov) | | | | | | | ++ | |
| Comments | | | * Principal component analysis was used to combine age, body mass index, Charlson Comorbidity Inedex, APACHE II score and presence of sepsis into two summary components for use in Logistic Regression to preserve power. * Adjusted for mental status previous day, two summary components, daily use (yes/no) of each psychoactive drug | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pisani 2007 [25] | | Prospective Cohort | | | 214/304  (70%) | | Medical ICU | | | | | CAM-ICU  24hrly  Chart  review  *Research* | ≥60 years of age | | No informed consent  Transferred from another ICU  Inability to communicate <ICU  LOS ICU < 24hrs | | | | Dementia (IQCODE>3.3)  Benzodiazepines <ICU  Creatinine > 2mg/dL  Arterial pH <7.35 | | 6.3  3.4  2.1  2.1 | | | | (2.9-13.8)  (1.6-7.0)  (1.1-4.0)  (1.1-3.9) | | Delirium first 48hours  Logistic Regression | | | | | | | ++ | |
| Comments | | | * Internal validation final model using bootstrapping procedure | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ICU: Intensive Care unit, CAM-ICU: Confusion Assessment Method for use in the ICU, MV: mechanical ventilated, APACHE II: Acute Physiology and Chronic Health Evaluation, ns: non significant, GEE: GEE: Generalized Estimated Equations, GCS: Glasgow coma Scale, hrly: hourly, hrs:hours, LOS: Length of stay, IQCODE: Informant Questionnaire on Cognitive Decline for the Elderly. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Article** | | **Study Design** | | | **Number of delirious / Total (%)** | | **Type IC** | | | | | **Method Delirium Assessment** | **Inclusion** | | **Exclusion** | | | | **Risk Factor** | | **Effect estimate**  **Risk Factor** | | | | | | **Outcome**  **Model** | | | | | | | **Quality** | | | |
| Pandharipande 2009 [26] | | Prospective Cohort nested in MENDS trial | | | ?/97  (?%) | | Medical and Surgical ICU | | | | | CAM-ICU  24hrly  *Bedside* | MV | | Neurological disease  Active seizure disorder  Child-Pugh Class B/C cirrhosis  Alcohol abuse  Active myocardial ischemia  2nd or 3rd degree heart block  Severe dementia  Pregnancy  Severe hearing loss  No informed consent | | | | Tryptophan/LNAA ratio  Tyrosine/LNAA ratio  Phenylalanine/LNAA ratio  Age  Modified APACHE II  IQCODE  Dexmedetomidine <24hrs  Lorazepam <24hrs  Fentanyl <24hrs  Mental status <24hrs | | p-value  p-value  p-value  p-value  p-value  p-value  p-value  p-value  p-value  p-value | | | | | <0.05  <0.05  ns  <0.05  2x<0.05  ns  ns  ns  ns  1x<0.05 | Transition towards delirium day after (day 2 and day 4) measurement  Logistic Regression  (GEE + Markov) | | | | | | | ++ | | | |
| Comments | | | * No data on total number of observations, nor on number of patients who became delirious * No effect estimates/confidence intervals provided * Blood samples collected on study days 1 and 3 * Three separate models for each factor. Each model adjusted for age, IQCODE, modified APACHE II (minus GCS), Dexmedetomidine -, Lorazepam - , Fentanyl on previous day, mental status previous day * Modified APACHE II non-significant in Phenylalanine/LNAA ratio model, Fentanyl<24hrs non-significant in both Tyrosine- and Phenylalanine/LNAA ratio model | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pisani 2009 [27] | | Prospective Cohort | | | 239/304  (79%) | | Medical ICU | | | | | CAM-ICU  24hrly  Chart  review  *Research* | ≥60 years of age | | No informed consent  Transferred from another ICU  Inability to communicate <ICU  LOS ICU < 24hrs  Persistent coma | | | | Benzodiazepine/opioid use  Dementia (IQCODE>3.3)  Haloperidol  Modified APACHE II | | 1.6  1.2  1.4  1.01 | | | | (1.3-2.1)  (1.1-1.3)  (1.2-1.5)  (1.00-1.02) | | Duration first delirium episode in ICU  Poisson Regression (Rate Ratio) | | | | | | | + | | | |
| Comments | | | * End of delirium episode with two consecutive days without delirium * Modified APACHE II (minus GCS) * Not clear if benzodiazepine exposure is before delirium episode * Internal validation final model using bootstrapping procedure | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ICU: Intensive Care unit, CAM-ICU: Confusion Assessment Method for use in the ICU, MV: mechanical ventilated, APACHE II: Acute Physiology and Chronic Health Evaluation, ns: non significant, GEE: GEE: Generalized Estimated Equations, GCS: Glasgow coma Scale, hrly: hourly, hrs:hours, LOS: Length of stay, IQCODE: Informant Questionnaire on Cognitive Decline for the Elderly. | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Article** | | **Study Design** | | | **Number of delirious / Total (%)** | | **Type IC** | | | | | **Method Delirium Assessment** | **Inclusion** | | **Exclusion** | | | | **Risk Factor** | | **Effect estimate**  **Risk Factor** | | | | | | **Outcome**  **Model** | | | | | | | **Quality** | | | |
| Schreiber 2014 [28] | | Prospective  Cohort  Multicenter | | | 274/330  (83%) | | Mixed  ICU | | | | | CAM-ICU  24hrly  *Research* | MV  Acute lung injury | | Illness with life expectancy < 6 months  Cognitive impairment  Communication barriers  No fixed address  Transferred from other hospital and ALI > 24 hours  MV > 5 days before onset ALI  Previous lung resection | | | | Age  < 40 years  40-60 years  > 60 years  Male  Home use of opioids  APACHE II score  Daily SOFA score  Daily sepsis status  Corticosteroid administration  Corticosteroid dose  Benzodiazepine administration  Benzodiazepine dose | | Ref  1.81  2.52  1.34  1.11  1.01  1.03  1.06  1.52  0.97  1.32  1.02 | | | | (1.26-2.62)  (1.62-3.87)  (0.96-1.86) (ns)  (0.97-1.27) (ns)  (1.00-1.03)  (0.99-1.07) (ns)  (0.79-1.41) (ns)  (1.05-2.21)  (0.89-1.07) (ns)  (0.93-1.89) (ns)  (0.99-1.04) (ns) | | Transition from a normal state into delirium the next day  Logistic Regression (First-order Markov model) | | | | | | | ++ | | | |
| Serafim 2012 [29] | | Prospective Cohort | | | 43/465  (9%) | | Surgical ICU | | | | | CAM 12hrly  *Bedside* | RASS > -3 | | MV  Pregnancy  Inability to verbalize  Hearing or visual impairment  No informed consent | | | | Age  APACHE II APS  Benzodiazepine use first 24hr  Emergency surgery  Trauma patient | | 1.04  1.1  2.3  8.1  6.2 | | | | (1.02-1.1)  (1.04-1.2)  (1.04-5)  (3.6-18.1)  (4.1-6.5) | | ICU delirium occurrence  Logistic Regression | | | | | | | ++ | | | |
| Comments | | | * Delirium assessment in all non-mechanically ventilated patients using the CAM | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Seymour 2012 [30] | | Prospective Cohort nested in ABC trial | | | ?/140  (?) | | Medical ICU | | | | | CAM-ICU  24hrly  *Research* | MV > 12hrs | | Cardiac arrest  Ventilated ≥ 2 weeks  Moribund  Neurological disease  No informed consent | | | | Change in sedative dosing:   * Benzodiazepine, mg/hr * Propofol, mcg/kg/min   Daytime sedative dosing:   * Benzodiazepine, mg/hr * Propofol, mcg/kg/min | | 2.5  1.4  1166  3.2 | | | | (1.0-6.3) (ns)  (0.8-2.5) (ns)  (16-82719)  (1.0-10.6)(ns) | | Transition towards delirium day after exposure  Logistic Regression  (GEE + Markov) | | | | | | | ++ | | | |
| Comments | | | * Total of 485 patient days observed with observed delirium in 160 (33%) days. Results based on complete case analysis with n=272 patient days * Adjusted for age, modified SOFA (with removal of neurological component) and mental status day of exposure * The OR reflect change in odds of being delirious next day with change in exposure from 10th percentile to 90th percentile value. * 10th-90th percentiles for exposure variables respectively (-0.19 – 0.25), (-7.7 – 5.7), (0, 2.4), (0, 40.1) | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ICU: Intensive Care unit, CAM(-ICU): Confusion Assessment Method (for use in the ICU), MV: mechanical ventilated, ALI: acute lung injury, APACHE II (-APS): Acute Physiology and Chronic Health Evaluation II (Acute Physiology Score), SOFA: Sequential Organ Failure Assessment, ns: non significant, GEE: Generalized Estimated Equations, hrly: hourly, hrs:hours, hr: hour, LOS: Length of stay, RASS: Richmond Agitation and Sedation Scale, HR: hazard ratio | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Article** | | **Study Design** | | | **Number of delirious / Total (%)** | | **Type IC** | | | | | **Method Delirium Assessment** | **Inclusion** | | **Exclusion** | | | | **Risk Factor** | | **Effect estimate**  **Risk Factor** | | | | | | **Outcome**  **Model** | | | | | | | **Quality** | | | |
| Shehabi 2013 [31] | | Prospective Cohort  Multicenter | | | 114/259  (44%) | | Mixed  ICU | | | | | CAM-ICU  4hrly  *Research* | MV ≤24hrs  MV expected >24hrs  Sedative/analgesics | | Neurological impairment  Psychiatric illness  Burns  Dementia  Palliative care  Unable to communicate | | | | Early deep sedation  Cumulative dose of Dexmedetomidine first 48hr  APACHE II  Age  Male  Operative  Elective  Cardiac  Respiratory  Sepsis  Gastrointestinal  Vasopressors  Dialysis | | 1.0  1.4  1.0  1.01  1.4  1.1  1.3  1.2  0.9  1.2  0.9  1.2  1.0 | | | | (0.9-1.0) (ns)  (1.1-1.8)  (0.96-1.0) (ns)  (1.00-1.03)  (0.9-2.0) (ns)  (0.6-1.0) (ns)  (0.7-2.6) (ns)  (0.6-2.3) (ns)  (0.5-1.7) (ns)  (0.7-2.3) (ns)  (0.5-1.9) (ns)  (0.7-1.9) (ns)  (0.6-1.8) (ns) | | Time to delirium in 28-day period after first 48hrs of ICU admission  Cox Regression  (Hazard Rations) | | | | | | | ++ | | | |
| Comments | | | * CAM-ICU performed only in RASS range of -2 to +1 so risk of detection bias of delirium * HR interpret chance of achieving desired outcome (shorter time to delirium), so HR of 1.4 is 40% increased chance of shorter time to delirium | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Shi 2010 [32] | | Prospective Cohort | | | 73/164  (45%) | | Surgical ICU | | | | | Nu-DESC  24hrly  *Bedside*  *Research (ward)* | All patients | | Psychiatric diseases  Glucocorticoids>5dys within 1yr  Neurosurgery  Adrenal gland disease/surgery  Need of glucocorticoids  Moribund | | | | Age (/10years increase)  History of stroke  APACHE II  Serum cortisol  (first postoperative day) | | 2.6  4.5  1.4  3.4 | | | | (1.4-4.9)  (1.2-16.5)  (1.2-1.6)  (1.7-6.8) | | Postoperative Delirium Occurrence up to day 7  Logistic Regression | | | | | | | + | | | |
| Comments | | | * Delirium assessment with the Nu-DESC which is validated in non-mechanically ventilated ICU patients | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Simons 2014 [33] | | Retrospective  Cohort | | | 998/3198  (31,2%) | | Mixed  ICU | | | | | CAM-ICU  12hrly  *Bedside* | All patients | | ICU admission after >30 days of hospital admission | | | | Sex (male)  Age (per year)  Infection  Sedation  Season  Spring  Summer  Autumn  Winter  Diagnostic category  Surgical  Medical  Trauma  Neurologic  APACHE II  28-day photoperiod | | 1.03  1.02  3.37  3.78  Ref  1.00  1.06  0.88  Ref  0.90  3.11  3.70  1.10  1.00 | | | | (0.85-1.23) (ns)  (1.01-1.02)  (2.74-4,15)  (3.14-4.56)  (0.79-1.26) (ns)  (0.77-1.46) (ns)  (0.62-1.26) (ns)  (0.72-1.13) (ns)  (1.82-5.32)  (2.72-5.02)  (1.09-1.12)  (1.00-1.00) (ns) | | ICU Delirium Incidence  Logistic Regression | | | | | | | + | | | |
| ICU: Intensive Care unit, CAM(-ICU): Confusion Assessment Method (for use in the ICU), MV: mechanical ventilated, APACHE II(-APS): Acute Physiology and Chronic Health Evaluation II (Acute Physiology Score), ns: non significant, GEE: Generalized Estimated Equations, hrly: hourly, hrs:hours, hr: hour, LOS: Length of stay, RASS: Richmond Agitation and Sedation Scale, HR: hazard ratio, Nu-DESC: Nursing Delirium Screening Scale | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Article** | | **Study Design** | | | **Number of delirious / Total (%)** | | **Type IC** | | | | | **Method Delirium Assessment** | **Inclusion** | | **Exclusion** | | | | **Risk Factor** | | **Effect estimate**  **Risk Factor** | | | | | | **Outcome**  **Model** | | | | | | | **Quality** | | | |
| Skrobik 2013 [34] | | Prospective  Cohort | | | 64/99  (65%) | | Mixed  ICU | | | | | ICDSC  8hrly  *Bedside* | ICU LOS > 24 hrs  Receiving IV midazolam and/or  IV fentanyl | | Cerebral anoxia  CNS lesion that could cause or mimic coma | | | | Gender male  Age  APACHE II score  Body Mass Index  Smoking  Alcohol consumption  Hepatic dysfunction  Renal dysfunction  IV midazolam levels  IV fentanyl levels | | ns  ns  ns  ns  ns  ns  ns  ns  ns | | | | p=0.34  p=0.34  p=0.90  p=0.49  p=0.33  p=0.61  p=0.07  p=0.26  p=0.001  p=0.40 | | ICU Delirium Incidence  Cox Regression Model | | | | | | | + | | | |
| Comments | | | * No Odds Ratios or Confidence Intervals given, only p-values * IV midazolam levels were significantly lower in patients with delirium than in patients without delirium * Time to first occurrence of delirium was not associated with the presence (p=0.3) of midazolam or midazolam dose (p=0.4) | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Svenningsen 2013 [35] | | Prospective Cohort  Multicenter | | | 416/640  (65%) | | Mixed  ICU | | | | | CAM-ICU  12hrly  *Research* | All patients | | LOS ICU <48hrs  Inability to communicate  Readmission to ICU >24hrs | | | | RASS change >2  Propofol bolus  Propofol continuous  Midazolam bolus  Midazolam continuous  Alfentanil | | 5.2  1.5  0.9  0.7  0.4  1.5 | | | | (3.8-7.1)  (0.4-1.0) (ns)  (0.7-1.2) (ns)  (0.4-1.2) (ns)  (0.2-0.7)  (1.08-2.2) | | ICU Delirium Incidence  Logistic regression | | | | | | | + | | | |
| Comments | | | * 41 patients already delirious at ICU admission whom were not included in logistic regression analysis due to outcome of incident delirium * Interpret OR Alfentanil as compared to no opiates, OR propofol bolus/continuous and midazolam bolus/continuous compared to no sedatives * Adjusted for: gender, age (in quartiles), SAPS II, ICU Center, ICU setting (medical/surgical) * No adjustments for repeated measurements! Poor statistical method! | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| van Rompaey 2009 [36] | | Prospective Cohort  Multicenter | | | 155/523 (30%) | | Mixed  ICU | | | | | NEECHAM  24hrly | LOS >24hrs  GCS>10 | | MV at inclusion  No informed consent | | | | >3 Alcohol units/day  Cognitive impairment  Medical admission  Psychoactive medication in ICU  Artificial airway  >3 medication perfusions  Lack of windows  Isolation  Lack of visits | | 3.2  2.4  4.0 3.3  8.1  2.7  2.4  2.9  3.7 | | | | (1.3-8.0)  (1.2-4.8)  (1.5-11.0)  (1.5-11.2)  (1.2-55.1)  (1.1-7.1)  (1.3-4.5)  (1.0-8.4)  (1.8-7.9) | | ICU delirium Occurrence  Logistic Regression | | | | | | | + | | | |
| Comments | | | * no blinding of outcome assessment and subjective risk factors | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| ICU: Intensive Care unit, ICDSC: Intensive Care Delirium Screening Checklist, LOS: length of stay, CNS: central nervous system, APACHE II(-APS): Acute Physiology and Chronic Health Evaluation II (Acute Physiology Score), IV: intravenous, ns: non significant, CAM(-ICU): Confusion Assessment Method (for use in the ICU), RASS: Richmond Agitation and Sedation Scale, NEECHAM: Neelon and Champagne Confusion Scale, GCS: Glasgow Coma Scale, MV: mechanical ventilated, hrly: hourly, hrs: hours, hr: hour | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Article** | | **Study Design** | | | **Number of delirious / Total (%)** | | **Type IC** | | | | | **Method Delirium Assessment** | **Inclusion** | | **Exclusion** | | | | **Risk Factor** | | **Effect estimate**  **Risk Factor** | | | | | | **Outcome**  **Model** | | | | | | | **Quality** | | | |
| Veiga 2012 [37] | | Prospective Cohort | | | 128/680  (19%) | | PACU | | | | | ICDSC  8hrly | Hospital stay <48hrs | | No informed consent  Cardiac/neurological surgery  CNS/Parkinson’s disease  Delirium/antipsychotics use  Drug/alcohol/opioid abuse  Readmission to PACU  Persistent Coma | | | | Age  ASA III/IV  Emergency surgery  Fresh Frozen Plasma | | 1.05  2.2  2.7  1.7 | | | | (1.04-1.1)  (1.3-4.0)  (1.6-4.5)  (1.3-2.2) | | PACU Delirium Incidence  Logistic Regression | | | | | | | ++ | | | |
| Comments | | | * Delirium assessments only performed in the PACU. Median (IQR) LOS PACU for patients without delirium 19 (16-30) and with delirium 40 (18-87).  Difference observed in this study could be explained merely due to increased length of stay (due to disease severity/complications) with increased time to develop delirium | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Whitlock 2014 [38] | | Nested  Prospective  Cohort | | | 73/310  (23,5%) | | Cardio-  thoracic  ICU | | | | | CAM-ICU  12hrly  *Bedside* | Cardiothoracic surgery  General anesthesia  Increased risk for intraoperative awareness | | Surgery with wake-up test  Unable to provide informed consent  Pre-existing dementia  Stroke with residual neurological deficits | | | | Nested cohort:  ASA score 4 (vs 1,2 and 3)  EuroSCORE (per 1 point)  Packed RBC’s (per 1 unit)  Average maintenance ETAC (per 0,1 aaMAC increase) | | 2,88  1,20  1,26  0,70 | | | | (1,18-6,94)  (1,07-1,36)  (1,10-1,43)  (0,53-0,92) | | ICU Delirium Incidence  Logistic Regression | | | | | | | ++ | | | |
| Comments | | | * Single-center substudy of the BAG-RECALL trial * Used a a Bayesian stochastic search variable selection approach to select variables | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Wolters 2015 [39] | | Prospective  Cohort | | | 535/1112  (48%) | | Mixed  ICU | | | | | CAM-ICU  +  Chart review  24hrly  *Bedside*  *Research* | ICU LOS >24 hrs | | Transfer from other ICU or hospital  Neurological disorder  Delirium assessment not possible | | | | Corticosteroid administration  Corticosteroid dose | | 1.08  1.00 | | | | (0.89-1.32) (ns)  (0.99-1.01) (ns) | | Transition into delirium  Logistic Regression | | | | | | | ++ | | | |
| Yoshitaka 2013 [40] | | Prospective Cohort | | | 13/40  (33%) | | Surgical  ICU | | | | | CAM-ICU  5 times  *1 Physician* | >20 years of age  LOS ICU > 48hrs  Elective surgery | | Emergency surgery  Cardiopulmonary bypass  Brain surgery  Psychosis/dementia  Substance/alcohol abuse  Vision/hearing impairment  No Informed consent | | | | Age  APACHE II  Postoperative epidural  Postoperative MV  Duration of operation  Δ melatonin 1hr postoperative | | 1.2  1.8  0.3  14.1  1.0  0.5 | | | | (1.02-1.4)  (1.09-2.9)  (0.0-3.4) (ns)  (0.4-519.2) (ns)  (0.99-1.01) (ns)  (0.3-0.99) | | Delirium incidence  (up to day 2 postoperative)  Logistic Regression | | | | | | | ++ | | | |
| Comments | | | * Δ melatonin 1hr postoperative is difference with preoperative melatonin concentration in pg/mL | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| PACU: Post Anesthesia Care Unit, ICDSC: Intensive Care Delirium Screening Checklist, CNS: Central Nervous System, ASA: American Society of Anesthesiologists, IQR: interquartile range, ICU: Intensive Care unit, CAM-ICU: Confusion Assessment Method for use in the ICU, EuroSCORE: European System for Cardiac Operative Risk Evaluation, RBC: red blood cell, ETAC: end tidal anesthetic concentration, aaMAC: age-adjusted minimum alveolar concentration, LOS: Length of stay, APACHE II: Acute Physiology and Chronic Health Evaluation II, MV: mechanical ventilated, ns: non significant, hrly: hourly, hrs:hours, hr: hour, OR: Odds Ratio, AUC: Area under the Curve, | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Article** | | **Study Design** | | | **Number of delirious / Total (%)** | | **Type IC** | | | | | **Method Delirium Assessment** | **Inclusion** | | **Exclusion** | | | | **Risk Factor** | | **Effect estimate**  **Risk Factor** | | | | | | **Outcome**  **Model** | | | | | | | **Quality** | | | |
| Zhang 2014 [41] | | Prospective  Cohort | | | 54/223  (24,2%) | | Mixed  ICU | | | | | CAM-ICU  8hrly  *Bedside* | GCS > 10  RASS ≥ -3  ICU LOS > 48 hrs | | Acute structural brain disease  Do-not-resuscitation order  Delirious at ICU admission | | | | Age  Sex  APACHE II  Intubated (vs non-intubated)  Living alone  Physical restraint  Alcohol drinking  Smoking  Hospital LOS before ICU | | 1.00  0.67  1.13  1.50  1.75  2.80  2.23  0.94  1.01 | | | | (0.97-1.04) (ns)  (0.27-1.62) (ns)  (1.06-1.21)  (0.56-4.04) (ns)  (0.51-5.94) (ns)  (0.99-7.90) (ns)  (0.84-5.98) (ns)  (0.32-2.79) (ns)  (0.97-1.05) (ns) | | ICU Delirium Incidence  Logistic Regression | | | | | | | ++ | | | |
| ICU: Intensive Care unit, CAM-ICU: Confusion Assessment Method for use in the ICU, GCS: Glasgow Coma Scale, RASS: Richmond Agitation and Sedation Scale, LOS: Length of stay, APACHE II: Acute Physiology and Chronic Health Evaluation II, ns: non significant, hrly: hourly, hrs:hours, hr: hour | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Article** | | | | **Study Design** | | **Number of delirious / Total (%)** | | **Type IC** | | | | **Method Delirium Assessment** | | **Inclusion** | | **Exclusion** | | | | **Risk Factor** | | | | **Effect estimate**  **Risk Factor** | | | | | | **Outcome**  **Model** | | | | | **Quality** | | | | |
| Zaal 2012 [42] | | | | B/A | | 62/130  (48%) | | Mixed  ICU | | | | CAM-ICU  +  Chart Review  24hrly  *Research* | | All patients | | ICU LOS<24hrs  Persistent Coma | | | | Single-Room ICU  Maximum SOFA score  APACHE II  Age  Female  Emergency admission  Charlson Comorbidity Index ≥1  Charlson Comorbidity Index ≥3  Surgical Admission  Medical Admission  Neurological Admission | | | | 0.7  1.1  0.98  1.01  1.0  1.7  1.4  2.1  1.8  1.1  2.0 | (0.5-0.9)  (1.1-1.2)  (0.96-1.0)  (1.0-1.02)  (0.8-1.4) (ns)  (0.9-3.1) (ns)  (1.0-2.1) (ns)  (1.4-3.3)  (1.1-2.9)  (0.7-1.8) (ns)  (1.2-3.1) | | | | | Total number of delirium days during ICU  Poisson Regression  (Rate Ratio) | | | | | + | | | | |
| Comments | | * Intervention: transition from traditional ICU with wards and a single-room ICU with, among others, improved daylight and improved orientation * OR Charslon Comorbidty index interpret as compared to Charlson Comorbidity Index of 0. * OR Surgical/Medical/Neurological admission compared to cardiovascular admission * No blinding | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Girard 2008 [43] | | | | RCT  Multicenter | | ?/335  (?) | | Medical ICU | | | | CAM-ICU  24hrly  *Research* | | MV > 12hrs | | Cardiac arrest  Ventilated ≥ 2 weeks  Moribund  Neurological disease  No informed consent | | | | Paired sedation and ventilator weaning protocol vs sedation per usual care plus daily ventilator weaning | | | | 2 vs 3 (ns) | | | | | | Total number of delirium days during ICU, median | | | | | ++ | | | | |
| Pandharipande 2007 [44] | | | | RCT  Multicenter | | 83/106  (81%) | | Mixed  ICU | | | | CAM-ICU  12hrly  *Research* | | MV > 24hrs | | Neurological disease  Active seizure disorder  Child-Pugh Class B/C cirrhosis  Alcohol abuse  Active myocardial ischemia  2nd or 3rd degree heart block  Severe dementia  Pregnancy  Severe hearing loss  No informed consent | | | | Sedation dexmedetomidine up to 120 hrs vs lorazepam sedation up to 120 hrs | | | | 9 vs 7 (ns)  3 vs 4 (ns)  79% vs 82% (ns) | | | | | | Delirium free days, median  Delirium days, median  Delirium prevalence, % | | | | | ++ | | | | |
| Riker 2009 [45] | | | | RCT  Multicenter | | 225/375  (60%) | | Mixed  ICU | | | | CAM-ICU  24 hrly  *Research* | | MV for less <96hrs  Anticipated MV >3d | | Trauma/burns  Dialysis  Pregnancy/lactation  Epidural/spinal analgesia  CNS pathology  Acute hepatitis/liver disease  Child-Pugh Class C cirrhosis  Hepatitis  Active myocardial ischemia  2nd or 3rd degree heart block  left ventricular EF < 30%  HR < 50/min, SBP<90mmHg  No informed consent | | | | Sedation with dexmedetomidine (I) vs midazolam (C) up to 30days to achieve light sedation | | | | 54% vs 77% p<0.001  33% vs 55% p=0.030  3 vs 2 p=0.002 | | | | | | Delirium prevalence, %  Delirium incidence, %  Delirium-free days, mean | | | | | ++ | | | | |
| Comments | | * Prevalence including patients with delirium at study enrollment 138 (I) and 70 (C) leaving respectively 76 (I) and 40 (C) patients for incidence measure | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| B/A: Before/after study, ICU: Intensive Care unit, CAM-ICU: Confusion Assessment Method for use in the ICU, MV: mechanical ventilated, APACHE II: Acute Physiology and Chronic Health Evaluation II, ns: non significant, hrly: hourly, hrs:hours, hr: hour, LOS: Length of stay, CNS: Central Nervous System, OR: Odds Ratio, SOFA: Sequential Organ Failure Assessment, RCT: randomized controlled trial, EF: ejection fraction, HR: heartrate, SBP: systolic blood pressure, I: intervention, C: control | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| **Article** | | | | **Study Design** | | **Number of delirious / Total (%)** | | **Type IC** | | | | **Method Delirium Assessment** | | **Inclusion** | | **Exclusion** | | | | **Risk Factor** | | | | **Effect estimate**  **Risk Factor** | | | | | | **Outcome**  **Model** | | | | | | **Quality** | | | |
| Ruokonen 2009 [46] | | | | RCT  Multicenter | | 15/85  (18%) | | Mixed  ICU | | | | CAM-ICU  24hrly  *Research* | | LOS ICU <72hrs  MV  Sedation need>24hrs  ICU stay >48hrs | | Acute neurological disorder  MAP<55mmHg, HR<50/min  2nd or 3rd degree heart block  Hepatic SOFA >2  Pregnancy/lactation  Vision/hearing loss  Use 2-agnosit at inclusion  No informed consent | | | | Dexmedetomidine sedation vs standard care (propofol or midazolam) | | | | 44% vs 25% p=0.035 | | | | | | Delirium Occurence, %  (combined CAM-ICU positive and adverse event) | | | | | | + | | | |
| Comments | | * Delirium not assessed at inclusion. Delirium secondary outcome (not powered) * More CAM-ICU assessments in intervention group because of less deep sedation, consequently higher risk of CAM-ICU positive assessment measure | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Schweickert 2009 [47] | | | | RCT  Multicenter | | ?/104  (?) | | Mixed  ICU | | | | CAM-ICU  24hrly  *Research* | | MV <72hrs  Sedated  MV need >24hrs  Baseline functional independence | | Neuromuscular disease  Cardiac arrest  Raised intracranial pressure  Absent limbs  6month survival<50%  No informed consent | | | | Early exercise and mobilsation vs standard care (both with daily sedation interruption) | | | | 2 vs 4 p=0.030  33% vs 57% p=0.020  2 vs 4 p=0.020  28% vs 41% p=0.010 | | | | | | ICU delirium days, md  Time ICU with delirium,%  Hospital delirium days,md  Hospital with delirium,% | | | | | | ++ | | | |
| Van Rompaey 2012 [48] | | | | RCT | | /136 | | Mixed  ICU | | | | NEECHAM  8hrly  *Bedside* | | LOS >24hrs  GCS>10 | | Hearing impairment  Dementia/confusion/delirium  Sedation use | | | | Earplugs (I)  SOFA  Age  Smoking | | | | 0.5  1.09  1.03  1.9 | (0.3-0.8)  (1.01-1.2)  (1.01-1.05)  (1.1-3.5) | | | | | Time to delirium/mild confusion  Cox Regression (HR) | | | | | | + | | | |
| ICU: Intensive Care unit, CAM-ICU: Confusion Assessment Method for use in the ICU, MV: mechanical ventilated, APACHE II: Acute Physiology and Chronic Health Evaluation II, ns: non significant, hrly: hourly, hrs:hours, hr: hour, LOS: Length of stay, HR: hazard ratio, GCS: Glasgow Coma Scale, NEECHAM: Neelon and Champagne Confusion Scale, SOFA: Sequential Organ Failure Assessment, RCT: randomized controlled trial, HR: heartrate, MAP: mean arterial ressure, I: intervention, C: control | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | | |

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