**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 | ICDSC8 hrly*??* | Major elective surgeryexpected hospital stay >48hrs | Neurological or cardiac surgeryCNS conditionParkinsonDeliriumAntipsychotics useDrug/alcohol/opioid abuseNo informed consent | Age ≥ 65 yearsEmergency surgeryCongestive 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-ICU24 hrly*??* | >24 hrs MVBurn injuries | Neurological conditionPostanoxic encephalopathyMoribundImpaired hearing | Delirious previous day Comatose previous dayBenzodiazepines dose <24 hrOpiates dose <24 hrMethadone dose <24 hrBaseline Component | 26.5 44.9 6.8 0.5 0.70.6 | (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 deliriumLogistic 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%) | SurgicalICU | DSM-III 24hrly*Research* | All patients | None | Respiratory diseaseInfectionFeverHypotensionAnemiaHypocalcemiaHyponatremiaElevated serum urea nitrogenElevated hepatic enzymesHyperamylasemiaHyperbilirubinemiaMetabolic acidosis | 30.618.014.319.85.430.98.24.66.343.48.74.5 | (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 OccurrenceForward StepwiseLogistic 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%) | TraumaICU | CAM-ICU 24hrly *??*+ chart review<24hrs *R* | TraumaISS ≥ 8 | Impaired vision/hearingNo informed consent | Age ISS GCS at Emergency Department Transfusion, unitsMaximum MOF score | 1.03 1.1 0.6 1.48.8 | (1.0-1.1)(1.0-1.1)(0.6-1.1) (ns)(1.0-1.9)(1.7-45.1) | Delirium ICU OccurrenceLogistic Regression | ++ |
| Comments | * OR GCS at Emergency Department just not significant (p=0.08)
 |
| Bryczkowski 2014 [5] | Prospective cohort | 70/115 (61%) | Surgical ICU | CAM-ICU12 hrly*Research* | Trauma patientsAge > 50 yearsAdmission ≥ 24 hours | Age ≤ 50 yearsDied in SICUHistory of dementiaTransferred from jail or in active police custody | Vent-free daysChest injury (chest AIS score ≥ 3)AgeInitial GCS scoreBenzo-free daysTBIDeep sedation, hours RASS low (≤ -3) | 0.790.281.10.850.840.650.99 | (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 IncidenceLogistic Regression | + |
| Colombo 2012 [6] | B/A | 80/314 (26%) | MixedICU | CAM-ICU 12hrly*Research* | All patients | Cognitive disordersDementiaPsychosisDisability after strokeMoribund | AgeMidazolam + opiate infusionReorientation 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] | ProspectiveCohort | 40/198 (19%) | Mixed ICU | DSM-IV screening ICDSC 24hrly*Bedside* *Nurse* | >24hrs | Moribund No informed consent | HypertensionSmokingBilirubine (per 10% increase)EpiduralMorphine 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 ICULogistic 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%) | MedicalICU | CAM-ICU12hrly*Research team* | MV>24hrs | None | APOE4 presentAge, yearsAPACHE IIComa days, quintilesSepsis/ARDS/pneumoniaTotal dose lorazepam, mg  | 7.31.01.01.31.71.0 | (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 daysLogistic Regression(Proportional Odds) | ++ |
| Girard 2012 [9] | ProspectiveCohort | 107/138(78%) | Medical ICU | CAM-ICU24hrly*Research team* | MV>12 hrs | MoribundAfter cardiac arrestNeurological diseaseMV ≥ 2 weeks | MMP-9 (ng/mL)sTNFR1 (pg/mL)Protein C (% control) | 0.42.1 0.4 | (0.2-0.8)(1.2-3.6)(0.2-0.9) | Delirium day after biomarker assessmentLogistic 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%) | TraumaICU | CAM-ICU12hrly *??* | ISS > 15 | Intracranial hemorrhageNo continuous oxygen saturation data. | Ventilator daysPulse (Emergency Department) | 1.21.02 | (1.1-1.3)(1.00-1.04) | Delirium ICU OccurenceLogistic 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 | DDS8hrly*Bedside nurse* | All patients | Deep sedation (RASS≤-3)Psychiatric diseasesCognitive disordersSevere braininjuries (GCS≤8) | HyperglycemiaAPACHE IISOFAHAP/VAPAlcohol abusePolytraumaTISS | 4.23.1 1.21.11.58.02.37.22.314.52.71.1 | (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 RegressionCox 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 CohortMulticenter | 244/564 (43%) | Mixed ICU | CAM-ICU24 hrly*Research Team* | Adult patients | Non-Englisch or non-Spanish languageDevelopmental delayEnd-stage dementia | ARDS status Not Intubated, no ARDS Intubated, no ARDS Intubated, with ARDSAgeCharlson Comorbidity IndexAPACHE IVDementiaNon-English languageAlcohol abuseIllicit drug useSevere sepsisAny benzodiazepineAny opiateAny propofolAny steroid | Ref1.986.551.001.211.226.762.202.421.971.111.931.144.161.06 | (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 PrevalenceLogistic 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-ICU12 hrly*Bedside* | Admission to ICU | - | Age, per yearRace White Black OtherUses pharmacological sleep aids at homeHome sleep quality Very good Somewhat good Somewhat/very bad Unkown/not answeredTotal quality on RCSQReceiving mechanical ventilation without sedationReceived sedative infusion while not mechanically ventilatedReceived sedative infusion while mechanically ventilated | 1.01 (1.00-1.02) (ns)Ref0.76 (0.49-1.17) (ns)1.63 (0.65-4.12) (ns)0.40 (0.20-0.80) (ns)Ref1.01 (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 deliriumLogistic Regression | ++ |
| Leite 2014 [14] | Prospective cohort | 34/64(53,1%) | Mixed ICU | CAM-ICUtwice daily*Research Team* | Age ≥ 18 yearsAdmission to ICUMV > 24 hoursBeing in the process of weaning from MV  | Degenerative neurological diseasePrior known psychiatric conditionsRecent psychiatric events including suicide attemptsHistory of drug addiction or alcoholismCompromised level of consciousness (GCS ≤ 8 or RASS < -3) at beginning of studyPresence of tracheostomy | AgeSOFA scoreAPACHE II scoreNeurological causeSex | p-value 0.01p-value 0.03p-value 0.01p-value 0.01p-value 0.93 (ns) |  | Incidence of deliriumPrincipal component analysis | + |
| Comments | * No odds ratio’s or confidence intervals provided
 |
| Limpawattana 2016 [15]  | Prospective Cohort | 44/99 (44,4%) | Medical ICU | CAM-ICU24 hrly*Research Team* | ≥65 years of age | Readmission to ICUNo informed consentComa (RASS score < -3)Severe aphasiaSevere hearing impairment | Previous strokeBed change > 3Physical restraintsUse of bladder catheterOn mechanical ventilators | 6.35 15.7521.462.030.86 | (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 deliriumLogistic 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%) | MedicalICU | CAM-ICU24hrly*Research Team* | MV | Neurological diseasePsychological disordersHigh dose morphineHigh dose midazolamGeneral anesthesia/neuro-muscular blocking agents3/5 Consecutive days comatose No informed consent | HypoalbuminemiaDiabetes MellitusSepsis | 5.9 2.53.7 | (1.2-28.8)(0.9-7.4) (ns)(1.03-12.9) | Delirium incidence first 5 days of ICU admissionLogistic Regression | ++ |
| Lin 2015 [17] | Prospective cohort | 68/90 (75,6%) | Medical ICU | CAM-ICUtwice daily | ≥65 years of ageRASS score ≥ -3Admission in previous 24 hours | Readmission to ICU | No. of sedatives usedAgeLength of stayAPACHE IIRASSCOPDStrokeDays of ventilator useNo. of anesthetic analgesics usedTotal no. of medications usedDuration of trachea useUse of steroids before ICU admissionDuration of dehydrationSensory impairmentMalnutrition | 0.780.981.010.921.0615.872.161.100.053.530.930.012.100.36NA | (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 incidenceLogistic Regresiion | + |
| McNicoll 2003 [18] | ProspectiveCohort | 83/118(70%) | Medical ICU | CAM-ICU24hrly*Research team* | ≥65 years of age | No informed consentTransfer from another ICUAphasia/advanced dementiaDeath 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 CohortNested in SLEAP trialMulticenter | 226/420 (53,8%) | Mixed ICU | ICDSC24 hrly*Bedside nurse* | MV ≥ 48 hoursContinuous IV opioid and/or benzodiazepine infusion | Cardiac arrestTraumatic brain injuryNeuromuscular blockersEnrolled in a related trialPreviously enrolled in SLEAPLacking commitment to maximal therapy | Age < 40 41-65 66-80 > 80APACHE II <19 19-24 24-29 >29TabaccoAlcohol (≥ 2 drinks/day)Neurologic conditionCardiac diseaseRandomization groupComaRenal replacementPhysical restraintTotal midazolam (1mg increase)Total fentanyl (0,1 mg increase)Antipsychotic use in ICU | Ref0.920.910.85Ref0.940.980.641.4010180.861.330.940.551.051.870.9981.01.67 | 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 prevalenceCox proportional hazards regression analysis | + |
| Morandi 2011 [20] | Prospective CohortNested in ABC trial | 40/62(64%) | MedicalICU | CAM-ICU12hrly*Research Team* | MV > 12hrs | Cardiac arrestVentilated ≥ 2 weeksMoribundNeurological diseaseNo informed consent | IGF-1 | 1.0  | (0.6-1.8) (ns) | Delirium day after IGF-1 measurementLogistic 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 CohortNested in VALID study | ?/?(?%) | Medical ICU | CAM-ICU24hrly*Research Team* | All patients | ICU LOS >3daysCardiac arrestSevere chronic lung diseaseElective cardiothoracic surgery Uncomplicated overdoseDied/discharged ≤48hrs | 25-OHD, nmol/LAgeAPACHE II | 1.01.01.1 | (0.99-1.0) (ns)(0.95-1.0) (ns)(1.03-1.2) | Delirium day after 25-OHD measurementLogistic 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%) | MixedICU | ICDSC1-8hrly*Bedside* | All patients | MoribundComatose >5 days/until death | Hypertension (History)Alcoholism (History)APACHE IIIatrogenic ComaPain (assessed by NRS)Anxiety | 1.92.01.053.70.91.8 | (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 OccurrenceLogistic 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-ICU24hrly*Research Team* | MV | Neurological diseasePersistent comaLack of 2 consecutive cognitive assessments | LorazepamMidazolamFentanylMorphinePropofolAPACHE IIAgeAntipsychoticsAnticholinergic drugsCross products | 1.21.71.21.11.21.061.02nsnsns | (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 deliriumLogistic 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-ICU24hrly*Bedside* | MV > 24hrs | Neurological diseaseHearing lossMoribundPersistent coma | AnestheticsH2 BlockersLorazepamMidazolamFentanylMorphine | 0.51.50.52.81.90.4  | (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 deliriumLogistic 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-ICU24hrlyChartreview*Research*  | ≥60 years of age | No informed consentTransferred from another ICUInability to communicate <ICULOS ICU < 24hrs | Dementia (IQCODE>3.3)Benzodiazepines <ICU Creatinine > 2mg/dLArterial pH <7.35 | 6.33.42.12.1 | (2.9-13.8)(1.6-7.0)(1.1-4.0)(1.1-3.9) | Delirium first 48hoursLogistic 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-ICU24hrly*Bedside* | MV | Neurological diseaseActive seizure disorderChild-Pugh Class B/C cirrhosisAlcohol abuseActive myocardial ischemia2nd or 3rd degree heart blockSevere dementiaPregnancySevere hearing lossNo informed consent | Tryptophan/LNAA ratioTyrosine/LNAA ratioPhenylalanine/LNAA ratioAgeModified APACHE IIIQCODEDexmedetomidine <24hrsLorazepam <24hrsFentanyl <24hrsMental status <24hrs | p-valuep-valuep-valuep-valuep-valuep-valuep-valuep-valuep-valuep-value | <0.05<0.05ns<0.052x<0.05nsnsnsns1x<0.05 | Transition towards delirium day after (day 2 and day 4) measurementLogistic 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-ICU24hrlyChartreview*Research*  | ≥60 years of age | No informed consentTransferred from another ICUInability to communicate <ICULOS ICU < 24hrsPersistent coma | Benzodiazepine/opioid useDementia (IQCODE>3.3)HaloperidolModified APACHE II | 1.61.21.41.01 | (1.3-2.1) (1.1-1.3) (1.2-1.5) (1.00-1.02) | Duration first delirium episode in ICUPoisson 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 CohortMulticenter | 274/330(83%) | MixedICU | CAM-ICU24hrly*Research* | MVAcute lung injury  | Illness with life expectancy < 6 monthsCognitive impairmentCommunication barriersNo fixed addressTransferred from other hospital and ALI > 24 hoursMV > 5 days before onset ALIPrevious lung resection  | Age < 40 years 40-60 years > 60 yearsMaleHome use of opioidsAPACHE II scoreDaily SOFA scoreDaily sepsis statusCorticosteroid administrationCorticosteroid doseBenzodiazepine administrationBenzodiazepine dose | Ref1.812.521.341.111.011.031.061.520.971.321.02 | (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 dayLogistic Regression (First-order Markov model) | ++ |
| Serafim 2012 [29] | Prospective Cohort | 43/465(9%) | Surgical ICU | CAM12hrly*Bedside*  | RASS > -3 | MVPregnancyInability to verbalizeHearing or visual impairmentNo informed consent | AgeAPACHE II APSBenzodiazepine use first 24hrEmergency surgeryTrauma patient | 1.041.12.38.16.2 | (1.02-1.1)(1.04-1.2)(1.04-5)(3.6-18.1)(4.1-6.5) | ICU delirium occurrenceLogistic 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-ICU24hrly*Research* | MV > 12hrs | Cardiac arrestVentilated ≥ 2 weeksMoribundNeurological diseaseNo informed consent | Change in sedative dosing:* Benzodiazepine, mg/hr
* Propofol, mcg/kg/min

Daytime sedative dosing:* Benzodiazepine, mg/hr
* Propofol, mcg/kg/min
 | 2.51.411663.2 | (1.0-6.3) (ns)(0.8-2.5) (ns)(16-82719)(1.0-10.6)(ns) | Transition towards delirium day after exposureLogistic 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 CohortMulticenter | 114/259(44%) | Mixed ICU | CAM-ICU4hrly*Research* | MV ≤24hrsMV expected >24hrsSedative/analgesics | Neurological impairmentPsychiatric illnessBurnsDementiaPalliative careUnable to communicate | Early deep sedation Cumulative dose of Dexmedetomidine first 48hrAPACHE IIAgeMaleOperativeElectiveCardiacRespiratorySepsisGastrointestinalVasopressorsDialysis | 1.01.41.01.011.41.11.31.20.91.20.91.21.0 | (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 admissionCox 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-DESC24hrly*Bedside* *Research (ward)* | All patients | Psychiatric diseasesGlucocorticoids>5dys within 1yrNeurosurgeryAdrenal gland disease/surgeryNeed of glucocorticoids Moribund | Age (/10years increase)History of strokeAPACHE IISerum cortisol (first postoperative day) | 2.64.51.43.4 | (1.4-4.9)(1.2-16.5)(1.2-1.6)(1.7-6.8) | Postoperative Delirium Occurrence up to day 7Logistic Regression | + |
| Comments | * Delirium assessment with the Nu-DESC which is validated in non-mechanically ventilated ICU patients
 |
| Simons 2014 [33] | RetrospectiveCohort | 998/3198(31,2%) | MixedICU | CAM-ICU12hrly*Bedside* | All patients | ICU admission after >30 days of hospital admission | Sex (male)Age (per year)InfectionSedationSeason Spring Summer Autumn WinterDiagnostic category Surgical Medical Trauma NeurologicAPACHE II28-day photoperiod | 1.031.023.373.78Ref1.001.060.88Ref0.903.113.701.101.00 | (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 IncidenceLogistic 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] | ProspectiveCohort | 64/99(65%) | MixedICU | ICDSC8hrly*Bedside* | ICU LOS > 24 hrsReceiving IV midazolam and/orIV fentanyl | Cerebral anoxiaCNS lesion that could cause or mimic coma | Gender maleAgeAPACHE II scoreBody Mass IndexSmokingAlcohol consumptionHepatic dysfunctionRenal dysfunctionIV midazolam levelsIV fentanyl levels | nsnsnsnsnsnsnsnsns | p=0.34p=0.34p=0.90p=0.49p=0.33p=0.61p=0.07p=0.26p=0.001p=0.40 | ICU Delirium IncidenceCox 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 CohortMulticenter | 416/640(65%) | Mixed ICU | CAM-ICU12hrly*Research* | All patients | LOS ICU <48hrsInability to communicateReadmission to ICU >24hrs | RASS change >2 Propofol bolusPropofol continuousMidazolam bolusMidazolam continuousAlfentanil  | 5.21.50.90.70.41.5 | (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 IncidenceLogistic 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 CohortMulticenter | 155/523 (30%) | Mixed ICU | NEECHAM24hrly | LOS >24hrsGCS>10 | MV at inclusionNo informed consent | >3 Alcohol units/dayCognitive impairmentMedical admissionPsychoactive medication in ICUArtificial airway >3 medication perfusionsLack of windowsIsolationLack 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 OccurrenceLogistic 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 | ICDSC8hrly | Hospital stay <48hrs | No informed consentCardiac/neurological surgeryCNS/Parkinson’s diseaseDelirium/antipsychotics useDrug/alcohol/opioid abuseReadmission to PACUPersistent Coma | AgeASA III/IVEmergency surgeryFresh Frozen Plasma | 1.052.22.71.7 | (1.04-1.1)(1.3-4.0)(1.6-4.5)(1.3-2.2) | PACU Delirium IncidenceLogistic 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] | NestedProspectiveCohort | 73/310(23,5%) | Cardio-thoracicICU | CAM-ICU12hrly*Bedside* | Cardiothoracic surgeryGeneral anesthesiaIncreased risk for intraoperative awareness | Surgery with wake-up testUnable to provide informed consentPre-existing dementiaStroke 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) | 2,881,201,260,70 | (1,18-6,94)(1,07-1,36)(1,10-1,43)(0,53-0,92) | ICU Delirium IncidenceLogistic 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] | ProspectiveCohort | 535/1112(48%) | MixedICU | CAM-ICU+Chart review24hrly*Bedside**Research* | ICU LOS >24 hrs | Transfer from other ICU or hospitalNeurological disorderDelirium assessment not possible | Corticosteroid administrationCorticosteroid dose | 1.081.00 | (0.89-1.32) (ns)(0.99-1.01) (ns) | Transition into deliriumLogistic Regression | ++ |
| Yoshitaka 2013 [40] | Prospective Cohort | 13/40(33%) | SurgicalICU | CAM-ICU5 times*1 Physician* | >20 years of ageLOS ICU > 48hrsElective surgery | Emergency surgeryCardiopulmonary bypass Brain surgeryPsychosis/dementiaSubstance/alcohol abuseVision/hearing impairmentNo Informed consent | AgeAPACHE IIPostoperative epidural Postoperative MVDuration of operationΔ melatonin 1hr postoperative | 1.21.80.314.11.00.5 | (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] | ProspectiveCohort | 54/223(24,2%) | MixedICU | CAM-ICU8hrly*Bedside* | GCS > 10RASS ≥ -3ICU LOS > 48 hrs | Acute structural brain diseaseDo-not-resuscitation orderDelirious at ICU admission | AgeSexAPACHE IIIntubated (vs non-intubated)Living alonePhysical restraintAlcohol drinkingSmokingHospital LOS before ICU | 1.000.671.131.501.752.802.230.941.01 | (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 IncidenceLogistic 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%) | MixedICU | CAM-ICU+Chart Review24hrly*Research* | All patients | ICU LOS<24hrsPersistent Coma | Single-Room ICUMaximum SOFA scoreAPACHE IIAge FemaleEmergency admissionCharlson Comorbidity Index ≥1Charlson Comorbidity Index ≥3Surgical AdmissionMedical AdmissionNeurological Admission | 0.71.10.981.011.01.71.42.11.81.12.0 | (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 ICUPoisson 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] | RCTMulticenter | ?/335(?) | Medical ICU | CAM-ICU24hrly*Research* | MV > 12hrs | Cardiac arrestVentilated ≥ 2 weeksMoribundNeurological diseaseNo 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] | RCTMulticenter | 83/106(81%) | MixedICU | CAM-ICU12hrly*Research* | MV > 24hrs | Neurological diseaseActive seizure disorderChild-Pugh Class B/C cirrhosisAlcohol abuseActive myocardial ischemia2nd or 3rd degree heart blockSevere dementiaPregnancySevere hearing lossNo 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, medianDelirium days, medianDelirium prevalence, % | ++ |
| Riker 2009 [45] | RCTMulticenter | 225/375(60%) | MixedICU | CAM-ICU24 hrly*Research* | MV for less <96hrsAnticipated MV >3d | Trauma/burnsDialysisPregnancy/lactationEpidural/spinal analgesiaCNS pathologyAcute hepatitis/liver diseaseChild-Pugh Class C cirrhosisHepatitisActive myocardial ischemia2nd or 3rd degree heart blockleft ventricular EF < 30%HR < 50/min, SBP<90mmHgNo informed consent | Sedation with dexmedetomidine (I) vs midazolam (C) up to 30days to achieve light sedation | 54% vs 77% p<0.00133% 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] | RCTMulticenter | 15/85(18%) | MixedICU | CAM-ICU24hrly  *Research* | LOS ICU <72hrsMV Sedation need>24hrsICU stay >48hrs | Acute neurological disorderMAP<55mmHg, HR<50/min2nd or 3rd degree heart blockHepatic SOFA >2Pregnancy/lactationVision/hearing lossUse 2-agnosit at inclusionNo 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] | RCTMulticenter | ?/104(?) | Mixed ICU | CAM-ICU24hrly*Research* | MV <72hrsSedatedMV need >24hrsBaseline functional independence | Neuromuscular diseaseCardiac arrestRaised intracranial pressureAbsent limbs6month survival<50%No informed consent | Early exercise and mobilsation vs standard care (both with daily sedation interruption) | 2 vs 4 p=0.03033% vs 57% p=0.0202 vs 4 p=0.02028% vs 41% p=0.010 | ICU delirium days, mdTime ICU with delirium,%Hospital delirium days,mdHospital with delirium,% | ++ |
| Van Rompaey 2012 [48] | RCT | /136 | Mixed ICU | NEECHAM8hrly*Bedside* | LOS >24hrsGCS>10 | Hearing impairmentDementia/confusion/deliriumSedation use | Earplugs (I)SOFAAgeSmoking | 0.51.091.031.9 | (0.3-0.8)(1.01-1.2)(1.01-1.05)(1.1-3.5) | Time to delirium/mild confusionCox 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 |

**References**

1. Abelha FJ, Fernandes V, Botelho M, Santos P, Santos A, Machado JC, Barros H: **Apolipoprotein E e4 allele does not increase the risk of early postoperative delirium after major surgery**. *Journal of anesthesia* 2012.

2. Agarwal V, O'Neill PJ, Cotton BA, Pun BT, Haney S, Thompson J, Kassebaum N, Shintani A, Guy J, Ely EW *et al*: **Prevalence and risk factors for development of delirium in burn intensive care unit patients**. *Journal of burn care & research : official publication of the American Burn Association* 2010, **31**(5):706-715.

3. Aldemir M, Ozen S, Kara IH, Sir A, Bac B: **Predisposing factors for delirium in the surgical intensive care unit**. *Critical care (London, England)* 2001, **5**(5):265-270.

4. Angles EM, Robinson TN, Biffl WL, Johnson J, Moss M, Tran ZV, Moore EE: **Risk factors for delirium after major trauma**. *American journal of surgery* 2008, **196**(6):864-869; discussion 869-870.

5. Bryczkowski SB, Lopreiato MC, Yonclas PP, Sacca JJ, Mosenthal AC: **Delirium prevention program in the surgical intensive care unit improved the outcomes of older adults**. *J Surg Res* 2014, **190**(1):280-288.

6. Colombo R, Corona A, Praga F, Minari C, Giannotti C, Castelli A, Raimondi F: **A reorientation strategy for reducing delirium in the critically ill. Results of an interventional study**. *Minerva Anestesiol* 2012, **78**(9):1026-1033.

7. Dubois MJ, Bergeron N, Dumont M, Dial S, Skrobik Y: **Delirium in an intensive care unit: a study of risk factors**. *Intensive Care Med* 2001, **27**(8):1297-1304.

8. Ely EW, Girard TD, Shintani AK, Jackson JC, Gordon SM, Thomason JW, Pun BT, Canonico AE, Light RW, Pandharipande P *et al*: **Apolipoprotein E4 polymorphism as a genetic predisposition to delirium in critically ill patients**. *Crit Care Med* 2007, **35**(1):112-117.

9. Girard TD, Ware LB, Bernard GR, Pandharipande PP, Thompson JL, Shintani AK, Jackson JC, Dittus RS, Ely EW: **Associations of markers of inflammation and coagulation with delirium during critical illness**. *Intensive Care Med* 2012, **38**(12):1965-1973.

10. Guillamondegui OD, Richards JE, Ely EW, Jackson JC, Archer KR, Archer-Swygert K, Norris PR, Obremskey WT: **Does hypoxia affect intensive care unit delirium or long-term cognitive impairment after multiple trauma without intracranial hemorrhage?** *J Trauma* 2011, **70**(4):910-915.

11. Heymann A, Sander M, Krahne D, Deja M, Weber-Carstens S, MacGuill M, Kastrup M, Wernecke K, Nachtigall I, Spies C: **Hyperactive delirium and blood glucose control in critically ill patients**. *Journal of International Medical Research* 2007, **35**(5):666-677.

12. Hsieh S, Soto GJ, Pittignano V, Martinez M, Chen J, Ferguson NC, Cheng A, Hope AA, Leung S, Gong MN: **Acute respiratory distress syndrome increases the risk of delirium in critically ill patients**. In: *C55 ACUTE RESPIRATORY DISTRESS SYNDROME.* Am Thoracic Soc; 2013: A4468-A4468.

13. Kamdar BB, Niessen T, Colantuoni E, King LM, Neufeld KJ, Bienvenu OJ, Rowden AM, Collop NA, Needham DM: **Delirium transitions in the medical ICU: Exploring the role of sleep quality and other factors**. *Crit Care Med* 2015, **43**(1):135-141.

14. Leite MA, Osaku EF, Costa CR, Candia MF, Toccolini B, Covatti C, Costa NL, Nogueira ST, Ogasawara SM, de Albuquerque CE *et al*: **Delirium during Weaning from Mechanical Ventilation**. *Critical care research and practice* 2014, **2014**:546349.

15. Limpawattana P, Panitchote A, Tangvoraphonkchai K, Suebsoh N, Eamma W, Chanthonglarng B, Tiamkao S: **Delirium in critical care: a study of incidence, prevalence, and associated factors in the tertiary care hospital of older Thai adults**. *Aging & mental health* 2016, **20**(1):74-80.

16. Lin SM, Huang CD, Liu CY, Lin HC, Wang CH, Huang PY, Fang YF, Shieh MH, Kuo HP: **Risk factors for the development of early-onset delirium and the subsequent clinical outcome in mechanically ventilated patients**. *J Crit Care* 2008, **23**(3):372-379.

17. Lin WL, Chen YF, Wang J: **Factors Associated with the Development of Delirium in Elderly Patients in Intensive Care Units**. *Journal of Nursing Research* 2015, **23**(4):322-329.

18. McNicoll L, Pisani MA, Zhang Y, Ely EW, Siegel MD, Inouye SK: **Delirium in the intensive care unit: occurrence and clinical course in older patients**. *J Am Geriatr Soc* 2003, **51**(5):591-598.

19. Mehta S, Cook D, Devlin JW, Skrobik Y, Meade M, Fergusson D, Herridge M, Steinberg M, Granton J, Ferguson N *et al*: **Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults**. *Crit Care Med* 2015, **43**(3):557-566.

20. Morandi A, Gunther ML, Pandharipande PP, Jackson JC, Thompson JL, Shintani AK, Ely EW, Girard TD: **Insulin-like growth factor-1 and delirium in critically ill mechanically ventilated patients: a preliminary investigation**. *International psychogeriatrics* 2011, **23**(7):1175-1181.

21. Morandi A, Barnett N, Miller RR, 3rd, Girard TD, Pandharipande PP, Ely EW, Ware LB: **Vitamin D and delirium in critically ill patients: a preliminary investigation**. *J Crit Care* 2013, **28**(3):230-235.

22. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y: **Incidence, risk factors and consequences of ICU delirium**. *Intensive Care Med* 2007, **33**(1):66-73.

23. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, Bernard GR, Ely EW: **Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients**. *Anesthesiology* 2006, **104**(1):21-26.

24. Pandharipande P, Cotton BA, Shintani A, Thompson J, Pun BT, Morris JA, Jr., Dittus R, Ely EW: **Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients**. *The Journal of trauma* 2008, **65**(1):34-41.

25. Pisani MA, Murphy TE, Van Ness PH, Araujo KL, Inouye SK: **Characteristics associated with delirium in older patients in a medical intensive care unit**. *Archives of internal medicine* 2007, **167**(15):1629-1634.

26. Pandharipande PP, Morandi A, Adams JR, Girard TD, Thompson JL, Shintani AK, Ely EW: **Plasma tryptophan and tyrosine levels are independent risk factors for delirium in critically ill patients**. *Intensive Care Med* 2009, **35**(11):1886-1892.

27. Pisani MA, Murphy TE, Araujo KL, Slattum P, Van Ness PH, Inouye SK: **Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population**. *Crit Care Med* 2009, **37**(1):177-183.

28. Schreiber MP, Colantuoni E, Bienvenu OJ, Neufeld KJ, Chen KF, Shanholtz C, Mendez-Tellez PA, Needham DM: **Corticosteroids and transition to delirium in patients with acute lung injury**. *Crit Care Med* 2014, **42**(6):1480-1486.

29. Serafim RB, Dutra MF, Saddy F, Tura B, de Castro JE, Villarinho LC, da Gloria Santos M, Bozza FA, Rocco JR: **Delirium in postoperative nonventilated intensive care patients: risk factors and outcomes**. *Annals of intensive care* 2012, **2**(1):51.

30. Seymour CW, Pandharipande PP, Koestner T, Hudson LD, Thompson JL, Shintani AK, Ely EW, Girard TD: **Diurnal sedative changes during intensive care: impact on liberation from mechanical ventilation and delirium**. *Crit Care Med* 2012, **40**(10):2788-2796.

31. Shehabi Y, Bellomo R, Reade MC, Bailey M, Bass F, Howe B, McArthur C, Murray L, Seppelt IM, Webb S *et al*: **Early goal-directed sedation versus standard sedation in mechanically ventilated critically ill patients: a pilot study**. *Crit Care Med* 2013, **41**(8):1983-1991.

32. Shi CM, Wang DX, Chen KS, Gu XE: **Incidence and risk factors of delirium in critically ill patients after non-cardiac surgery**. *Chinese medical journal* 2010, **123**(8):993-999.

33. Simons KS, Workum JD, Slooter AJC, van den Boogaard M, van der Hoeven JG, Pickkers P: **Effect of preadmission sunlight exposure on intensive care unit-acquired delirium: a multicenter study**. *J Crit Care* 2014, **29**(2):283-286.

34. Skrobik Y, Leger C, Cossette M, Michaud V, Turgeon J: **Factors predisposing to coma and delirium: fentanyl and midazolam exposure; CYP3A5, ABCB1, and ABCG2 genetic polymorphisms; and inflammatory factors**. *Crit Care Med* 2013, **41**(4):999-1008.

35. Svenningsen H, Egerod I, Videbech P, Christensen D, Frydenberg M, Tonnesen EK: **Fluctuations in sedation levels may contribute to delirium in ICU patients**. *Acta anaesthesiologica Scandinavica* 2013, **57**(3):288-293.

36. Van Rompaey B, Elseviers MM, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Bossaert L: **Risk factors for delirium in intensive care patients: a prospective cohort study**. *Crit Care* 2009, **13**(3):R77.

37. Veiga D, Luis C, Parente D, Fernandes V, Botelho M, Santos P, Abelha F: **Postoperative delirium in intensive care patients: risk factors and outcome**. *Rev Bras Anestesiol* 2012, **62**(4):469-483.

38. Whitlock EL, Torres BA, Lin N, Helsten DL, Nadelson MR, Mashour GA, Avidan MS: **Postoperative delirium in a substudy of cardiothoracic surgical patients in the BAG-RECALL clinical trial**. *Anesthesia and analgesia* 2014, **118**(4):809-817.

39. Wolters AE, Zaal IJ, Veldhuijzen DS, Cremer OL, Devlin JW, Van Dijk D, Slooter AJC: **Anticholinergic Medication Use and Transition to Delirium in Critically Ill Patients: A Prospective Cohort Study**. *Crit Care Med* 2015, **43**(9):1846-1852.

40. Yoshitaka S, Egi M, Morimatsu H, Kanazawa T, Toda Y, Morita K: **Perioperative plasma melatonin concentration in postoperative critically ill patients: its association with delirium**. *J Crit Care* 2013, **28**(3):236-242.

41. Zhang Z, Pan L, Deng H, Ni H, Xu X: **Prediction of delirium in critically ill patients with elevated C-reactive protein**. *J Crit Care* 2014, **29**(1):88-92.

42. Zaal IJ, Slooter AJC: **Delirium in critically ill patients: epidemiology, pathophysiology, diagnosis and management**. *Drugs* 2012, **72**(11):1457-1471.

43. Girard TD, Kress JP, Fuchs BD, Thomason JW, Schweickert WD, Pun BT, Taichman DB, Dunn JG, Pohlman AS, Kinniry PA *et al*: **Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial**. *Lancet* 2008, **371**(9607):126-134.

44. Pandharipande P, Cotton BA, Shintani A, Thompson J, Costabile S, Truman Pun B, Dittus R, Ely EW: **Motoric subtypes of delirium in mechanically ventilated surgical and trauma intensive care unit patients**. *Intensive Care Med* 2007, **33**(10):1726-1731.

45. Riker RR, Shehabi Y, Bokesch PM, Ceraso D, Wisemandle W, Koura F, Whitten P, Margolis BD, Byrne DW, Ely EW *et al*: **Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial**. *Jama* 2009, **301**(5):489-499.

46. Ruokonen E, Parviainen I, Jakob SM, Nunes S, Kaukonen M, Shepherd ST, Sarapohja T, Bratty JR, Takala J: **Dexmedetomidine versus propofol/midazolam for long-term sedation during mechanical ventilation**. *Intensive Care Med* 2009, **35**(2):282-290.

47. Schweickert WD, Pohlman MC, Pohlman AS, Nigos C, Pawlik AJ, Esbrook CL, Spears L, Miller M, Franczyk M, Deprizio D *et al*: **Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial**. *Lancet* 2009, **373**(9678):1874-1882.

48. Van Rompaey B, Elseviers MM, Van Drom W, Fromont V, Jorens PG: **The effect of earplugs during the night on the onset of delirium and sleep perception: a randomized controlled trial in intensive care patients**. *Crit Care* 2012, **16**(3):R73.