Epidemiology of delirium in the Intensive Care Unit

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Epidemiology of delirium in the Intensive Care Unit

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(met een samenvatting in het Nederlands)

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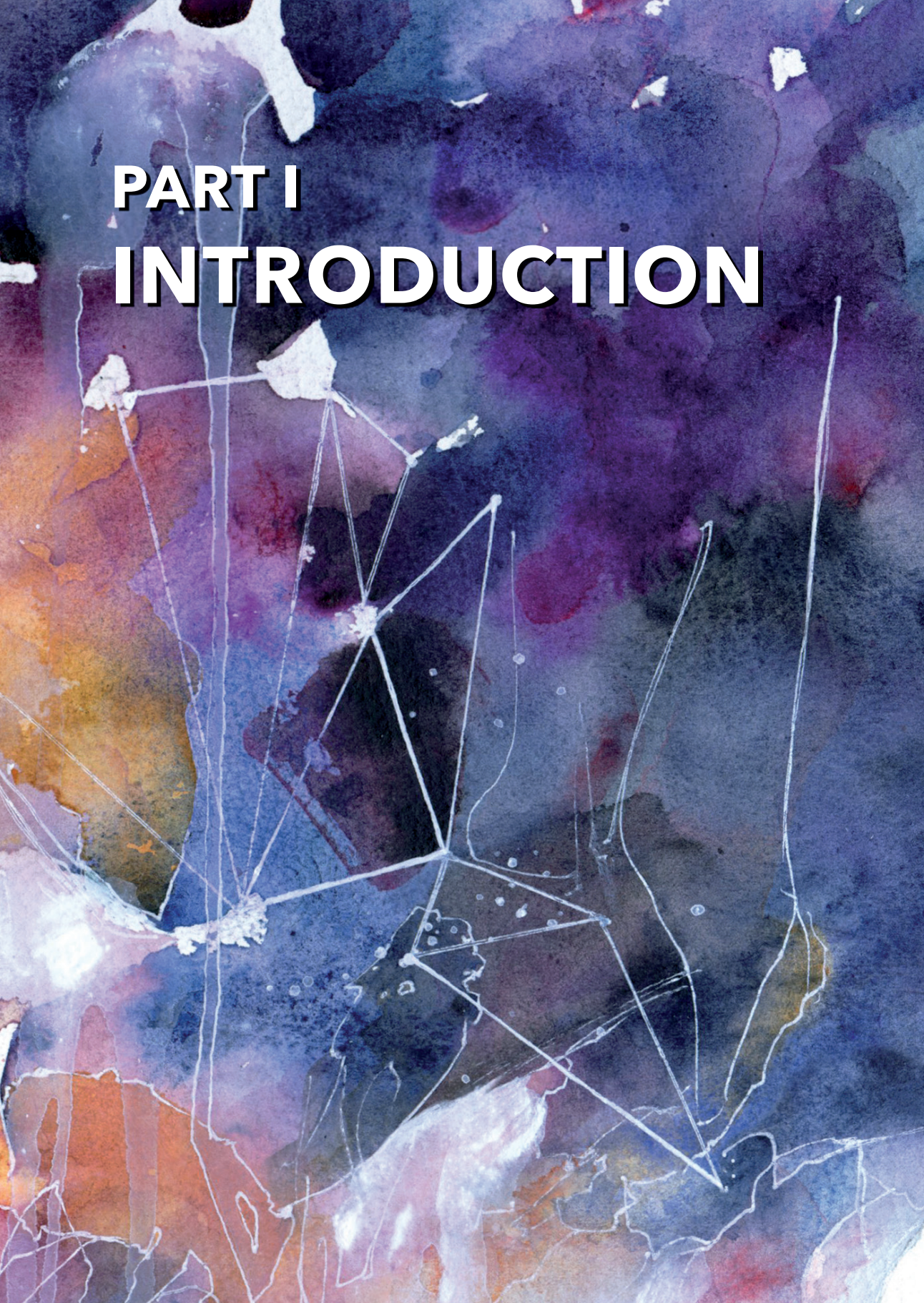

PART I
INTRODUCTION

General introduction

1

INTRODUCTION

Delirium is a common neuropsychiatric syndrome in hospitalized patients, especially in those admitted to the Intensive Care Unit (ICU). The term delirium derives from the Latin word 'delirare' and literally means 'out of track'. This is illustrative as it is clinically characterized by a disturbance in both attention and cognition that develops over a short period of time.[1] Delirium is not a new phenomenon as it has been known about for centuries, albeit described under different names and classifications. Gradually the term delirium started to be more consistently used and nowadays it is defined by subsequent editions of the Diagnostic and Statistical Manual of Mental Disorders (DSM).[1] Although many associate delirium with hallucinations and delusions, these symptoms are not required for the diagnosis. By definition, delirium must be caused by an organic process, and thus it is not a disease in itself, but rather a set of clinical symptoms.[1] For many years, delirium in the ICU was considered an inevitable consequence of critical illness. However, over the past two decades it has become clear that delirium is not only disturbing for the patients, their relatives, and health care professionals, but that it is associated with poor patient outcomes. For example an increased ICU morbidity and length of stay, but also long-term effects such as cognitive impairment 1 year after ICU discharge.[2] Affecting around 20-60% of the patients admitted to the ICU, delirium imposes a significant (economic) burden on health care systems.[3]

Little is known about the pathophysiological changes resulting in the disruption of brain function in delirium. Yet, it is clear that delirium has a multifactorial nature. It is believed that in a given patient, the interplay between predisposing factors and precipitating factors results in the development of delirium.[4] To put it simply, in patients admitted to the hospital with a set predisposing factors that make them susceptible to develop delirium, a single insult could be the trigger to develop delirium. The predisposing factors render a patient more prone to develop delirium. Many of them, such as increased age or dementia, cannot be changed. Alternatively, patients without predisposing vulnerability for delirium could still experience this syndrome because of (many) noxious insults such as systemic inflammation and metabolic disorders. Not all cases of delirium seem to be inherent to the critical illness itself, some cases could be iatrogenic, i.e. a consequence of medical treatment or advice. These modifiable, iatrogenic factors should be of special interest for a better understanding of delirium causation, prevention and possible therapeutic interventions. ICU clinicians should therefore consider delirium as a modifiable condition.

OUTLINE OF THE THESIS

This thesis is entitled 'Epidemiology of delirium in the Intensive Care Unit', referring to the search for modifiable risk factors for delirium, with an emphasis on iatrogenic risk factors (Part II), and the effects of delirium on ICU mortality (Part III).

Part I of this thesis provides a general overview of delirium in the ICU starting with a narrative review of the incidence, diagnosis, pathophysiology and management of delirium in chapter 2. Despite its clinical relevance, health care professionals in the ICU often fail to recognize delirium.[5] It is challenging to diagnose delirium in the ICU as patients are often sedated or mechanically ventilated which both hamper verbal communication. The development of screening methods to detect delirium in mechanically ventilated patients by non-psychiatrists facilitated the diagnosis of delirium. From these screening methods, the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are most used and best validated.[6-8] Although the CAM-ICU showed superior sensitivity compared to the ICDSC,[5] it remains a brief assessment in time, while delirium is a highly fluctuating disorder. Moreover, based on these prior studies, it remained unclear how to define a reliable daily classification of mental status based on the CAM-ICU. In chapter 3, a 5-step algorithm for research purposes is presented and validated to daily define the mental status of a patient admitted to the ICU as 1) coma, 2) delirium, or 3) awake without delirium. Using this algorithm, the incidence and duration of different delirium episodes was evaluated.

Part II contemplates the search for iatrogenic, modifiable risk factors. Numerous risk factors for delirium in the ICU have been proposed over the years. In chapter 4, risk factors for delirium in critically ill patients and the strength of evidence supporting each of these risk factors was identified in a systematic review. To date, treatment options for delirium in the ICU remain limited.[8] Clinicians should therefore aim for delirium prevention by, among other interventions, applying a risk reduction strategy, focusing on those risk factors that can be modified.[8] The administration of medication and aspects of the ICU environment could be examples of these iatrogenic, modifiable risk factors. Chapter 5 describes a cohort study on anticholinergic drug exposure at ICU admission and the development of delirium. In chapter 6, in the same cohort of

critically ill patients, the association between the administration of benzodiazepines and delirium was studied. A before-after study design was used in chapter 7 to compare the occurrence and duration of delirium in two different ICU environments; a ward-like ICU and a single-room ICU.

Delirium has been associated with poor outcome for a long time. While it is plausible that delirium results in long-term cognitive impairment,[2] it remains unclear how delirium would be causal related to increased mortality rate in the ICU. Previous studies reported up to three-fold increased risk of death with delirium, but failed to adjust for confounding caused by time-varying severity of disease and competing events that occur during ICU admission. In Part III, chapter 8, the proportion of deaths attributed to delirium was estimated in a large cohort of critically ill patients.

In chapter 9 the results as described in this thesis are summarized and critically reviewed together with a discussion of the implications of the findings and future perspectives for research on delirium in the ICU.

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Delirium in the ICU

2

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ABSTRACT

Delirium is commonly observed in critically ill patients and is associated with negative outcomes. The pathophysiology of delirium is not completely understood. However, alterations to neurotransmitters, especially acetylcholine and dopamine, inflammatory pathways and an aberrant stress response are proposed mechanisms leading to intensive care unit (ICU) delirium. Detection of delirium, using a validated delirium assessment tool, makes early treatment possible which may improve prognosis. Patients at high risk of delirium, especially those with cognitive decline and advanced age, should be identified in the first 24 hours of ICU admission. Whether these high-risk patients benefit from haloperidol prophylaxis deserves further study. The effectiveness of a multicomponent, non-pharmacological approach is shown in non-ICU patients, which provides proof of concept for use in the ICU. The few studies on this approach in ICU patients suggest that the burden of ICU delirium may be reduced by early mobility, increased daylight exposure and the use of earplugs. In addition, the combined use of sedation-, ventilation-, delirium-, and physical therapy protocols can reduce the frequency and severity of adverse outcomes and should become part of routine practice in the ICU, as should avoidance of deliriogenic medication such as anticholinergic drugs and benzodiazepines. Once delirium develops, symptomatic treatment with antipsychotics is recommended, with haloperidol being the drug of first choice. However, there is limited evidence on the safety and effectiveness of antipsychotics in ICU delirium.

INTRODUCTION

History and definition

Delirium is a syndrome with many synonyms and a long history. In ancient times, Hippocrates needed 16 terms to describe the syndrome.[1] In De Medicina (around AD 1), Celsus was the first to use the term delirium, derived from the Latin 'delirare' which means 'being deranged/deviating from track'.[1] Over past decades, researchers and clinicians have still used 30 or more synonyms for describing intensive care unit (ICU) delirium such as 'ICU psychosis', 'acute confusion' and 'ICU syndrome'.[2,3] The advent of the Diagnostic and Statistical Manual of Mental Disorders, third edition (DSM-III) in 1980 and subsequently the fourth revised edition (DSM-IV-R) brought cohesion to the terms describing delirium, and defined it as a disturbance of consciousness and a change in cognition that develops over a short period of time and tends to fluctuate during the day.[2,4] Of all cognitive domains, attention is particularly affected in delirium.[5,6] Currently, delirium is considered as a disease with a range of severity rather than a binary phenomenon. Subsyndromal delirium has been defined as patients with one or more symptoms that never progress to meet full DSM-IV-R delirium diagnosis.[7]

Literature search

We searched Medline between January, 1966, and May, 2012, using the following terms: "delirium", "confusion", "disorientation", "illusion(s)", "hallucination(s)", "psychotic disorder(s)" and "inattentiveness", in combination with "intensive care unit(s)", "ICU", "critical ill(ness)", "critical care", "critical ill patient(s)" and "intensive care patient(s)". Only articles in human adult populations with full text available in Dutch, English or German were selected. Additionally, we screened the references to identify other relevant studies. We graded the level of evidence of selected studies using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.[8]

Frequency

The reported occurrence rate of delirium in ICU studies varies between 16% and 89%.[9,11] This variation may be explained by different factors. Firstly in many investigations the delirium status on admission to an ICU is either not recorded, or the authors fail to mention how delirium was assessed, or both. The second reason for variability of the

frequency of delirium is case-mix. Age and disease severity are strong determinants of delirium, and may differ between different ICU settings.[12] Other factors include the instruction and training of ICU staff and the use of different protocols on sedation and analgesia. Finally, the diagnostic method used may cause discrepancies.[9,10,13,14] Although the frequency of ICU delirium varies, what is known is that it is common and that the frequency of ICU delirium will further rise because of aging of the population and subsequently an increasing proportion of elderly ICU patients.[11,15] The median duration of ICU delirium was found to be 3 days (range 1-44 days),[16,17] but this can vary strongly between patients. Occasionally, delirium lasts months or continues as a dementia syndrome.

Diagnosis and screening

Diagnosing delirium in ICU patients can be challenging as patients are frequently unable to verbally communicate because of endotracheal intubation or the effects of sedatives. Without a screening tool, up to 75% of delirium cases are missed by ICU physicians.[18] Because of this poor recognition, brief screening tools have been developed for standardized delirium testing by trained staff such as ICU nurses or ICU physicians. As prognosis may be better in patients who are treated early,[19] American and European guidelines (UK and Germany) strongly recommend standard screening to enable early treatment of delirium in ICU patients.[5,20-22]

Although numerous screening tools have been developed, the Intensive Care Delirium Screening Checklist (ICDSC) and the Confusion Assessment Method adapted for use in the ICU (CAM-ICU) are the most used and best validated, with adequate sensitivity in the research setting.[9,23-25] Both tools are based upon and validated against the DSM-IV criteria for delirium. The CAM-ICU has a binary outcome (no delirium or delirium), whereas the ICDSC, which consists of eight items scored as 1 (present) or 0 (absent), has cutoffs for 'no delirium' (score=0), 'subsyndromal delirium' (score=1-3) and 'delirium' (score ≥ 4). We showed that the CAM-ICU had superior sensitivity compared with the ICDSC.[18] However, when used in routine, daily practice, the CAM-ICU did not detect half of the delirious patients.[26] Although the ICDSC is able to grade different delirium symptoms and define subsyndromal delirium, until now, no severity score for ICU delirium has been validated, as until now, no universal criteria for the severity have been determined. For example, is the length of a delirium episode important, more or less hyper- or hypoactivity or, the presence or absence of delusions, hallucinations, disorientation, to determine severity of ICU delirium.

The reported frequencies of ICU delirium vary depending on whether the ICDSC or the CAM-ICU is used: ranging between 16% and 45% with the ICDSC,[9,13] and between 30-89% with the CAM-ICU.[10,14]

Subtypes

Many different patients fulfil DSM-IV-R criteria for delirium, but in clinical practice, delirious patients may differ in clinical presentation, treatment response and underlying causes.[2] The identification of clinical subtypes could help to unravel the pathophysiology, and may allow for more specific prevention and treatment.

Most studies focus on subtyping based on psychomotor features.[2,27] Of these, hyperactive delirium is characterized by psychomotor restlessness and agitation. Though easy to recognize, purely hyperactive delirium seems to be rare in ICU patients with a frequency of 1% (range 0-2%).[2,27,28] In the same cohorts, 56% (range 45-64%) experienced hypoactive delirium, characterized by slowing or lack of movement, apathy and diminished responsiveness.[2,27,28] Mixed delirium alternates between hyper- and hypoactive periods and represented 23% (range 6-55%) of the cases.[2,27,28] There may be some association between etiology and motor subtypes, suggesting differences in pathophysiology.[29] For instance, delirium associated with substance withdrawal or intoxication seems to be more often hyperactive, whereas in metabolic disturbances, delirium tends to be more often hypoactive.[29] Although used in numerous publications, the hyper- and hypoactive subclassification of delirium has not been validated and classifications in these studies were based on brief observations, which may not capture the usual fluctuations in delirium over time.[2]

PATHOPHYSIOLOGY

The pathophysiology of delirium is highly heterogeneous and not completely understood. Several theories have been proposed, which are not necessarily exclusive.

Neurotransmitter alterations

An important hypothesized mechanism is based on an imbalance in neurotransmitter systems, particularly reduced acetylcholine activity.[30] This is supported by observations that the use of anticholinergic drugs increase the risk of delirium.[31] The acetylcholinergic

neurotransmitter system is involved in processes of attention, memory, concentration and learning which are all disturbed in delirium.[32] Other neurotransmitter disturbances that may be associated with delirium are an excess of dopamine and serotonin, which both influence the cholinergic system.[33] Dopamine is an important neurotransmitter for motor function, attention and cognition. Intoxication with dopaminergic drugs may trigger hyperactive delirium.[29,34] It is also hypothesized that the release of gamma-amino-butyric-acid (GABA), the primary inhibitory neurotransmitter in the central nervous system, is involved in the pathogenesis of delirium as GABA-ergic drugs are associated with an increased risk for the development of delirium.[12,35]

Anatomical considerations

Neuropathological studies suggest involvement of lesions in various areas of the brain in patients with delirium; these include the basal ganglia, fusiform or lingual gyri, prefrontal cortex, thalamus and hippocampus.[34,36] More diffuse abnormalities including leukoencephalopathy and increased blood–brain barrier permeability have been observed in sepsis-associated encephalopathy.[37] Multiple cerebral micro-emboli have been detected in patients who underwent cardiopulmonary bypass surgery, although it is not completely clear that these are causally related to the development of postoperative delirium.[38] However, neuroimaging in delirium is still in its infancy.

Inflammatory pathway

The inflammatory cascade that is associated with sepsis may also lead to delirium. Inflammatory mediators may lead to disseminated intravascular coagulation and extensive neuroinflammation, the latter because these pass the blood-brain barrier.[29,32,39] Elevated levels of interleukin (IL)-6, IL-8, C-reactive protein and procalcitonine have been found to be associated with delirium.[40-42] However, the level of these cytokines changes rapidly over time, and previous studies show wide variations in the timing of cytokine measurement. Furthermore, the levels of these cytokines are influenced by a multitude of factors, which could account for inconsistent findings between studies.

Aberrant stress response

The hypothesis of an aberrant stress response in the pathophysiology of delirium suggests that delirium results from the adverse effects of stress-response pathways that are adaptive in healthy individuals.[43] Central nervous system disease and ageing are two

important predisposing factors for delirium, but are also associated with changes in the stress response pathway.[43] One of the most important stress hormones in humans is cortisol, regulated in the hypothalamic-pituitary-adrenal axis.[43-45] In stressful conditions such as surgery or severe illness, including sepsis, the brain promotes adrenocortical function.[44,45] Because of their liposoluble characteristics corticosteroids easily pass through the blood-brain barrier where they might have harmful effects on the brain and may cause changes in cognition, impairment of attention or psychosis.[43,44] Indeed, in patients undergoing elective coronary artery bypass surgery, a high level of serum cortisol was associated with an increased risk of postoperative delirium.[45]

Alcohol withdrawal delirium

Alcohol withdrawal delirium, also called delirium tremens, seems to be different from other forms of delirium. Besides the typically hyperactive motor behaviour, it is also associated with an increase in electroencephalography (EEG) activity whereas slowing of EEG activity is typically observed in other forms of delirium.[2,29,46] The central nervous system depressant effects of ethanol are the result of interactions with the GABA type A ($GABA_A$) receptor and N-metyl-D-aspartate (NMDA) receptor.[29,47] Ethanol augments the GABA activity on the $GABA_A$ receptor leading to increased inhibition, and thus a more profound sedative effect.[47] $GABA_A$ receptors are downregulated with chronic alcohol use.[47] When alcohol is withdrawn and ethanol is no longer present, the inhibitory effect of GABA binding to the receptor decreases, with the same amount of GABA available.[29,47] This increases neural activity, which may explain some of the hyperactive aspects of delirium tremens.[29,47] The second receptor affected by ethanol is the NMDA receptor. Ethanol inhibits its excitatory function.[47] In chronic alcohol use there is upregulation of these receptors.[29,47] During withdrawal, the inhibition is removed, allowing for an increase in excitatory conduction, potentiated by the increased number of NMDA receptors due to the upregulation.[47]

Patient-related risk factors

At a patient level, delirium is often a multifactorial condition with over 100 risk factors described in the literature in different populations. In an ICU patient an average of 11 of these risk factors have been observed at the same time.[16] The development of delirium supposedly results from an interaction between predisposing and precipitating factors, whereby the individual risk of delirium is defined by the sum of these factors;

the more predisposing factors present, the fewer precipitating events are required to cause delirium.[48]

The most important predisposing factors for ICU delirium seem to be advanced age and pre-existing cognitive decline.[12,49-52] For example, the risk of developing ICU delirium increases by 2% for each additional year of age.[12] Precipitating factors include acute physiological changes, exposure to medications and environmental factors such as lack of daylight and isolation.[12,53,54] For instance, with each additional point on the Acute Physiological and Chronic Health Evaluation (APACHE)-II score the risk of delirium increases by 6%.[12] Some of these precipitating factors may be (partially) modifiable by preventive or therapeutic interventions. Recently, a risk model has been developed to identify patients at high risk of delirium based on ten risk factors available within 24 hours of ICU admission. These factors were age, APACHE II score, admitting discipline, coma, infection, metabolic acidosis, use of sedatives and morphine, urea concentration and urgent admission.[51] Table 1 gives a summary of predisposing and precipitating risk factors described in non-ICU and ICU patients.

Table 1. Common risk factors for delirium

Predisposing factors	Precipitating factors
advanced age	acute illness
history of alcohol abuse	medication such as:
impaired vision/hearing	dopaminergic drugs
pre-existing cognitive impairment	anticholinergic drugs
dementia	benzodiazepines
	environmental factors
	sleep deprivation
	infection/sepsis
	metabolic disturbances
	immobilization

PROGNOSIS

ICU nurses and physicians have, for a long time, regarded delirium as an inconvenient symptom, that is reversible after successful treatment of the underlying condition.[11] To date, ICU delirium has been found to be associated with longer ICU and hospital length of stay,[16,52,55-57] higher ICU and hospital costs,[58] higher hospital and 6-month mortality,[55,56,59] more severe long-term cognitive impairment,[60] and an increased number of auto-extubations.[61,62] Patients experiencing subsyndromal delirium still experience worse outcomes than those who have no delirium at all.[7,63,64] It is possible that hypoactive delirium is associated with worse outcome than the hyperactive or mixed subtypes of delirium.[27] The duration of delirium also matters: each additional day of delirium was found to be associated with a 10% increased risk of death at 6 months and 1 year.[56,59] It is still unclear whether delirium is really independently associated with impaired outcome. In previous studies, adjustments were made for age, comorbidity and severity of illness, as assessed at ICU admission.[65] However, in these investigations, no adjustments were made for disease severity during ICU admission, and scores on disease severity and co-morbidity lack detail.[65] The observed association of delirium with poor outcome may therefore in part be subject to residual confounding.[65] It is further unclear what the mechanism could be for the impaired outcome of delirious patients.

NON-PHARMACOLOGICAL MEASURES FOR PREVENTION AND TREATMENT

The first step in the management of ICU delirium is treatment of the underlying conditions. Non-pharmacological measures aimed at minimizing precipitating factors may be applicable to all ICU patients. Importantly, ICU patients are exposed to many more factors that can induce delirium than other patients. For example, ICU patients stay in a unit with more personnel, working around the clock and with continuous exposure to noise and light.[11,53] It can be difficult to implement non-pharmacological measures when caregivers may believe such measures will increase their workload without improving outcomes for patients.[66-68]

In non-ICU patients however, these strategies have appeared to be successful in several studies.[69] Using a multicomponent approach, including repeated reorientation, early mobilization, noise reduction and a non-pharmacological sleep protocol, a 40% decrease in the incidence of delirium was established.[70,71] The applied interventions were simple such as providing a board with names of care-team members and day schedules, a warm drink at bedtime, relaxation tapes, noise reduction and visual/hearing aids, but also limiting night-time exams and interruptions to sleep.[70,71]

Recently, in a randomized controlled trial (RCT) conducted in ICU patients, 69 patients sleeping with earplugs during the night were compared with 67 patients sleeping without earplugs. The use of earplugs lowered the incidence of mild confusion (40% versus 15%), assessed with the Neelon and Champagne Confusion Scale.[72]

We have shown that patients who were admitted to a conventional ICU with wards had a longer duration of delirium than patients who were admitted to a single-room ICU, designed to reduce noise and with improved exposure to daylight. The number of days patients spent delirious was, on average, 0.4 days shorter in the single-room ICU than in the ICU with wards, although the occurrence rate of delirium did not differ between the two groups.[73]

Immobilization is considered to be a risk factor for delirium. An early exercise and mobilization protocol for ICU patients showed lower incidence and shorter duration of ICU delirium in one before-after study and in one RCT.[74,75] The latter showed, as a secondary endpoint, a reduction of delirium days from 4 days in the control group to 2 days in the intervention group.

In summary, studies in non-ICU patients give proof of concept that non-pharmacological measures are effective in the prevention and treatment of delirium in ICU patients (see Table 2). The few studies that have been performed in ICU patients suggest that the burden of delirium may be reduced by preventing immobility, minimizing noise, use of earplugs during the night and increasing exposure to daylight.

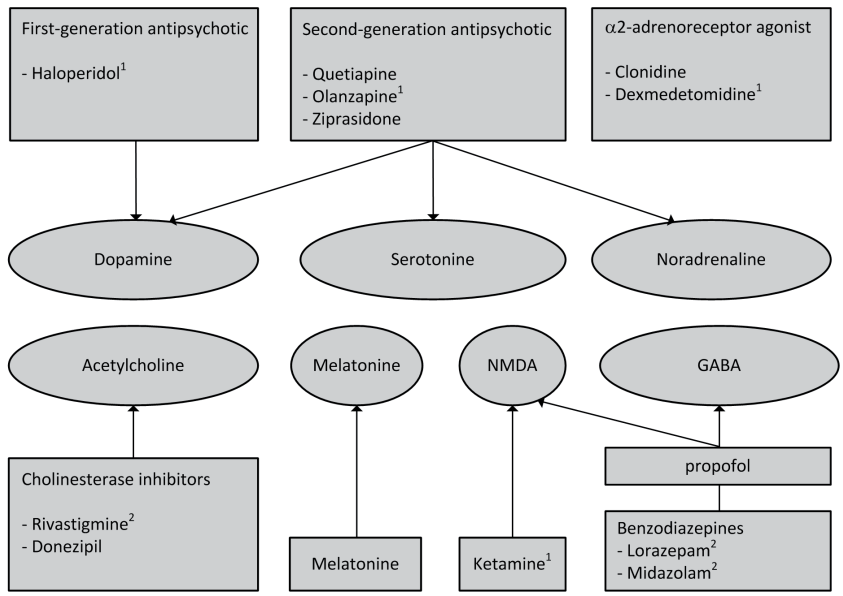
PHARMACOLOGICAL PREVENTION STRATEGIES

Based on suggested neurotransmitter alterations in the pathophysiology of delirium, several groups of drugs could theoretically be of use in the prevention and treatment of delirium (see Figure 1). In this section we focus on delirium prevention in ICU patients. Pharmacological prevention strategies in non-ICU patients have been discussed in recent reviews.[76-78] Pharmacological prevention strategies may be applied to all ICU patients or to patients at high risk of delirium. This group of high-risk patients may be identified with a prediction model within 24 hours of ICU admission.[51] To date, only four double-blind placebo-controlled RCTs have been performed using pharmacological prophylaxis for delirium in ICU patients. Unfortunately these studies were limited to patients undergoing elective surgical procedures.

Prophylactic administration of haloperidol, a first-generation antipsychotic, was investigated in 457 non-cardiac surgery patients. Low-dose haloperidol (0.5 mg intravenous bolus injection followed by continuous infusion at a rate of 0.1 mg/hour) during the first 12 hours postoperatively was found to decrease the incidence of delirium (15% in intervention group vs 23% in the control group).[79]

A postoperative single-dose administration of risperidone 1 mg, a second-generation antipsychotic, was investigated in a double-blind RCT in 126 patients who underwent cardiac surgery with cardiopulmonary bypass.[80] The patients who did receive risperidone (n=63) showed lower incidence of postoperative delirium (11% in the intervention group versus 32% in the control group). Another RCT investigated rivastigmine, a cholinesterase inhibitor based on the hypothesis of reduced acetylcholinergic activity in delirium.[81] In 120 patients undergoing elective cardiac surgery, oral rivastigmine 1.5 mg three times daily, starting the evening before surgery and continuing until the sixth postoperative day, was compared with placebo. In this study, no difference was found in the incidence of delirium nor in the duration of postoperative delirium.

Figure 1. Pharmacological approaches to delirium



Pharmacological approaches to delirium based on (i) suggested pathophysiology of delirium in relationship with (ii) natural agonist (action site) of the suggested medications. NMDA= N-metyl-D-aspartate; GABA= gamma-amino-butyric-acid. 1. Positive effect in prophylaxis or treatment shown in randomized control trials (RCTs), 2. Negative associations in prophylaxis or treatment shown in RCTs.

In a placebo-controlled RCT, the use of intravenous ketamine bolus 0.5 mg/kg during anaesthetic induction in the presence of fentanyl and etomidate, in cardiac surgery with cardiopulmonary bypass, showed a lower incidence of postoperative delirium (1/29 patients) than in the placebo group (9/29 patients).[82] Ketamine is a rapid-acting NMDA-receptor antagonist, the pharmacological action of which is characterized by analgesia, intact pharyngeal-laryngeal reflexes, mild cardiac stimulation and mild respiratory depression. Ketamine induces a state called 'dissociative anaesthesia'. One of the major drawbacks of the use of ketamine is the high association with hallucinations.

Disruption of the sleep-wake cycle is frequently observed in delirium.[83] Melatonin, derived from serotonin, plays an important role in regulating the sleep-wake cycle.[83] However, exogenous melatonin supplementation as delirium prophylaxis has only been suggested in case reports.[83,84]

In summary, there is evidence for the efficacy of pharmacological prevention of postoperative delirium in surgical ICU patients (see Table 2). Care must be taken when extrapolating the results of these studies concerning postoperative delirium to all critically ill patients. More studies regarding pharmacological prevention of ICU delirium are needed in a general ICU population or in high-risk ICU patients.

OTHER PHARMACOLOGICAL AND PROTOCOL-DRIVEN PREVENTION STRATEGIES

An important category of modifiable risk factors is the use of medication that may induce or prolong delirium.[85,86] However, when this medication is stopped, it may be unclear whether a delirious patient will benefit or will deteriorate because of the underlying condition for which this medication had been started.[11] Anticholinergic and GABA-ergic drugs seem to be important contributors to delirium.[12,17,31,35] Over 600 medications with presumed anticholinergic (side) effects are currently known.[87] More importantly, there are striking discrepancies between studies in the extent of anticholinergic side-effects of particular drugs, which may be explained by the use of different measures of anticholinergic exposure and confounding by other risk factors such as dementia or age.[31] However, it seems that in most cases it is the accumulation of drugs with anticholinergic effects rather than one single agent that produces side effects.[87] Increasing doses of benzodiazepines, which are $GABA_A$ agonists, increase the risk of delirium in a dose-dependent fashion.[12,75] Because of conflicting data on the role of opiates as a risk factor for ICU delirium, recommendations cannot be made about use or non-usage.[51,88,89] However, adequate treatment of pain is likely to reduce the risk for delirium.[90]

Importantly, there may be acceptable alternatives for both benzodiazepines and opiates. In two RCTs, the use of dexmedetomidine, a potent alpha-2-adrenergic receptor agonist, was found to decrease the number of delirium days (studied as a secondary endpoint), compared with either lorazepam or midazolam.[35,91] A double-blind RCT found a decrease in the number of delirium days but not in the prevalence of delirium, using dexmedetomidine (n=152) compared with morphine (n=147) with equal analgesia and sedation levels (using propofol in the morphine-arm to reach the targeted sedation level and morphine in the dexmedetomidine-arm to reach targeted

analgesia level).[92] Unfortunately, the twintrials, comparing dexmedetomine versus midazolam (MIDEX) and propofol (PRODEX) sedation in 1000 patients in 75 ICUs in Europa did not include routine standardized delirium assessments.[93] However, these twintrials reported that patients receiving dexmedetomidine have a greater ability to interact, report pain and cooperate with the ICU care. Therefore sedation with dexmedetomidine can indirectly be related to early exercise and reduced pain which may ultimately improve patient outcomes and delirium. The main concern with using dexmedetomidine in ICU patients is that dexmedetomidine is more expensive than midazolam or propofol, which are both off patent. The mechanisms by which sedation with dexmedetomidine improves delirium outcomes remains unclear. Improvement may result from withdrawal of benzodiazepines or opioids and/or the beneficial prevention or treatment effects of dexmedetomidine sedation. In conclusion, sedation with dexmedetomidine might be favorable in delirium prevention and management but is more expensive.

Although the use of benzodiazepines and the presence of pain are associated with delirium, the excessive use of sedatives is associated with increased incidence of delirium.[94] The systematic management of pain, sedation and delirium in the ICU using validated monitoring and screening tools, daily spontaneous awakening trials, spontaneous breathing trials and early physical exercise have improved clinical outcomes (e.g. reduced length of stay on the ICU and the duration of mechanical ventilation).[94-96] These recommendations have recently been combined in different protocols including the 'Awake and Breathing Coordination, Delirium monitoring, Early mobility and exercise' approach.[97,98] In a prospective cohort study, 1214 patients were compared before and after the implementation of a protocol-driven non-pharmacological and pharmacological management of sedation, pain and delirium. The patient group after implementation showed lower mortality, decreased length of stay in the ICU and lower incidence of subsyndromal delirium. The incidence of delirium was similar in both groups. Because of the beneficial effects the implementation of such protocols is an important part of a multidisciplinary approach to improving outcomes in ICU patients.[98]

PHARMACOLOGICAL TREATMENT OPTIONS

To date, the pharmacological treatment of ICU delirium is mainly based on case series, retrospective studies and non-blinded, non placebo-controlled RCTs. Reviews on pharmacological treatment options in non-ICU patients have been previously described.[76,77,99,100] Only three double-blind, placebo-controlled RCTs of delirium in ICU patients have been published (see Table 2).[101-103] It should be noted that when starting pharmacologic treatment, reducing one or more symptoms of delirious patients may not necessarily resolve all aspects of delirium. The management, both pharmacological and non-pharmacological, of ICU delirium is summarized in Table 3.

Antipsychotics

The first-generation antipsychotics, including haloperidol, were developed around the 1950s and are also known as typical, classical or conventional antipsychotics. Haloperidol has strong central antidopaminergic activity, which may lead to extrapyramidal side effects such as parkinsonism, rigidity and akathisia.[104] The second-generation antipsychotics, also known as atypical antipsychotics are suggested to have a more favorable safety profile because of serotinergic activity and faster dissociation from dopaminergic receptors.[104]

Haloperidol

Haloperidol administration has been common clinical practice in ICU patients.[105,106] Whereas American guidelines recommend haloperidol as drug of first choice in ICU delirium, the European guidelines only recommend the use of haloperidol in ICU delirium if psychotic symptoms or agitation exists.[5,20-22] Haloperidol can be administered orally, intramuscularly or intravenously, the latter being favorable in critically ill patients who often have changes in enteral absorption. To date, the US Food and Drug Administration have not approved the use of intravenous haloperidol for this indication.

The above-mentioned guidelines suggest a dosage of 2 mg intravenously in hyperactive patients followed by repeated doses every 20 minutes while agitation persists. Once agitation subsides, scheduled doses every 4-6 hours may be continued for a few days followed by tapered doses for several days.[5,22,99] It should be noted that this suggested dosage regimen is based on experience in non-ICU patients. In ICU patients, these dosages may be less suitable as consequences of agitation may be more severe and other sedatives are available to more quickly control agitation or

hyperactivity. On the other hand, benzodiazepines and possibly also propofol, acting on the $GABA_A$- and NMDA receptor, may be deliriogenic. The intravenous haloperidol dosage for critically ill patients is usually 1-2.5 mg (0.5-1 mg in elderly patients), given two or three times daily. Haloperidol should be avoided in patients with Parkinson's and Lewy Body disease because of the extrapyramidal side effects. Other side effects are neuroleptic malignant syndrome, tardive dyskinesias, QT-interval prolongation and torsade de pointes, but these are probably rare in low dosages <10 mg per day.[5,22]

Second-generation antipsychotics

Second-generation antipsychotics can also be used in the treatment of ICU delirium. One RCT compared olanzapine with haloperidol in ICU patients with delirium. A similar efficacy and lower incidence of sedation and extrapyramidal side effects was observed with olanzapine compared to haloperidol.[107] This study suggested that olanzapine could be beneficial in patients whom safe administration of haloperidol is precluded. Unfortunately, olanzapine cannot be administered intravenously. Quetiapine compared with as-needed haloperidol in a double-blind, placebo-controlled RCT in ICU patients resulted in faster resolution of delirium (1 day vs 4.5 days with haloperidol).[102] A limitation of this study is the small sample size (n=36). Quetiapine is only available in tablet form, which is a disadvantage in ICU patients.

In a double-blind RCT in 103 ICU patients, treatment with either haloperidol, ziprasidone or placebo all resulted in similar number of days without delirium and without coma, suggesting that antipsychotic medication has little effect on the course of delirium.[101] No differences were observed in the frequency of extrapyramidal side effects.[101] As mentioned by the authors, several factors may have hindered the detection of differences in the outcomes including the relatively small sample size and lack of a standardized sedation protocol.[101]

In early studies, the adverse effects of haloperidol seemed to exceed those of second-generation antipsychotics.[107,108] However, the administration of second-generation antipsychotics also poses the risk of extrapyramidal symptoms, neuroleptic malignant syndrome, tardive dyskinesia, QT-interval prolongation and torsade de pointes, albeit at a lower frequency. In summary, there is no evidence that one antipsychotic class of drugs is superior over another in the treatment of ICU delirium in terms of clinical effectiveness or side effects.

Cholinesterase inhibitors

Previous studies in non-ICU patients and the presumed deficiency of acetylcholine in delirium suggested that cholinesterase inhibitors may have a beneficial effect.[109-111] However, a double-blind, placebo-controlled, multicenter trial in delirious ICU patients with rivastigmine as add-on to standard treatment with haloperidol was halted at 104 patients because of increased mortality in patients receiving rivastigmine (12 on rivastigmine, 4 on placebo), without evidence of a beneficial effect.[103] In a pilot study in 16 non-ICU patients aged 70 years or older with hip fracture, donepezil or placebo was administered.[112] Patients in the donepezil arm had no improvement in delirium presence or severity, but did experience more side effects than those on placebo.[112] Both studies suggest that cholinesterase inhibitors have no role in the symptomatic treatment of delirium in ICU patients.[103,112]

Other medication

One open-label pilot RCT studied infusion of dexmedetomidine versus haloperidol in 20 patients requiring mechanical ventilation only because their agitated delirium required such high doses of sedative medication that extubation was not possible. The patients treated with dexmedetomidine (n=10) had a shorter time to extubation and an increased proportion of time spent with minimal or no delirium symptoms.[114]

Methylphenidate improved cognitive and psychomotor functions in 14 non-ICU patients with hypoactive delirium.[115] On the other hand, methylphenidate may induce symptoms of psychosis. More research is needed on the role of methylphenidate in the pharmacological treatment of ICU delirium.

Exogenous melatonin supplementation in delirium treatment has been described only in case reports. Delirium resolved within 1 day after administration of low-dose melatonin in a patient with persistent delirium. Further supporting evidence is needed.[83,84]

Table 2. Studies regarding non-pharmacological and pharmacological

Study, y of publication	Design (n)	Delirium assessment	Intervention
Non-pharmacological prevention and treatment			
Needham, 2010	B/A, no randomization, not blinded (27 before, 30 after)	CAM-ICU	↓sedation, early physical therapy and rehabilitation
van Rompaey, 2012	RCT, researchers blinded (69 intervention, 67 control)	NEECHAM	earplugs during night
Pharmacological prevention strategies			
Gamberini, 2009	RCT, db (56 rivastigmine, 57 PL)	CAM	CAM Rivastigmine 1.5mg q8h (22 doses)
Hudetz, 2010	RCT, partly blinded (29 ketamine,29 PL)	ICDSC	IV ketamine 0.5mg/kg anaesthetic induction
Pandharipande, 2007	RCT, db (52 dexmed, 51 lorazepam)	CAM-ICU	sedation 120 h with dexmed vs lorazepam
Prakanrattana and Prapaitrakool, 2007	RCT, db (63 risperidone, 63 PL)	CAM-ICU Neurologist	PO risperidone 1mg
Wang, 2012	RCT, db (229 haloperidol, 228 PL)	CAM-ICU	IV haloperidol bolus 0.5mg followed by 0.1mg/h continuous IV q12h
Pharmacological treatment strategies			
Devlin 2010	RCT, db (18 quetiapine, 18 PL)	ICDSC	PO quetiapine 50mg q12h (/24 h › to 100,150, 200 mg q12h)

B/A= before/after, CAM= Confusion Assessment Method, CAM-ICU= Confusion Assessment Method Dexmedetomidine, DI= Delirium Index, EPS= extrapyramidal symptoms, ICDSC= Intensive Care Neelon and Champagne Confusion Scale, PL= placebo, PO= per oral, QI= quality improvement, [a]Only studies in ICU patients and with delirium as primary outcome measure are included in this mand Evaluation (GRADE) approach.

Primary outcome	Grade[b]	Remarks
↑days alert and not delirious,↑functional mobility	low	set-up as QI project
↓ incidence early onset of 'mild confusion' ↑sleep perception	moderate	beneficial effect strongest within 48 h ICU admission, only 8/69 and 4/67 had follow-up of 5 days
no difference in delirium incidence within 6 days postoperative	low	postoperative CPB
↓ incidence delirium	very low	postoperative CPB, follow-up max 5 days
↑days without delirium/ coma, ↑days at targeted sedation level	high	↑ bradycardia in dexmed group
↓ incidence delirium	low	postoperative CPB
↓ incidence delirium	moderate	no side effects, follow-up max 7 days, differences in baseline
↑resolution of delirium, ↓agitation	moderate	multicenter pilot study

for use in the Intensive Care Unit, CPB= cardiopulmonary bypass, db= double-blinded, dexmed= Delirium Screening Checklist, ICU= intensive care unit, IV=intravenous, max= maximum, NEECHAM= qxh= every x hours, RCT= randomized controlled trial,↑indicates increase, ↓indicates decrease. summary, [b]Level of evidence graded with the Grades of Recommendation, Assessment, Development,

Table 2. Studies regarding non-pharmacological and pharmacological prevention

Study, y of publication	Design (n)	Delirium assessment	Intervention
Pharmacological treatment strategies			
Girard 2010	RCT, db (35 haloperidol, 30 ziprasidone, 36 PL)	CAM-ICU	IV haloperidol 5mg q6h IV ziprasidone 40mg q6h
Skrobik 2004	RCT (45 haloperidol, 28 olanzapine)	ICDSC; DI	PO haloperidol 2.5–5mg q8h PO olanzapine 5mg q24h
Van Eijk 2010	RCT, db (54 rivastigmine, 50 PL)	CAM-ICU	rivastigmine 1.5–6mg q12h

B/A= before/after, CAM= Confusion Assessment Method, CAM-ICU= Confusion Assessment Method Dexmedetomidine, DI= Delirium Index, EPS= extrapyramidal symptoms, ICDSC= Intensive Care Neelon and Champagne Confusion Scale, PL= placebo, PO= per oral, QI= quality improvement, [a]Only studies in ICU patients and with delirium as primary outcome measure are included in this mand Evaluation (GRADE) approach.

and treatment for Intensive Care Unit delirium *(continued)*

Primary outcome	Grade[b]	Remarks
similar number days alive without delirium or coma	moderate	multicenter
no EPS with olanzapine use, both effective in ↓symptoms	low	no blinding, uneven distribution, DI not validated in ICU
↑ mortality, ↑ median duration delirium	high	prematurely stopped due to safety concerns

for use in the Intensive Care Unit, CPB= cardiopulmonary bypass, db= double-blinded, dexmed= Delirium Screening Checklist, ICU= intensive care unit, IV=intravenous, max= maximum, NEECHAM= qxh= every x hours, RCT= randomized controlled trial,↑indicates increase, ↓indicates decrease. summary, [b]Level of evidence graded with the Grades of Recommendation, Assessment, Development,

Treatment in different subtypes

Pharmacological treatment of delirium is primarily focused on patients with hyperactive episodes. Because of the use of central venous, arterial or urinary catheters, endotracheal tubes and other devices, sedation can be indicated in extremely agitated patients to guarantee patient safety. Controversy exists over whether pharmacological treatment should differ between subtypes of delirium. As discussed, the distinction of subtypes may be unclear and may not have been used in previous investigations of medication in delirium. Still, sedative side effects are unwanted in hypoactive delirium. The use of pharmacological treatment in subsyndromal delirium has not yet been investigated. Published guidelines do not specifically give advice regarding treatment of either hypoactive or subsyndromal delirium.[5,22]

Treatment of alcohol withdrawal delirium

Alcohol withdrawal delirium seems to be different from other forms of delirium. Benzodiazepines are the medication of choice in the treatment of alcohol withdrawal delirium, which substitute for the $GABA_A$-enhancing effect of alcohol.[47] Lorazepam is an attractive agent for use in the critically ill patients because it is available for intravenous administration and does not have active metabolites.[47] Suggested dosages are 2-4 mg as needed every 1-4 hours.[47] In 60% of patients, the signs and symptoms associated with alcohol withdrawal delirium resolve in 5 days or less.[47] Propofol may be used as an alternative for benzodiazepines.[47] Patients on propofol require increased monitoring, as side effects can occur; hypotension being the most important of these. Haloperidol can be added to control symptoms of psychosis in alcohol withdrawal delirium. β-adrenoceptor agonists (β-blockers) and alpha-agonists are suggested for the treatment of symptoms of autonomic hyperactivity.[47] Parenteral thiamine 500 mg three times daily for 3 days should be started in patients suspected of having Wernicke's encephalopathy or who are malnourished.[116]

Table 3. Management of delirium in ICU patients

Non-pharmacological prevention strategies
1. Evaluation of risk factors
2. Multicomponent prevention protocols[71,113]
Pharmacological prevention strategies
1. Low dose haloperidol[79]
2. Risperidone 1 mg[80]
3. Avoid deliriogenic drugs (including benzodiazepines, anticholinergic medication)[12,17]
4. Sedation with dexmedetomidine[91,93,114]
5. Protocol-driven management of sedation, analgesia, delirium and early exercise[97,98]
Non-pharmacological treatment measures
1. Early exercise and mobilization[74,75]
2. Single-room ICU with improved exposure to day-light[73]
3. Use of earplugs[72]
Pharmacological treatment options
1. IV haloperidol 1-2.5mg (0.5-1 in elderly) q8-12h)[22]
2. PO olanzapine, start 5mg (2.5mg in elderly) titrated[107]
3. PO quetiapine, start 25-50mg AN, titrated to max 200mg q12h[102]
4. PO ziprasidone 40mg q6h[101]
5. Benzodiazepines, avoid in delirium, first choice in delirium tremens[12,35,47] IV lorazepam in delirium tremens, 2-4 mg as needed q4-6h

AN= ante noctum, ICU= Intensive Care Unit, IV= intravenous, PO= per os, qxh= every x hours.

CONCLUSION

Delirium in critically ill patients is a common, multifactorial disorder. Non-pharmacological measures are recommended, such as noise reduction and frequent orientation. Combined sedative, analgesic, physical therapy and delirium protocols seem to improve patient outcomes and reduce the burden of delirium. Recognizing patients with a high risk of delirium provides an opportunity to start prophylactic treatment. However, more research regarding the safety and efficacy of pharmacological prophylaxis is required. When patients develop delirium, symptomatic treatment with antipsychotics could be started. There is no evidence that one class of antipsychotic drugs is more efficacious in the treatment of ICU delirium than another. As haloperidol can be administered intravenously, it remains the drug of first choice. Double-blind, placebo-controlled randomized trials are needed to further study prophylaxis and treatment of delirium in critically ill patients. Future research in ICU delirium should focus on pharmacological prevention, pharmacological treatment and multicomponent intervention strategies that reveal subgroups of patients with greatest potential to benefit, such as high-risk patients or those with subsyndromal delirium. Important research questions for the future are whether medication should be given to all delirious patients or only to subjects with certain characteristics such as psychosis or agitation.[20]

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Classification of daily mental status in the ICU

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3

ABSTRACT

Objective

To develop a reliable tool for daily mental status classification in Intensive Care Unit (ICU) patients for research purposes. Secondly, using this tool, patients with delirium occurring only once, for one day during ICU admission were compared to patients with more delirium days or multiple episodes.

Methods

A 5-step algorithm was designed which includes Richmond Agitation Sedation Scale and Confusion Assessment Method for the ICU (CAM-ICU) scores from bedside nurses, initiation of delirium treatment, chart review, and the CAM-ICU administered by researchers. This algorithm was validated against a reference standard of delirium experts. Subsequently, a cohort study was performed in patients admitted to a mixed-ICU.

Results

In 65 paired observations, the algorithm had 0.75 sensitivity and 0.85 specificity. Applying the algorithm, interobserver agreement was high with mean Fleiss' kappa of 0.94 (5 raters) and 0.97 (4 raters). In the cohort study 1112 patients were included of whom 535 (48%) became delirious. Single, one-day episodes occurred in 43% of the delirious patients, whom had a lower age compared to those with more delirium days.

Conclusions

The algorithm for daily mental status classification seems to be a valid tool. In a substantial proportion of patients, delirium occurs once during ICU admission lasting only one day.

INTRODUCTION

Delirium is a common syndrome in patients admitted to the Intensive Care Unit (ICU), which negatively affects patient outcomes.[1,2] In previous studies, the incidence of delirium varied between 16 and 89%.[2-4] This striking variability may be due to differences in case-mix, and due to different assessment methods for delirium. To design future intervention studies on delirium in the ICU, it is important to have accurate frequency measures. In research on ICU delirium, mental status (e.g. coma, delirium, awake without delirium) is usually classified per day, but it is unclear how this should be based on available detection tools, such as the Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC).[5-7] Although the CAM-ICU showed superior sensitivity compared to the ICDSC,[8] it is only a two minute assessment, while delirium is a highly fluctuating condition. Further, little is known about the characteristics of ICU patients with recurrent or persistent episodes of delirium as opposed to patients with a one single day of delirium. Previous literature suggests that there is a relationship between the duration of delirium and negative outcomes, such as mortality and cognitive impairment,[1,9] and that rapidly reversible, sedation-related delirium is not associated with negative outcomes.[10]

The objectives of this study were twofold. Firstly, we aimed to validate a 5-step algorithm for daily classification of mental status based on the CAM-ICU. Secondly, we aimed to characterize the incidence and duration of delirium and different delirium episodes, and to explore differences in patient characteristics between ICU patients with only one day of delirium as compared to patients with prolonged or recurrent delirium episodes in the ICU.

METHODS

Setting, study design and population

An algorithm for daily mental status classification, described below, was developed and validated in a tertiary care center, the mixed ICU of the University Medical Center Utrecht (UMCU), the Netherlands. We performed a cross-sectional study on 10 days: six randomly selected days in the summer of 2010, two days in spring 2013 and two days in autumn 2013. All patients admitted on those days to our 32-bed ICU were included.

In addition, we performed a cohort study in the same center. For this cohort study, all adult consecutive patients admitted for at least 24 hours between January 2011 and June 2013 were prospectively evaluated. Patients were excluded with neurological injury or illness and due to a disorder impairing delirium assessments such as mental retardation, post cardiopulmonary resuscitation, and inability to speak Dutch or English. Patients who were transferred from the ICU of another hospital were excluded. The local ethic review board gave approval for a waiver to obtain informed consent (IRB number 010/056/c and 12/421/c). Patients or their legal representatives were notified of the study in writing at ICU admission with attached an opt-out card in case of unwillingness to participate.

Data collection

For both the validation and the cohort study, dedicated and trained physicians prospectively collected the following data from all patients: demographic data, chronic co-morbidities and medication use, ICU admission characteristics, daily physiological measurements and vital signs, daily disease severity scores, daily presence of sepsis/severe sepsis/septic shock, and therapeutic interventions (medication, fluids, lines, renal replacement therapy, and do-not-resuscitate (DNR) orders). When patients were readmitted to the ICU within 24 hours after ICU discharge, the two ICU admissions were merged into one admission. A protocol was in use throughout the study period that stressed that sedation should be minimized and interrupted on a daily basis.

Elective admissions were defined as planned admissions for a condition of which ICU admission could be postponed for at least 12 hours without adverse consequences. Surgical admissions were defined as an admission within 24 hours after surgery. Comorbidity was assessed using the Charlson Comorbidity Index.[11] Patients were considered to have dementia when indicated by (proxy) interview or described in the medical records as diagnosed by a geriatrician or neurologist. Hypertension was defined when positive in the medical record and/or when patients used antihypertensive medication. Patients were noted positive on current drinking status when they used more than three units of alcohol per day, as documented in the medical records or mentioned in the (proxy) history. Patients were defined as current smokers when smoking was noted in medical record or medical history. Severity of disease at ICU admission, admission diagnosis, and infection at ICU admission were classified using the Acute Physiology and Chronic Health Evaluation (APACHE) IV classification.[12]

Using a modified Sequential Organ Failure Assessment (SOFA), daily severity of illness was assessed, without the central nervous system component.[13] The presence of sepsis, severe sepsis and/or septic shock was classified daily using international sepsis definitions.[14-17] Those patients who were discharged from the ICU with palliative care were considered as deceased during ICU admission.

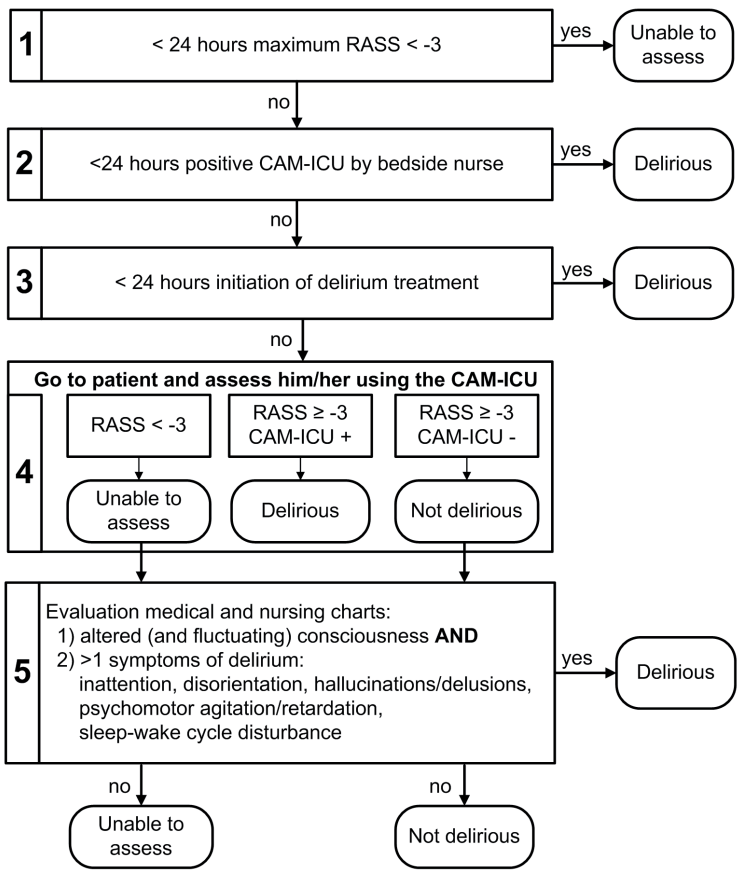
DELIRIUM ASSESSMENT

Description of the algorithm

The 5-step algorithm to define daily mental status is presented in Figure 1. The clinical staff, both physicians and nurses, was regularly trained in delirium and performing CAM-ICU assessments. In clinical practice, bedside nurses assessed sedation and agitation three hourly with the Richmond Agitation Sedation Scale (RASS).[18] In the first step of the algorithm, patients were classified as 'comatose' when a patient did not reach a RASS of -3 or more in the preceding 24 hours. Because of the high positive predictive value of the CAM-ICU as performed in routine clinical practice,[19] the second step of the 5-step algorithm included the twice daily CAM-ICU screening by the bedside nurse. With at least one positive CAM-ICU assessment by the bedside nurse, patients were classified as 'delirious' at any time in the previous 24 hours. In the third step of the algorithm, the initiation of delirium treatment was evaluated. In our ICU, haloperidol or quetiapine is only started by an ICU physician because of the diagnosis of delirium. With the start of haloperidol or quetiapine in the previous 24 hours, the patient was classified as 'delirious' in this third step. The start of sedatives or non-pharmacological treatment measures for delirium was not evaluated in this step. In patients not yet classified by step 1-3, the RASS and CAM-ICU were applied by a trained and experienced delirium researcher in step 4. With RASS of -3 or higher and CAM-ICU positive the patient was classified as 'delirious'. Whenever a patient was 'comatose' with RASS -4 or lower or scored CAM-ICU negative by the researcher, a review of the medical and nursing charts was performed in step 5 for: group 1 items) signs of altered level of consciousness (RASS<0) or fluctuation in consciousness using the 3 hourly RASS scores by bedside nurses, and group 2 items) two or more symptoms of delirium: inattention, disorientation, hallucinations or delusions, psychomotor agitation or retardation, inappropriate speech or mood, sleep wake cycle disturbances.

If both group 1 and group 2 items were present, patients were classified as 'delirious'. Patients with a negative CAM-ICU as scored by the researcher were classified as 'not delirious'. The remaining patients, who were classified 'comatose' by the researcher, were classified as 'comatose' in this fifth step.

Figure 1. 5-step Algorithm for mental status classification



CAM-ICU= Confusion Assessment Method for the Intensive Care Unit, hrs= hours, RASS= Richmond Agitation and Sedation Scale.

Delirium assessment in the validation study

The interrater reliability of the algorithm was determined on two days as follows. All patients were assessed by the research physicians and research nurses using the 5-step algorithm as either 'comatose', 'delirious' or 'not delirious' in the past 24 hours. The sensitivity, positive predictive value, specificity and negative predictive value of the algorithm were retrieved on eight selected days. Patients were assessed by two means: 1) an examination by a delirium expert team that consisted of a neurologist, a geriatrist, a psychiatrist and a research physician who assessed the patient together at 13:00 PM, 18:00 PM and 08:00 AM, and 2) the 5-step algorithm applied at 10:00 AM by a research physician who did not participate in the delirium expert team, and who was blinded to its results. The delirium expert team was blinded for the conclusion of the research physician who applied the 5-step algorithm, and for the medical and nursing charts, including the CAM-ICU assessments by the bedside nurses. Instead, the delirium expert team based their conclusion on neuropsychiatric examinations and on the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-revised criteria for delirium. The final classification of mental status in the past 24 hours was as either 'comatose', 'delirious' or 'not delirious'.

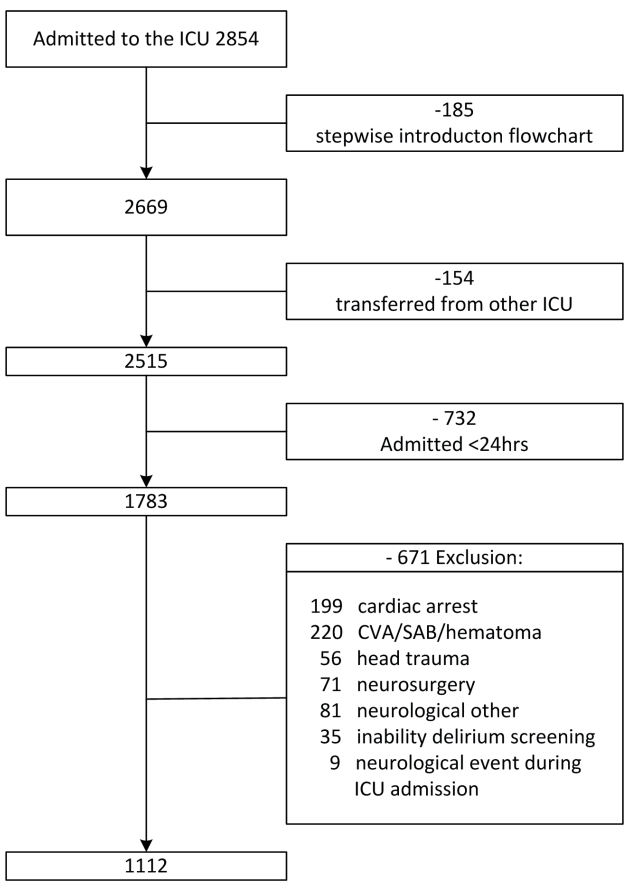
Delirium assessment in the cohort study

Each patient was assessed for prevalent delirium at ICU admission by the bedside physician. Additionally, patients using haloperidol at ICU admission were classified as having prevalent delirium. Each day, mental status of all included ICU-patients was assessed between 09:00 and 11:00 AM by the research team using the 5-step algorithm (Figure 1). Delirium status during ICU admission was classified in three groups: 'never delirium', 'ever delirium', and 'coma throughout ICU admission'. 'Ever delirium' was assigned to those patients with one or more days as 'delirious'. For these patients we also recorded different delirium episodes and delirium subtypes. A delirium episode ended when a patient scored ≥ 2 days as 'not delirious' or 'comatose'. The delirium subtype was classified using the 3 hourly registered RASS, a 10 point scale ranging from -5 (comatose) to +4 (heavily agitated).[18] When all RASS scores during this episode were 0 to -3, the delirium episode was defined as hypoactive, +1 to +4 as hyperactive, and -5 to +4 as mixed subtype.[20,21] Patients who exclusively scored "comatose" on the daily mental status classification were assigned 'coma throughout ICU admission'. Remaining patients were classified as 'never delirium'.

Statistical analysis

Differences between groups were assessed using the Chi Square test, Student's T-test, Mann-Whitney U test or Kruskal-Wallis test, where appropriate. Interrater reliability was computed using Fleiss' Kappa allowing agreement between multiple raters (in contrast to Cohen's Kappa).[22] SPSS 20 (IBM, New York, USA) was used to perform the statistical analysis. All statistical tests were performed against 2-sided alternatives and p-values <0.05 were defined as statistical significant.

Figure 2. Flowchart patient inclusion



hrs= hours, ICU= Intensive Care Unit.

RESULTS

Study population

VALIDATION STUDY

In the validation study, a total of 93 patients were included with mean age of 59 (standard deviation, SD 15) years, 59 (63%) males, 24 (26%) elective admissions and a mean APACHE IV score of 69 (SD 29). There were no differences between patients of the validation study and patients of the cohort study in age (p=0.24), sex (p=0.58), proportion of elective admissions (p=0.55) or APACHE IV score (p=0.10).

COHORT STUDY

During the cohort study period, 2669 consecutive patients were admitted to the ICU and prospectively assessed for delirium. Of these, 1112 met the inclusion, for a total of 9867 observation days (Figure 2). Table 1 gives an overview of the patient characteristics of the cohort study. In total 535 (48%) of the patients were diagnosed with 'ever delirium' during their ICU admission, 535 (48%) had 'never delirium', and 42 (4%) were 'comatose' throughout their whole ICU admission. The patients who were 'comatose' throughout ICU admission were statistically significantly more likely to be emergency admissions with higher severity of disease (APACHE IV and maximum SOFA scores) and more often severe sepsis, metabolic acidosis within 48 hours of ICU admission, compared to those patients with 'ever delirium' or 'never delirium'. Compared to cases who were never delirious, patients with 'ever delirium' were statistically significantly older and had more comorbidity and higher severity of disease.

Test characteristics of the algorithm for delirium detection

In total 122 paired observations were collected in the validation study. Interrater reliability of the algorithm was determined on two days. On the first day, in 30 paired observations with 5 different raters, the mean kappa was 0.94 (SD 0.04). The second day, in 27 paired observations assessed with 4 raters, the mean kappa was 0.97 (SD 0.05). On eight days the other test characteristics of the flowchart were evaluated in 65 paired observations, see Table 2. The 5-step algorithm showed a sensitivity of 0.75 (95% Confidence Interval (95% CI) 0.47-0.92), positive predictive value of 0.71 (95% CI: 0.44-0.89), specificity 0.85 (95% CI: 0.68-0.94) and negative predictive value 0.88 (95% CI: 0.71-0.96).

Table 1. Demographic features and clinical variables

Variables	All patients *n* = 1112		Delirium status: Never Delirium *n* = 535		Ever Delirium *n* = 535		Coma *n* = 42	
Age in years, mean (SD)	61	(16)	58	(16)[b]	63	(15)[b]	58	(16)
Male gender, n (%)	672	(60%)	306	(57%)[b]	344	(64%)[b]	22	(52%)
Comorbidity Index[a], median (IQR)	6	(0-10)	5	(0-10)[b]	7	(1-12)[b]	6	(1-10)
Dementia, n (%)	4	(0.4%)	0	(0%)	3	(1%)	1	(2%)
Hypertension, n (%)	384	(35%)	181	(34%)	193	(36%)	10	(24%)
Current drinking, n (%)	45	(4%)	10	(2%)[bd]	31	(6%)[b]	4	(10%)[d]
Current smoking, n (%)	90	(8%)	41	(8%)	45	(9%)	4	(10%)
Elective admission, n (%)	322	(29%)	187	(35%)[bd]	131	(25%)[bc]	4	(10%)[cd]
APACHE IV, mean (SD)	74	(28)	66	(26)[bd]	81	(26)[bc]	102	(37)[cd]
Admission category								
Medical, n(%)	493	(44%)	234	(44%)	234	(44%)	25	(60%)
Surgical, n (%)	544	(49%)	268	(50%)	262	(49%)	14	(33%)
Trauma, n (%)	75	(7%)	33	(6%)	39	(7%)	3	(7%)
Mechanical ventilation								
During admission, n (%)	1034	(93%)	477	(89%)[bd]	515	(96%)[b]	42	(100%)[d]
Days, median (IQR)	3	(1-8)	1	(1-3)[bd]	6	(3-14)[b]	3	(2-8)[d]
Severe sepsis/septic shock								
During admission, n (%)	401	(36%)	91	(17%)[bd]	279	(52%)[bc]	31	(74%)[cd]
Days, median (IQR)	0	(0-2)	0	(0-0)[bd]	1	(0-5)[bc]	2	(0-5)[cd]
Confirmed infection at admission, n (%)	339	(31%)	116	(22%)[bd]	204	(38%)[b]	19	(45%)[c]
Metabolic acidosis first ICU day, n(%)	270	(24%)	91	(18%)[bd]	154	(29%)[bc]	25	(61%)[cd]
Maximal daily SOFA, median (IQR)	7	(4-10)	5	(3-7)[bd]	8	(6-11)[bc]	13	(9-15)[cd]
LOS ICU in days, median (IQR)	5	(2-10)	3	(2-5)[b]	9	(5-18)[bc]	4	(2-9)[c]
Mortality ICU, n (%)	134	(12%)	24	(5%)[bd]	74	(14%)[bc]	36	(86%)[cd]
Observed days, n	9867		2274		7346		247	

ICU= Intensive Care Unit, LOS= Length of Stay, SD= standard deviation for normal distributed data, IQR= interquartile range for skewed data, APACHE= Acute Physiology and Chronic Health Evaluation, SOFA= Sequential Organ Failure Assessment. [a]Charlson Comorbidity Index, [b]Significant difference between 'Ever Delirium' and 'Never delirium', [c]Significant difference between 'Ever Delirium' and 'Coma throughout ICU admission', [d]Significant difference between 'Never delirium' and 'Coma throughout ICU admission'.

Table 2. Test characteristics for the algorithm for delirium detection

	Reference test		
Flowchart	**Delirious**	**Not Delirious**	**Comatose**
Delirious	12	5	3
Not delirious	4	29	0
Comatose	0	0	12
Exclusion	0	0	0
	Sensitivity = 0.75 (0.47-0.92)	**PPV =**	0.71 (0.44-0.89)
	Specificity = 0.85 (0.68-0.94)	**NPV =**	0.88 (0.71-0.96)

PPV= positive predictive value, NPV= negative predictive value.

Delirium incidence, episodes and subtypes

Of all patients, 535 (48%, 95% CI: 0.45-0.51) had ever delirium during their ICU admission (e.g. prevalence). A total of 513 patients (46%, 95% CI: 0.43-0.49) had new onset delirium during their ICU admission (e.g. incidence), with a total of 790 new delirium episodes.

Table 3 shows the characteristics of these new delirium episodes. In 219 (43%, 95% CI: 0.38-0.47) of the patients with delirium, delirium occurred only once, with a length of one day. From the patients who experienced delirium during their ICU stay, most patients (n=367, 72%, 95% CI: 0.67-0.75) developed one episode. A total of 78 (15%, 95% CI: 0.12-0.19) patients had 2 delirium episodes, 39 (8%, 95% CI: 0.06-0.10) 3 episodes and 29 (6%, 95% CI: 0.04-0.08) experienced more than 3 delirium episodes. Many delirium episodes (n=306, 39%, 95% CI: 0.35-0.42) lasted one day compared to 103 (13%, 95% CI: 0.11-0.16) that lasted more than 6 days.

Characteristics of the patients who developed a single, one day episode of delirium (n=219) versus those who developed either multiple delirium episodes or prolonged delirium (n=294) are shown in Table 4. Patients who developed one delirium episode of one day were younger, had lower comorbidity in general, had more cardiovascular risk factors (hypertension and smoking) and were more often surgical admissions, when compared to patients with either prolonged or multiple delirium episodes.

Of the delirium subtypes, the hypoactive delirium subtype was most common in 251 (32%, 95%CI: 0.29-0.35) episodes. Only one (0.1%, 95%CI: 0.0001-0.008) episode was purely hyperactive and 538 (68%, 95%CI: 0.65-0.71) episodes were classified as being mixed subtype. Episodes of mixed subtype delirium lasted longer compared to episodes of hypo-active delirium (median 3 (IQR 1-5) respectively 1 (IQR 1-2) days, p<0.001).

Table 3. Characteristics different delirium episodes and subtypes[a]

Variable	Number	
Characteristic per patient	**n = 513**	
Start first delirium episode, day ICU, median (IQR)	2	(1-4)
Duration first delirium episode in days, median (IQR)	1	(1-2)
Total delirious patients with 1 episode of 1 day, n (%)	219	(43%)
Total episodes during one ICU admission[b]		
1 episode, n (%)	367	(72%)
2 episodes, n (%)	78	(15%)
3 episodes, n (%)	39	(8%)
4 episodes, n (%)	16	(3%)
≥ 5 episodes, n (%)	13	(3%)
Characteristic per delirium episode	**n = 790**	
Subtypes delirium episodes		
Hypo-active, n (% of new episodes)	251	(32%)
Duration episode, median (IQR)	1	(1-2)[c]
Hyperactive, n (%)	1	(0.1%)
Duration episode, median (IQR)	3	
Mixed, n (%)	538	(68%)
Duration episode, median (IQR)	3	(1-5)[c]
Duration delirium episodes in days, median (IQR)	2	(1-4)
1 day, n (% of new episodes)	306	(39%)
2 days, n (%)	138	(18%)
3 days, n (%)	121	(15%)
4 days, n (%)	50	(6%)
5 days, n (%)	38	(5%)
6 days, n (%)	34	(4%)
≥ 7 days, n (%)	103	(13%)

ICU= intensive care medicine, IQR= interquartile range. [a]in 513 patients with incident delirium, [b]percentages do not count up to 100% due to rounding, [c]significant difference between hypo-active and mixed subtype.

DISCUSSION

In summary, our results show that a 5-step algorithm can be used to classify daily mental status for research purposes with high sensitivity and specificity. This is important, as classifications per day cannot be based directly on results from routine CAM-ICU or ICDSC screening alone, because of low sensitivity of routine CAM-ICU screening as well as the fluctuating nature of delirium during the day.[19,23-25] In addition, we have provided frequency measures of delirium and delirium duration, which can be used to design future studies on delirium in the ICU.

To our knowledge, this study is the first to describe and characterize different delirium episodes during ICU admission. In 43% of patients with delirium, delirium occurred only once for a duration of one day. These patients were found to have different characteristics compared to those having either prolonged delirium or multiple delirium episodes. Future studies should determine the differences between both groups in patient outcomes, such as ICU length of stay and ICU mortality. Our results on different delirium subtypes show that purely hyperactive delirium appears to be rare and that the mixed subtype is mostly frequently observed. The different subtypes of delirium are however difficult to classify in the ICU because of confounding effects of sedation. Recent investigations have shown that the diagnosis of delirium is influenced by sedation regimes with overlap between sedation, residual sedation and hypoactive delirium.[10,24,26,27] Another explanation for the low frequency of hyperactive delirium could be that, for example due to ICU acquired weakness or the use of sedatives, possible hyperactive delirious patients are less likely to score a RASS above 0. The finding that hypoactive delirium has a shorter duration when compared to the mixed subtype of delirium could also be explained by overlap with rapidly, reversible, sedation related delirium.

Being one of the largest high quality cohort studies on delirium in ICU patients, the findings of this study will be of use in clinical practice and in the design of future intervention studies. However, there are some limitations. First, the study was performed in one centre only, which may limit the generalizability of our findings. Yet, both our case-mix and findings are in line with previous literature. Secondly, as delirium was not assessed continuously, some short lasting episodes of delirium could have been missed with the use of the algorithm. Incorporating the chart review and bed-side delirium assessments by the researchers, we aimed to lower this risk of

Table 4. Characteristics patients with single episode of 1 day and those with more days of delirium[a]

Variables	1 Episode, 1 Day *n* = 219		>1 Day *n* = 294		p-value
Age in years, mean (SD)	61	(15)	64	(15)	<0.05
Male gender, n (%)	139	(64)	189	(64)	0.85
Comorbidity Index[b], median (IQR)	6	(0-10)	8	(3-13)	<0.05
Dementia, n (%)	0	(0)	3	(1)	0.27
Hypertension, n (%)	90	(41)	94	(32)	<0.05
Current drinking, n (%)	16	(7)	15	(5)	0.35
Current smoking, n (%)	28	(13)	17	(6)	<0.05
Elective admission, n (%)	54	(25)	75	(26)	0.83
Surgery before admission, n (%)	126	(58)	151	(51)	0.18
APACHE IV, mean (SD)	78	(26)	82	(26)	0.08
Admission category					<0.05
Medical, n (%)	84	(38)	138	(47)	
Surgical, n (%)	111	(51)	142	(48)	
Trauma, n (%)	24	(11)	14	(5)	
Mechanical ventilation					
Within first ICU day, n (%)	210	(96)	272	(93)	0.14
During admission, n (%)	218	(99.5)	278	(95)	<0.05
Ventilation days, median (IQR)	6	(4-10)	7	(2-22)	0.48
Severe sepsis/septic shock					
Within first ICU day, n (%)	89	(41)	112	(38)	0.58
During admission, n (%)	111	(51)	159	(54)	0.48
Severe sepsis days, median (IQR)	1	(0-5)	1	(0-7)	0.21
Confirmed infection at admission, n (%)	88	(40)	107	(36)	0.41
Metabolic acidosis within first ICU day, n(%)	68	(31)	79	(27)	0.38
Maximal daily SOFA, median (IQR)	8	(6-11)	8	(6-10)	0.23

ICU= Intensive Care Unit, LOS= Length of Stay, SD= standard deviation for normal distributed data, IQR= interquartile range for skewed data, APACHE= Acute Physiology and Chronic Health Evaluation, SOFA= Sequential Organ Failure Assessment. [a]In 513 patients with incident delirium, [b]Charlson Comorbidity Index.

misclassification bias. Also, in our specific ICU the use of haloperidol or quetiapine is only indicated in delirium. We incorporated the initiation of these drugs in the algorithm to prevent overlooking any case of delirium.

Little is known about the recurrence of delirium during ICU stay. To our knowledge this is the first study in the ICU to describe different delirium episodes. Moreover, we describe the differences between those patients developing only a single, one-day delirium episode, and those who develop either prolonged delirium or multiple episodes. From the patients who experience delirium, 28% will experience another episode during the same ICU admission. It is plausible, as in other psychiatric diseases such as affective disorders, that the likelihood of subsequent episodes increases with every new episode.[28]

CONCLUSION

Daily mental status can reliably be classified for research purposes using a 5-step algorithm in a setting where the CAM-ICU is implemented in clinical practice. In a substantial proportion of delirious ICU patients, delirium occurred once, and lasted one day. These patients have different characteristics when compared to patients with either prolonged, or multiple episodes of delirium. Our findings are important to design future studies on delirium in the ICU.

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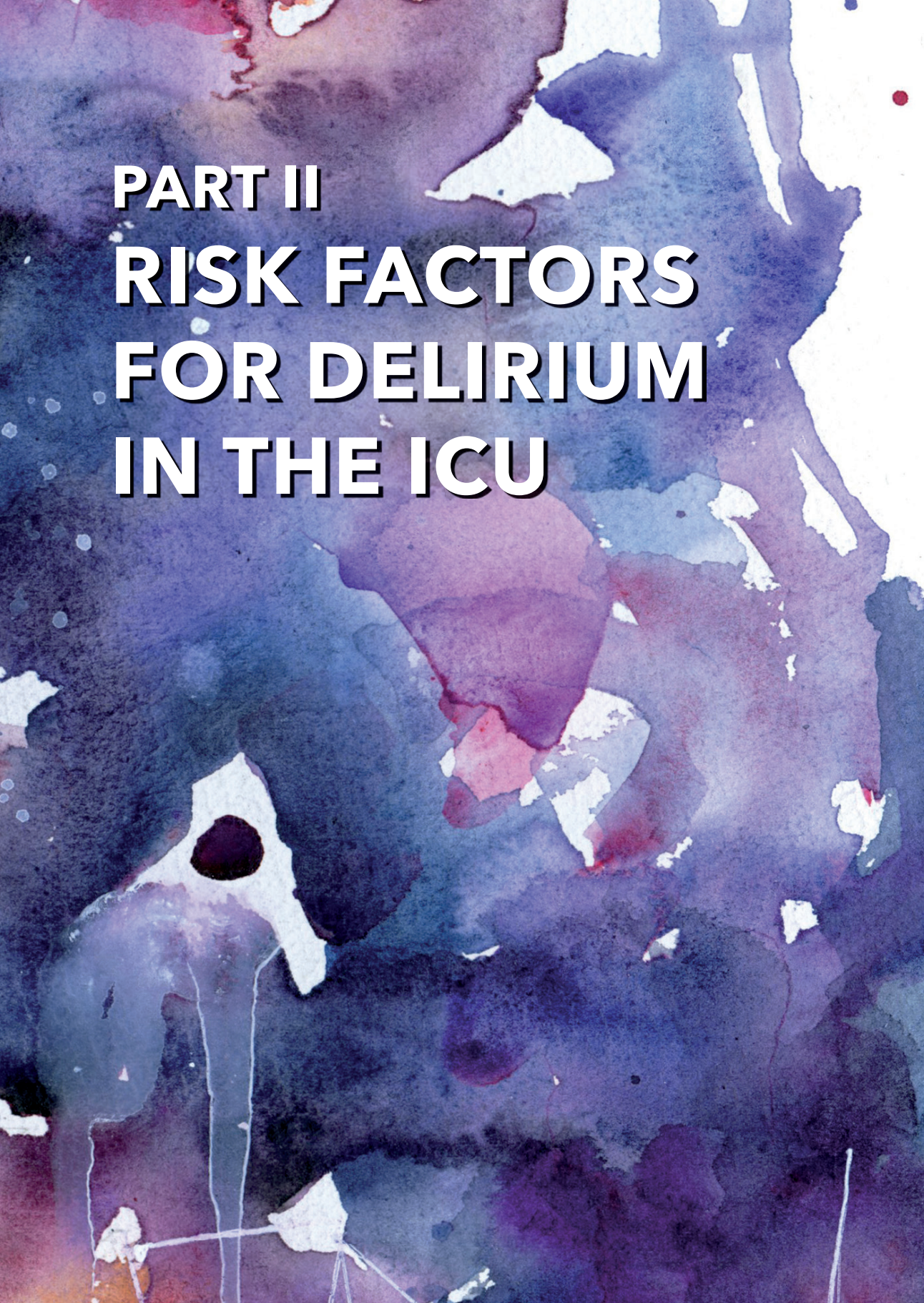

PART II
RISK FACTORS FOR DELIRIUM IN THE ICU

A systematic review of risk factors for delirium in the ICU

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ABSTRACT

Objective

While numerous risk factors for delirium in the Intensive Care Unit (ICU) have been proposed, the strength of evidence supporting each risk factor remains unclear. This study systematically identifies risk factors for delirium in critically ill adults where current evidence is strongest.

Data source and study selection

Five databases were searched for studies published from 2000 to February 2013 that evaluated critically ill adults, not undergoing cardiac surgery, for delirium, and used either multivariable analysis or randomization to evaluate variables as potential risk factors for delirium. Data were abstracted in duplicate, and quality was scored using SIGN checklists [i.e. high (HQ), acceptable (AQ), low (LQ)]. Using a best-evidence synthesis each variable was evaluated using 3 criteria: the number of studies investigating it, the quality of these studies, and whether the direction of association was consistent across the studies. Strengths of association were not summarized. Strength of evidence was defined as: strong (consistent findings in ≥2 HQ studies), moderate (consistent findings in 1 HQ study and ≥1 AQ studies), inconclusive (inconsistent findings or 1 HQ study or consistent findings in only AQ/LQ studies) or no evidence available.

Data extraction and synthesis

Among 33 studies included, 70% were HQ. There was strong evidence that age, dementia, hypertension, pre-ICU emergency surgery or trauma, APACHE II score, mechanical ventilation, metabolic acidosis, delirium on the prior day, coma are risk factors for delirium, that gender is not associated with delirium and that use of dexmedetomidine is associated with a lower delirium prevalence. There is moderate evidence that multiple organ failure is a risk factor for delirium.

Conclusions

Only 11 putative risk factors for delirium are supported by either strong or moderate level of evidence. These factors should be considered when designing delirium prevention strategies or controlling for confounding in future etiologic studies.

INTRODUCTION

Delirium occurs frequently during critical illness and is associated with negative outcomes such as increased time on the ventilator, longer Intensive Care Unit (ICU) and hospital length of stays and greater cognitive impairment after ICU discharge.[1-3] The risk of delirium is dependent on a complex interplay between predisposing- and precipitating risk factors.[4] With a current lack of treatment options, efforts should be made to prevent delirium.[5-7]

Over the past two decades, the number of publications on potential risk factors for delirium has increased dramatically.[8,9] Among potentially modifiable risk factors, it remains poorly elucidated which factors are well-established or most important when designing prevention programs. Moreover, it is poorly established which confounders should be incorporated in multivariable risk factor models. Failure to adequately adjust for confounding will limit strength of evidence that supports a variable from being a true delirium risk factor.

Taking into account these methodological concerns, we systematically reviewed the literature on potential risk factors for delirium in the ICU to identify those factors that currently have the strongest evidence to be characterized as delirium risk factor in critically ill adults.

METHODS

Study identifications

Five databases were searched (CINAHL, EMBASE, MEDLINE, the Cochrane Central Register for Controlled Trials, and the Cochrane Database of Systematic Reviews) for relevant articles or abstracts published from January 2001 through February 2013. With the guidance of an experienced medical librarian, we searched for eligible studies using separately formulated search strings for the domain (ICU patients), the determinants (risk factors) and the disease of interest (delirium). Subsequently, the results of these search strings were combined.

We reviewed personal files, reference lists of review articles, and reference lists of eligible studies for additional investigations. We chose 2001 as the initial search year since this was the year that the two ICU delirium screening instruments most

frequently used in ICU practice [i.e., Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC)] were published.[10-12] Articles or abstracts published in a language other than English, French, Dutch or German or in non-peer reviewed literature were excluded. Abstracts where a poster of the research findings was not available were also excluded.

Both the study protocol (*http://www.crd.york.ac.uk/NIHR_PROSPERO/display_record.asp?ID=CRD42013004886)* and the full search strategy *(http://www.crd.york.ac.uk/PROSPEROFILES/4886_STRATEGY_20130517.pdf*) were registered online prior to the start of the search.

Eligibility criteria

We included cohort studies or controlled trials that evaluated adults (≥18 years) admitted to an ICU, where at least one potential risk factor for the occurrence of delirium [i.e., delirium incidence, delirium prevalence, and/or the (daily) transition towards delirium] was considered, where the risk factor(s) was present before delirium was first detected and where delirium was evaluated in all patients at least once daily using a validated instrument. Studies that exclusively evaluated patients undergoing cardiothoracic surgery or included patients experiencing acute alcohol withdrawal were excluded given the difference(s) in the pathobiology of delirium between these populations and that of a general medical-surgical ICU population without these conditions. Studies that exclusively evaluated patients experiencing a cardiac arrest or an acute brain injury prior to the ICU admission were also excluded given the challenge of identifying delirium in these populations. Cohort studies that failed to evaluate risk factors using a multivariable approach were excluded. Studies not reporting delirium occurrence (e.g. only reporting delirium duration, days spent delirious, or days spent with coma and delirium) were excluded given that risk factors for these outcomes may be different.

Study selection and data extraction

Initially, all abstracts and titles from the search were screened in duplicate to identify potentially relevant studies (Figure 1). These studies were then re-screened in full-text form by two authors (IJZ and JWD). Further, the reference lists of all publications meeting the inclusion criteria and published practice guidelines as well as reviews were considered to identify additional relevant publications missed during the computerized search. All data was independently extracted by two authors (IJZ and JWD) using a

standardized, pre-piloted, evidence-synthesis form. Variables that could not be verified in full-text review as having been measured before the onset of delirium were excluded. The corresponding author was contacted for all articles where data was found to be missing and asked to provide the missing data or to confirm that this data had not been collected. Authors were contacted to provide additional information for 7 of the studies. All discrepancies were resolved through discussion with a third author (AJCS).

Risk of bias assessment

Two authors (IJZ and JWD) independently assessed the risk of bias for each included study by adapting the Scottish Intercollegiate Guidelines Network (SIGN) quality checklists for cohort studies and controlled trials so that those components relevant to the ICU setting were incorporated.[13,14] For cohort studies, the quality checklist considered: the risk on selection bias, performance bias, attrition bias, detection bias and the statistical analysis. For controlled trials, the quality checklist considered: randomization strategy, treatment allocation concealment, blinding, randomization success, use of intention-to-treat analysis, and the completeness of the reported outcome data. One point was given for each checklist criterion met. When a criterion was not met no point was given. When insufficient information about a particular criterion was provided, the item was scored as 'cannot state' and no point was given. Only studies using either Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) criteria or a delirium screening tool previously validated against DSM-IV criteria for use in ICU patients were given points for the 'reliable measurement of the outcome' criterion on each checklist.[15] Any disagreement during the quality scoring process was resolved through discussion with a third author (AJCS).

The maximum attainable score was 7 points for cohort studies and 9 points for controlled trials. A priori, cohort studies were deemed high quality (HQ) when the score was 6-7 points, acceptable quality (AQ) when the score was 5 and low quality (LQ) when the score was ≤4 points. For controlled trials these quality score definitions were ≥8 points, 5-7 points and ≤4 points, respectively.

Data synthesis

A priori, statistical pooling was considered for each potential delirium risk factor. After data extraction, all studies evaluating the same risk factor were reviewed to determine if differences existed between studies for one or more of the following methodological characteristics: study population, confounding variables included in the analysis, delirium assessment method, study quality and risk factor definition. Given that methodological heterogeneity was found to substantial for virtually all of the potential risk factors considered, much of which, was not anticipated at the time the analysis plan was first developed and registered, we decided to perform a semi-quantitative, best-evidence synthesis rather than a pooled statistical analysis. For the purposes of this synthesis, only variables where at least one study reported either a risk ratio (RR) or odds ratio (OR) above 1.5 or below 0.5 (regardless of statistical significance reported) or a statistically significant association (regardless of the OR/RR reported) were deemed to represent a true 'association'. We felt it was important not to depend solely on statistical significance as the sample size for many of the studies are small and the likelihood for statistical significance is highly dependent on the number other variables included in a multivariable model. A variable that was initially included in the initial stepwise selection procedure of the final multivariable model but was removed during this process, was categorized in our best-evidence synthesis as having no association with delirium tested using multivariable analysis.

Table 1. Level of evidence for being a risk factor for delirium

Level of evidence	Criteria
Strong evidence	Consistent findings (≥75%) in ≥ 2 high quality articles in multivariable analysis
Moderate evidence	Consistent findings (≥75%) in 1 high quality article **and** ≥ 1 acceptable quality article in multivariable analysis
Inconclusive evidence	Inconsistent findings irrespective of study quality **or** findings of 1 high quality article **or** only acceptable or low quality articles in multivariable analysis
No evidence	No association found in multivariable analysis **and** no association in > 3 high quality articles in univariable analysis

The ICU delirium risk factor literature meeting our study criteria was quantitatively evaluated using three criteria: 1) the number of studies evaluating a variable; 2) the scored quality of each study evaluating this variable, and 3) the consistency of the reported association between this variable and risk for delirium. For this latter criterion, association was deemed consistent if ≥75% of the studies evaluating the variable reported the same direction of association. In situations where definitions for the same risk factor varied little between studies, studies were combined together in the best-evidence synthesis. For example, the multiple organ failure (MOF) score or the sequential organ failure assessment (SOFA) score was each considered as a valid and similar way to characterize organ failure. As outlined in Table 1, the strength of the evidence of a variable as a risk factor for delirium, using multivariable analysis, was defined as: 1) Strong when the association was consistent in ≥2 HQ studies, 2) Moderate when the association was consistent in 1 HQ study and ≥1 AQ study(s), 3) Inconclusive when the association was not consistent (regardless of study quality) or evaluated in 1 HQ study or was consistent but was evaluated only in AQ/LQ studies.[16] A lack of evidence for a potential delirium risk factors was deemed to be present when no data on the variable was available (based on multivariable analysis) or >3 HQ studies showed no association based on univariable analysis alone.

RESULTS

Study identification

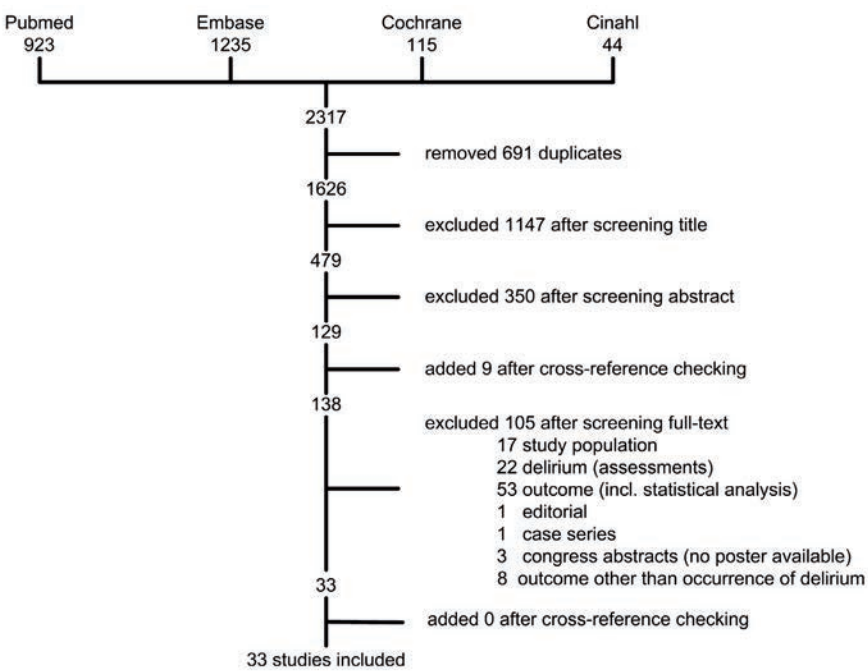
The search yielded 1626 unique references; 1497 of which were excluded based on title and abstract review. Another 9 publications were added after cross-reference checking, leaving 138 references for full-text review. Of these, 97 (70%) were excluded (Figure 1). During the article screening process, the potential inclusion of 3 articles was discussed with the third author. Of the 33 remaining studies, 25 evaluated potential risk factors in relation to the incidence or prevalence of delirium at any time during ICU stay,[17-41] and 8 studies incorporated (daily) transition to delirium as the primary outcome.[42-49]

Study characteristics

Of the 33 articles included (Supplementary data Table E1), 27 studies (82%), were cohort studies, 4 (12%) were randomized controlled trials and 2 (6%) were before-after

observational studies. The number of participants in each study ranged widely (40 to 3056). The case-mix of ICU patients varied with 13 (39%) of the studies evaluating mixed medical-surgical patients, 7 (21%) medical, 4 (12%) surgical and 3 (9%) trauma patients. The median [interquartile range (IQR)] occurrence rate of delirium was 44% [23-65] but ranged widely between 9 and 81%. The CAM-ICU (23, 70%), was used in more studies than the ICDSC (3, 9%). Five of the studies using the CAM-ICU also incorporated a daily chart reviewer to determine whether delirium was present to increase the sensitivity for delirium detection.[50,51] Delirium assessments were conducted by dedicated research personnel only in 18 (55%) of the studies, by bedside clinicians only in 6 (18%) and by a combination of researchers and clinicians in 9 (27%). Of the 29 cohort studies, 20 (69%) used a logistic regression model, 6 (21%) a markov logistic regression model, 2 (7%) a cox regression model and 1 (3%) both logistic and cox regression models (Supplementary data Table E2). Variable selection for the multivariable analysis was based on univariable analysis, followed by either block or stepwise entering of the variables in 14 (48%) of the studies or by a priori selection in 12 (41%) (Supplementary data Table E2).

Figure 1. Identification and selection of studies



Methodological quality

The results of the quality assessments are presented in Supplementary data Table E3 and E4. Across the 29 cohort studies, the median (range) quality score was 6 (4 to 7), with 22 (76%) of studies being graded as high quality (HQ), 4 (14%) as acceptable quality (AQ) and 3 (10%) as low quality (LQ). Only 7 cohort studies (24%) accounted for performance bias by evaluating for delirium at the time of inclusion.[17,21,24,33,38,39,42] Another 4 studies (19%) evaluated patients for delirium using an instrument that while validated against DSM-IV criteria, had not been validated for use in the ICU and thus lost one point on the detection bias quality criteria.[18,23,33,34]

The overall quality score for the 4 controlled trials ranged from 5 to 8 points; one was graded as HQ and 3 as AQ. Two studies had a drop-out rate >20%,[31,37] and in one study the method for allocation and concealment was not mentioned.[31] Although all controlled trials evaluated patients from multiple centers, none provided information as to whether the results were comparable between individual sites. During the methodological quality assessment of the 33 included articles and 239 criteria scored, the initial median (IQR) agreement on each article between the two evaluators was 71% (57%-86%). After discussion between these two evaluators only 10 criteria (4%) remained unresolved and were discussed with the third author.

Risk factor level of evidence

The results of the best-evidence synthesis are presented in Table 2. Additional information surrounding the point estimates reported in individual studies is presented in Supplementary data Table E5. The evidence supporting age, dementia, and hypertension as predisposing factors for delirium in critically ill adults is strong. There is no evidence that gender predisposes patients for delirium during their ICU stay. A number of precipitating risk factors for delirium in the ICU are associated with a strong level of evidence including (poly) trauma or emergency surgery prior ICU admission, the APACHE II score, (sedative-associated) coma, delirium on the previous day, use of mechanical ventilation, metabolic acidosis. There is moderate evidence to classify multiple organ failure as a risk factor for delirium. There is strong evidence that use of dexmedetomidine during the ICU stay reduces delirium prevalence.

Table 2. Best-evidence synthesis on variables to be associated with occurrence

Variables	Multivariable analysis	
	HQ + association	**+ association**
Predisposing variables		
Age	[17][19][32][33][38][39][40][46][48]	[20][34][37]
Gender		
Alcohol use	[26]	[23][36]
Smoking	[21]	[37]
Dementia	[25][28]	[36]
Hypertension	[21][26]	
ASA Physical Status	[39]	
Cardiac disease	[17]	
Precipitating variables		
Acute Illness		
Coma	[19][26][38][42][26][32]	
APACHE II	[38][40][45][46][48]	[23][34]
Delirium previous day	[42][48]	
Emergency surgery	[17][32][39]	
Mechanical ventilation	[22][40]	[36]
Acute respiratory disease		[18][23]
Kidney function/failure	[28]	
Medical admission	[38]	[36]
Organ Failure	[19]	[23][37]
(Poly)Trauma	[19][32][38]	[23]
Temperature/Fever		[18]
Medication		
Analgosedatives		[20][36]
Benzodiazepines	[32][38][42][46][47][48][49]	
Epidural analgesia	[21]	
Opiates	[21][38][47]	[35]
Propofol	[49]	[35]
Other		
Metabolic acidosis	[28][38]	[18]
Anemia	[30]	[18]
Bilirubine	[21]	[18]
Urea	[38]	[18]
Hypo/Hypernatremia		[18]
Room without daylight	[36]	
Variables associated with reduced delirium occurence		
Dexmedetomidine	[27][29][33]	[31]

[a]reported >1 multivariable or >4 univariable analysis. APACHE= Acute Physiology and Chronic Health
+ = positive association, - = negative association.

of delirium

Multivariable analysis		Univariable analysis	Level of
- association	no association	No association	Evidence
	[26][30][45]	[18][21][23][28][36]	Strong
	[20][33]	[17][21][23][26][28][32] [34][36][39][40]	No Evidence
	[21][28][30]	[19][24][34][38]	Inconclusive
	[26][36]	[28][34][36]	Inconclusive
		[21][32][38]	Strong
		[18][23][24][34][38]	Strong
	[17][34]		Inconclusive
	[20][33]	[18][21][23][24][34][36]	Inconclusive
	[20]	[21]	Strong
	[28][33]	[21][32][36]	Strong
			Strong
			Strong
	[19]	[21][34]	Strong
	[20][33][38]	[32][34]	Inconclusive
	[20]	[21][23][24]	Inconclusive
	[20]		Inconclusive
			Moderate
	[20]		Strong
	[20][38]	[17][21][32][36][38]	Inconclusive
			Inconclusive
[35]	[20][21][26][34]	[24][38]	Inconclusive
[40]	[26]	[34][38]	Inconclusive
[42][47]	[26]	[21][32]	Inconclusive
	[26][46]		Inconclusive
			Strong
	[19][38]	[26][28]	Inconclusive
	[38]	[24][26][28]	Inconclusive
		[21]	Inconclusive
	[21][28]	[24][30][38]	Inconclusive
	[21][41]		Inconclusive
			Strong

Evaluation, ASA= American Society of Anaesthesiologists, HQ= High Quality,

DISCUSSION

Awareness of which factors increase the risk for delirium in the ICU is crucial in better understanding this complex syndrome and for the design of prevention programs. Knowledge of risk factors is also essential when building multivariable models given the results of these analyses is highly dependent on which confounding variables are accounted for. While statistical pooling of available data for each of the proposed delirium risk factors we investigated was the initial goal of our systematic review, the substantial heterogeneity that exists between published studies evaluating each potential risk factor precluded pooling and forced us to complete a semi-quantitative best-evidence summary. This best-evidence synthesis is the first rigorous attempt to identify those variables that are well-established in the current literature to increase the risk of delirium in critically ill adults.

Our review has many strengths. It was designed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and registered in advance.[52] We searched multiple databases to identify risk factor studies published in multiple languages and included only cohort studies, where risk factor analysis was conducted using multivariable techniques, or randomized trials. We excluded studies involving populations where the mechanisms for delirium might be different. Article screening, data extraction and study quality rating were performed by two independent reviewers using clear and transparent definitions. Finally, by including only studies exploring the risk of developing delirium and excluding those with other outcomes (delirium duration, days spent delirious or days spent with coma and delirium), the risks studied can be considered equal.

A previous systematic review on this subject revealed that only 25 factors were described in the literature and concluded that risk factors for delirium were understudied and underreported.[53] Since this report in 2008, the literature regarding delirium risk factors has expanded considerably.[8,9] Although our best-evidence synthesis identified many more variables that have been hypothesized to increase delirium risk in the ICU, only 11 of these factors were associated with a level of evidence that was deemed either strong or moderate. Unfortunately most of the factors with conclusive evidence are non-modifiable such as age, comorbidities or admission characteristics. And although some interventions such as reorientation,[20] minimizing sedation levels,[35] seem promising, they merit more evaluation as there effect was not supported by our results. Minimizing the

duration of both (sedation-induced) coma and mechanical ventilation and promoting the use of dexmedetomidine are the interventions having the strongest evidence to reduce delirium in the critically ill. Whether dexmedetomidine reduces delirium occurrence in the ICU though a direct effect or simply because less benzodiazepines are administered remains unclear.[27,29]

While many of the risk factors we identified (e.g., severity of illness) are consistent with recent consensus guidelines,[12,54] there are some noteworthy exceptions. Unlike the 2013 Society of Critical Care Medicine (SCCM) Pain, Agitation and Delirium guidelines, our analysis identifies age as having strong evidence being a risk factor for delirium.[12,54] Our results, that are consistent with the National Institute for Health and Clinical Excellence (NICE) guidelines,[54] are most likely different from the SCCM guidelines given that they only included risk factors where statistical significance was documented and did not exclude risk factors that were based on univariable analysis alone. For both the use of benzodiazepines and opioids we found inconclusive evidence based on inconsistent results in the included studies. This finding could be explained by different definitions used in the studies, but also by an interplay between delirium, the indication for both benzodiazepines (anxiety, sleep disorders, induction of coma)[26,37,38,42] and opioids (pain)[26] and the potential direct harmful effect of the medication itself.[21,32,35,38,42,46-49]

Our review has potential limitations. Given that inter-study heterogeneity prevented statistical pooling between studies, we were forced to develop specific criteria to differentiate varying levels of evidence. By choice, we only incorporated variables tested in multivariable analysis. With the inclusion of only those variables presented in final models with either statistical significant association or an effect estimate above 1.5 or below 0.5, one variable changes from 'inconclusive evidence' to having 'strong evidence' (the use of benzodiazepines), and three variables change from 'inconclusive evidence' (alcohol use, nicotine use, medical admission category) to having 'moderate evidence'. Though, a system such as ours has been used to characterize prognostic factors for other non- ICU conditions, it has not been used for risk factor studies involving the critically ill nor for delirium.[16,55] The search strategy of this systematic review was thorough and multifaceted, however, it is possible that we missed studies on risk factors for delirium in the ICU. The impact of publication bias is difficult to estimate. It is also possible that other variables exist that may impact delirium occurrence that have yet to be formally evaluated and reported in the literature.

To be able to perform a best-evidence synthesis we had to assume that each risk factor was handled in a similar fashion across all studies. For a handful of risk factors, homogeneity did not always exist (Supplementary data Table E5). For example, in 13 studies age was entered as a continuous variable, in one as a binary variable, and in one as an odds ratio based on every 10 years of increased age. Removal of the latter two studies did not change the conclusion for the risk factor age. However, in other variables such as organ failure, the effect of combining studies where the variable was defined slightly differently (either MOF or SOFA), remains unclear.

With the use of better statistical techniques in observational cohort studies, important sources of (residual) confounding can be reduced. For delirium risk factors that could be present on any particularly ICU day, the importance of immortal time bias (i.e., a longer ICU survival periods exposes a patient to a greater exposure to the risk factor) is increasingly being recognized in time-dependent risk factors analyses.[56] Secondly, an ICU patient may die or be discharged from the ICU before delirium occurs.[57] Competing risk survival analysis or multinomial regression models incorporate these competing risks are needed given that traditional analytical methods like Kaplan-Meier estimates or Cox regression analysis are not designed to account for this and therefore may overestimate delirium risk.[57,58] The influence that repeated measures (e.g., the daily evaluation for the presence of a potential delirium risk factor) will have on the results of cohort studies can be minimized by using a mixed-effects analysis such as generalized estimating equations or a Markov Chain Monte Carlo method.

When conducting multivariable analyses of delirium risk factors, it is important that model overfitting does not occur. In general, no more than one risk factor variable should be incorporated in the model for every 10 patients who develop delirium. In small datasets, common in our best-evidence synthesis, more advanced methods to prevent overfitting such as propensity scoring or inversed probability weighting should be considered. Another strategy to reduce the number of covariables in an analysis, and used in two studies in our synthesis, is principal component analysis.[42,47]

CONCLUSION

Although many variables have been described as risk factors for delirium in the ICU, the results of our rigorous, best-evidence synthesis reveals that either moderate or strong level of evidence exists for only 11. The risk factors classified in this review should be taken into consideration when designing prevention programs and when controlling for confounding in future etiologic investigations. Additionally, adequately powered, prospective investigations, that incorporate key methodological issues we raised through the completion of this best-evidence synthesis, are required to further elucidate the risk factors for delirium in critically ill adults.

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SUPPLEMENTARY DATA

Table E1. Summary study characteristics included studies

First Author	Year	Study Design	Delirious patients /total (%)	Type IC
Abelha	2012	Cohort	26/173 (15%)	PACU
Agarwal	2010	Cohort	63/82 (77%)	Burn ICU
Aldemir	2001	Cohort	90/818 (11%)	SICU
Angles	2008	Cohort	41/69 (59%)	TICU
Colombo	2012	B/A	80/314 (26%)	Mixed ICU
Dubois	2001	Cohort	40/198 (19%)	Mixed ICU
Girard	2012	Cohort	107/138 (78%)	MICU
Guillamondegui	2011	Cohort	55/97 (57%)	TICU
Heyman	2007	Cohort	55/196 (28%)	PACU/MICU
Lin	2008	Cohort	31/143 (22%)	MICU
Morandi	2011	Cohort	40/62 (64%)	MICU
Morandi	2012	Cohort	*/120[a]	MICU
McNicoll	2003	Cohort	83/118 (70%)	MICU
Ouimet	2007	Cohort	243/764 (32%)	Mixed ICU
Pandharipande	2006	Cohort	*/198[a]	Mixed ICU
Pandharipande	2007	RCT	83/106 (81%)	Mixed ICU
Pandharipande	2008	Cohort	68/97 (70%)	SICU/TICU
Pandharipande	2009	Cohort	*/97[a]	MICU/SICU
Pisani	2007	Cohort	214/304 (70%)	MICU
Riker	2009	RCT	225/375 (60%)	Mixed ICU
Robinson	2009	Cohort	64/144 (44%)	SICU
Ruokonen	2009	RCT	15/85 (18%)	Mixed ICU
Serafim	2012	Cohort	43/465 (9%)	SICU
Seymour	2012	Cohort	*/140[a]	MICU
Shehabi	2013	Cohort	114/259 (44%)	Mixed ICU

B/A= Before after intervention study, CAM-ICU= Confusion Assessment Method for the ICU, FU=Follow-up, hrs= hours, ICDSC= Intensive Care Delirium Screening Checklist, ICU= Intensive Care patients, NEECHAM= Neelon and Champagne Confusion Scale, Nu-DESC= nursing delirium screening RCT= randomized controlled trial, RM= Regression Model, SICU= Surgical ICU, TICU= Trauma ICU, at ICU admission so frequency considered to be the same as prevalence of delirium, [b]in combination

Delirium Assessment	Delirium Assessors	Outcome	Statistical Model	Quality
ICDSC	*	Incidence	Logistic RM	++
CAM-ICU	*	Transition (daily)	Markov Logistic RM[c]	++
Interview DSM-IV	Research, Psychiatrist	Prevalence[a]	Logistic RM	-
CAM-ICU[b]	Research	Prevalence[a]	Logistic RM	++
CAM-ICU	Research	Prevalence[a]	Cox RM	+
DSM-IV ICDSC	Bedside, Psychiatrist	Incidence	Logistic RM	++
CAM-ICU	Research	Transition (daily)	Markov Logistic RM[c]	++
CAM-ICU	*	Prevalence[a]	Logistic RM	++
DDS	Bedside	Prevalence[a]	Logistic RM, Cox RM	-
CAM-ICU	Research	Incidence	Logistic RM	++
CAM-ICU	Research	Delirium next day	Logistic RM	++
CAM-ICU	Research	Delirium next day	Logistic RM	++
CAM-ICU	Research	Prevalence[a]	Logistic RM	++
ICDSC	Bedside	Prevalence[a]	Logistic RM	++
CAM-ICU	Research	Transition (daily)	Markov Logistic RM[c]	++
CAM-ICU	Research	Prevalence	Pearson χ^2 test	+
CAM-ICU	Research	Transition (daily)	Markov Logistic RM[c]	++
CAM-ICU	Bedside	Transition (daily)	Markov Logistic RM[c]	++
CAM-ICU[b]	Research	Prevalence[a]	Logistic RM	++
CAM-ICU	Research	Prevalence,Incidence	Fisher exact test	++
CAM-ICU[b]	Research	Prevalence[a]	Logistic RM	++
CAM-ICU	Research	Prevalence	Pearson χ^2 test Fisher exact test	+
CAM	Bedside	Prevalence[a]	Logistic RM	++
CAM-ICU	Research	Transition (daily)	Markov Logistic RM[c]	++
CAM-ICU	Research	Incidence	Cox RM	++

D= Delirious patients, DDS= Delirium Detection Score, DSM-IV=Diagnostic Statistic Manual version IV, Unit, IMCU= Intermediate Care Unit, ISS= Injury Severity Score, MICU= Medical ICU, ND= Non-delirious scale, OR= Odds Ratio, PACU= Post Anesthesia Care Unit, RASS= Richmond Agitation and Sedation Scale, * =unknown, ++=high quality, +=acceptable quality, - = low quality. [a] no clear measurement of delirium with Chart review, [c] with GEE.

Table E1. Summary study characteristics included studies *(continued)*

First Author	Year	Study Design	Delirious patients /total (%)	Type IC
Shi	2010	Cohort	73/164 (45%)	SICU
Svenningsen	2013	Cohort	416/640 (65%)	Mixed ICU
van Rompaey	2009	Cohort	155/523 (30%)	Mixed ICU
Van Rompaey	2012	RCT	*/136	Mixed ICU
vd Boogaard	2012	Cohort	911/3056 (30%)	Mixed ICU
Veiga	2012	Cohort	128/680 (19%)	PACU
Yoshitaka	2013	Cohort	13/40 (33%)	SICU
Zaal	2013	B/A	62/130 (48%)	Mixed ICU

B/A= Before after intervention study, CAM-ICU= Confusion Assessment Method for the ICU, FU=Follow-up, hrs= hours, ICDSC= Intensive Care Delirium Screening Checklist, ICU= Intensive Care patients, NEECHAM= Neelon and Champagne Confusion Scale, Nu-DESC= nursing delirium screening RCT= randomized controlled trial, RM= Regression Model, SICU= Surgical ICU, TICU= Trauma ICU, at ICU admission so frequency considered to be the same as prevalence of delirium, [b]in combination

Delirium Assessment	Delirium Assessors	Outcome	Statistical Model	Quality
Nu-DESC	Bedside, Research	Prevalence[a]	Logistic RM	+
CAM-ICU	Research	Prevalence[a]	Logistic RM	-
NEECHAM	*	Prevalence[a]	Logistic RM	+
NEECHAM	Bedside	Incidence	Cox RM	+
CAM-ICU	Bedside	Incidence	Logistic RM	++
ICDSC	*	Incidence	Logistic RM	++
CAM-ICU	1 Researcher	Prevalence[a]	Logistic RM	++
CAM-ICU[b]	Research	Prevalence[a]	Logistic RM	+

D= Delirious patients, DDS= Delirium Detection Score, DSM-IV=Diagnostic Statistic Manual version IV, Unit, IMCU= Intermediate Care Unit, ISS= Injury Severity Score, MICU= Medical ICU, ND= Non-delirious scale, OR= Odds Ratio, PACU= Post Anesthesia Care Unit, RASS= Richmond Agitation and Sedation Scale, * =unknown, ++=high quality, +=acceptable quality, - = low quality. [a] no clear measurement of delirium with Chart review, [c] with GEE.

Table E2. Description of the multivariable statistical model used in included cohort

First Author	Year	Study Design	Outcome	Statistical Model
Abelha	2012	Cohort	Incidence	Logistic RM Stepwise Forward
Agarwal	2010	Cohort	Transition (daily)	Markov Logistic RM[b] Block
Aldemir	2001	Cohort	Prevalence[a]	Logistic RM Stepwise Forward
Angles	2008	Cohort	Prevalence[a]	Logistic RM Stepwise Forward
Colombo	2012	B/A	Incidence	Cox RM Likelihood ratio test

AIS= Abbreviated Injury Scale, ADL= Activity Daily Living, APACHE= Acute Physiology and Chronic Health Chronic Obstructive Pulmonary Disease, DM= Diabetes Mellitus, ED= Emergency Department, GCS= ISS= Injury Severity Scale, LNAA= large neutral amino acids, LOS= length of stay, MDZ= midazolam, Sedation Scale, RCRI= Revised Cardiac Risk Index, RCT= Randomized Clinical Trial, RM= Regression Therapeutic Intervention Scoring System [a]no clear measurement of delirium at ICU admission, [b]and GEE, a priori, [e]not clear if measured before delirium onset.

Building the Multivariable Model

Included	Age group, emergency surgery, ASA Physical Status, hyperlipidemia, ischemic heart disease, congestive heart failure, RCRI, Lawton Scale, dependency in personal-ADL
Removed MV	Troponin I at admission post anesthesia care unit
Removed[c]	Age, gender, Body Mass Index, magnitude of surgery, type of anesthesia, length of anesthesia, temperature at admission Post Anesthesia Care Unit, SAPS II, Lawton scale personal-ADL, Apo lipoprotein E epsilon 4 allele
Included[d]	Previous day's mental status, doses of BZ (MDZ, lorazepam, diazepam), iv opiates (fentanyl and morphine), methadone, and a summary value using PCA of age, APACHE score, history of alcohol/substance abuse, burn%, presence inhalation injury.
Included	Respiratory disease, Infection[e], Fever[e], Hypotension[e], Anemia[e], Hypocalcaemia[e], Hyponatremia[e], Elevated level serum urea nitrogen[e], Elevated level hepatic enzymes[e], Hyperamylasemia[e], Hyperbilirubinemia[e], Metabolic acidosis[e]
Removed MV	Not described in manuscript
Removed	Hypertension, hypo/hyperpotassemia, hypernatremia, hypoalbuminemia, hypo-/hyperglycemia, cardiac disease, emergency admission, age, LOS ICU, LOS hospital
Included	Age, ISS, arrival GCS, Multi-Organ failure score[e], ICU transfusions[e]
Removed MV	Number of surgeries, Time under anesthesia, Lowest hematocrit level, mechanical ventilation
Removed[c]	Alcohol abuse, Charlson Index (comorbidities) Head AIS, Abdomen AIS, Extremity AIS, Systolic blood pressure at arrival, Heart rate at arrival, Maximum base excess
Included	Age, analgosedatives (MDZ + opiate)[e], reorientation strategy
Removed MV	Gender, SAPS II, GCS, DM, medical/surgical/trauma admission, respiratory failure, liver failure, kidney failure, heart failure, septic-shock, coma, acid base equilibrium disorder, sedation, analgosedatives (propofol + opiate)

Evaluation, ASA= Anesthesiologists Physical Status, B/A= Before/After, BZ = benzodiazepines, COPD= Glasgow Coma Scale, HAP/VAP= Hospital/ventilator associated pneumonia, ICU= Intensive Care Unit, MV= multivariable analysis, PCA= Principal Component Analysis, RASS= Richmond Agitation and Model, SAPS= Simplified Acute Physiology Score, SOFA= Sequential Organ Failure Assessment, TISS= [c]p-value univariable analysis before stepwise/block regression analysis [d]decided a priori [e]not decided

Table E2. Description of the multivariable statistical model used in included cohort

First Author	Year	Study Design	Outcome	Statistical Model
Dubois	2001	Cohort	Incidence	Logistic RM Stepwise Block
Girard	2012	Cohort	Transition (daily)	Markov Logistic RM[b] Block
Guillamondegui	2011	Cohort	Prevalence[a]	Logistic RM Block
Heyman	2007	Cohort	Prevalence[a]	Logistic RM Block
				Cox RM Block

AIS= Abbreviated Injury Scale, ADL= Activity Daily Living, APACHE= Acute Physiology and Chronic Health Chronic Obstructive Pulmonary Disease, DM= Diabetes Mellitus, ED= Emergency Department, GCS= ISS= Injury Severity Scale, LNAA= large neutral amino acids, LOS= length of stay, MDZ= midazolam, Sedation Scale, RCRI= Revised Cardiac Risk Index, RCT= Randomized Clinical Trial, RM= Regression Therapeutic Intervention Scoring System [a] no clear measurement of delirium at ICU admission, [b] and GEE, a priori, [e] not clear if measured before delirium onset.

Building the Multivariable Model

Included	Hypertension, active smoking, bilirubin[e], use epidural[e], morphine mean daily dosage[e]
Removed MV	COPD, alcohol abuse, sodium level, glucose level, lorazepam mean daily dosage, rooms without windows, rooms with windows
Removed[c]	Age, sex, admission diagnosis, APACHE II, GCS, DM, coronary disease, renal failure, Central nervous system disease, stroke, dementia, psychiatric history, visual and auditory impairment, drug abuse, family visits, endotracheal intubation, total numbers catheters and tubes, fever, infection, creatinine, urea, calcium, albumin, pCO2, fentanyl, other analgesics, other sedatives, haloperidol, other antipsychotic, corticosteroid
Included[d]	C-reactive protein/ matrix metalloproteinase-9/ myeloperoxidase/ neutrophil gelatinase-associated lipocalin/ soluble tumor necrosis factor receptor-1/D-Dimer/Protein-C/plasminogen activator inhibitor 1/ Von Willebrand factor antigen al separately tested with: age, severity of illness, severe sepsis
Included[d]	Heart rate at ED, ventilator days, ISS, SpO2 90% for 5 minutes[e], blood transfusions, and blood pressure at ED
Included	Hyperglycemia[f], APACHEII, SOFA[e], HAP/VAP[e], alcohol abuse, polytrauma
Removed[c]	Age, gender, DM, hypertension, carcinoma, liver failure, renal failure, heart failure, thyroid dysfunction, extremity fracture, hip endoprothesis, Acute respiratory distress syndrome, gastrointestinal surgery, liver surgery, urogenital surgery, abdominal arterial vessel surgery, peripheral arterial vessel surgery, ear-nose-throat, oral surgery
Included	Hyperglycemia[e], APACHEII, TISS[e], HAP/VAP[e], alcohol abuse, polytrauma
Removed[c]	Age, gender, DM, hypertension, carcinoma, liver failure, renal failure, heart failure, thyroid dysfunction, extremity fracture, hip endoprothesis, Acute respiratory distress syndrome, gastrointestinal surgery, liver surgery, urogenital surgery, abdominal arterial vessel surgery, peripheral arterial vessel surgery, ear-nose-throat, oral surgery

Evaluation, ASA= Anesthesiologists Physical Status, B/A= Before/After, BZ = benzodiazepines, COPD= Glasgow Coma Scale, HAP/VAP= Hospital/ventilator associated pneumonia, ICU= Intensive Care Unit, MV= multivariable analysis, PCA= Principal Component Analysis, RASS= Richmond Agitation and Model, SAPS= Simplified Acute Physiology Score, SOFA= Sequential Organ Failure Assessment, TISS= [c]p-value univariable analysis before stepwise/block regression analysis [d]decided a priori [e]not decided

Table E2. Description of the multivariable statistical model used in included cohort

First Author	Year	Study Design	Outcome	Statistical Model
Lin	2008	Cohort	Incidence	Logistic RM Stepwise (forward/backward)
Morandi	2011	Cohort	Delirium next day	Logistic RM Block
Morandi	2012	Cohort	Delirium next day	Logistic RM Block
McNicoll	2003	Cohort	Prevalence[a]	Logistic RM Block
Ouimet	2007	Cohort	Prevalence[a]	Logistic RM Stepwise (forward/backward)
Pandharipande	2006	Cohort	Transition (daily)	Markov Logistic RM[b] Block
Pandharipande	2008	Cohort	Transition (daily)	Markov Logistic RM[b] Block
Pandharipande	2009	Cohort	Delirium next day	Markov Logistic RM[b] Block

AIS= Abbreviated Injury Scale, ADL= Activity Daily Living, APACHE= Acute Physiology and Chronic Health Chronic Obstructive Pulmonary Disease, DM= Diabetes Mellitus, ED= Emergency Department, GCS= ISS= Injury Severity Scale, LNAA= large neutral amino acids, LOS= length of stay, MDZ= midazolam, Sedation Scale, RCRI= Revised Cardiac Risk Index, RCT= Randomized Clinical Trial, RM= Regression Therapeutic Intervention Scoring System [a]no clear measurement of delirium at ICU admission, [b]and GEE, a priori, [e]not clear if measured before delirium onset.

Building the Multivariable Model

Included	DM, sepsis, hypoalbuminemia
Removed MV	None
Removed[c]	Hypertension, alcohol abuse, chronic airway disease, chronic heart disease, shock, hypoxemia, hypercapnia, hyponatremia, elevated serum level creatinine, elevated serum level urea nitrogen, elevated serum level total bilirubin, administration of tranquilizers/narcotics/benzodiazepines/steroids
Included[d]	Age, APACHEII, severe sepsis at ICU admission, Insulin-like growth factor 1
Included[d]	Age, APACHE II, 25-OH vitamin D
Included	Charlson comorbidity score, APACHE II, impairment basic ADL, any invasive procedures other than mechanical ventilation, dementia
Removed[c]	Not described in manuscript
Included	Hypertension, alcoholism, APACHE II, pain[e], anxiety[e], coma[e]
Removed MV	Age, active smoking, epidural analgesia, opiate dose, benzodiazepine dose, propofol dose, indomethacin dose
Removed[c]	Gender, admission diagnosis, history of prior or current neurological disease, bilirubin/albumin/hemoglobin abnormalities, corticosteroids
Included[d]	Age, sex, visual and hearing deficits, dementia, depression, APACHE II, sepsis, history of neurologic disease, hematocrit, daily serum glucose concentrations. Analgesics, sedatives
Included[d]	Morphine/fentanyl/lorazepam/propofol/midazolam/anesthetics/ antipsychotics/H2-blockers all separately tested with age, body mass index, Charlson comorbidities index, APACHE II, presence of sepsis combined in summary value using PCA and 24-hour prior mental status
Included[d]	Tryptophan/LNAA, Phenylalanine/LNAA, Tyrosine/LNAA all separately tested with age, IQCODE, APACHE II, daily sedation regimen and 24-hour prior mental status

Evaluation, ASA= Anesthesiologists Physical Status, B/A= Before/After, BZ = benzodiazepines, COPD= Glasgow Coma Scale, HAP/VAP= Hospital/ventilator associated pneumonia, ICU= Intensive Care Unit, MV= multivariable analysis, PCA= Principal Component Analysis, RASS= Richmond Agitation and Model, SAPS= Simplified Acute Physiology Score, SOFA= Sequential Organ Failure Assessment, TISS= [c]p-value univariable analysis before stepwise/block regression analysis [d]decided a priori [e]not decided

Table E2. Description of the multivariable statistical model used in included cohort

First Author	Year	Study Design	Outcome	Statistical Model
Pisani	2007	Cohort	Incidence	Logistic RM Block
Robinson	2009	Cohort	Prevalence[a]	Logistic RM Stepwise (forward)
Serafim	2012	Cohort	Prevalence[a]	Logistic RM Block
Seymour	2012	Cohort	Transition (daily)	Markov Logistic RM[b] Block

AIS= Abbreviated Injury Scale, ADL= Activity Daily Living, APACHE= Acute Physiology and Chronic Health Chronic Obstructive Pulmonary Disease, DM= Diabetes Mellitus, ED= Emergency Department, GCS= ISS= Injury Severity Scale, LNAA= large neutral amino acids, LOS= length of stay, MDZ= midazolam, Sedation Scale, RCRI= Revised Cardiac Risk Index, RCT= Randomized Clinical Trial, RM= Regression Therapeutic Intervention Scoring System [a] no clear measurement of delirium at ICU admission, [b] and GEE, a priori, [e] not clear if measured before delirium onset.

Building the Multivariable Model

Included	Dementia, Receipt BZ before ICU, creatinine, arterial pH
Removed MV	Race, medicaid status, alcohol use, depression, APACHE II Chronic Health Evaluation, Impairment ADL, receipt BZ as an outpatient, respiratory/neurologic/other admission diagnosis, heart rate, respiratory rate, temperature, mean arterial pressure at admission, sodium, potassium, ratio urea nitrogen/creatinine, white blood cell count, partial thromboplastin time, aspartate aminotransferase,
Removed[c]	Age, gender, marietal status, admitted from nursing home, education, vision impairment, hearing impairment, tobacco use, APACHE II, Charlson comorbidity index, full code status, Receipt Narcotics before ICU, P:F ratio, bicarbonate, hematocrit, prothrombin time, alanine aminotransferase, direct bilirubin, total bilirubin
Included	hematocrit, dementia, Charlson Comorbidity Index,
Removed MV	Age, albumin, functional status, history of alcohol abuse
Removed[c]	Sodium, creatinine, glucose, intraoperative: blood loss, duration of operation, intra-operative hypotension, oxygen saturation, blood transfusion, age of blood transfusion
Included[d]	Age, type of surgery, emergency surgery, Acute Physiologic Score; BZ use first 24hours,
Removed MV	Hypoxemia, hypotension
Removed[c]	Gender, APACHE II, DM, hypertension, COPD, cancer, chronic renal disease, dementia, site of surgery (abdominal, orthopedic, head and neck, urologic, vascular, thoracic, cardiac, trauma, gynecological), fever, need oxygen therapy, use opioids first 24hours
Included[d]	Randomization arm (nested in RCT), SOFA, age, mental status, mean daytime doses propofol, BZ and nighttime change in mean propofol BZ

Evaluation, ASA= Anesthesiologists Physical Status, B/A= Before/After, BZ = benzodiazepines, COPD= Glasgow Coma Scale, HAP/VAP= Hospital/ventilator associated pneumonia, ICU= Intensive Care Unit, MV= multivariable analysis, PCA= Principal Component Analysis, RASS= Richmond Agitation and Model, SAPS= Simplified Acute Physiology Score, SOFA= Sequential Organ Failure Assessment, TISS= [c]p-value univariable analysis before stepwise/block regression analysis [d]decided a priori [e]not decided

Table E2. Description of the multivariable statistical model used in included cohort

First Author	Year	Study Design	Outcome	Statistical Model
Shehabi	2013	Cohort	Prevalence[a]	Cox RM Block
Shi	2010	Cohort	Prevalence[a]	Logistic RM Forward Stepwise
Svenningsen	2013	Cohort	Incidence	Logistic RM Block
van Rompaey	2009	Cohort	Prevalence[a]	Logistic RM Stepwise Forward

AIS= Abbreviated Injury Scale, ADL= Activity Daily Living, APACHE= Acute Physiology and Chronic Health Chronic Obstructive Pulmonary Disease, DM= Diabetes Mellitus, ED= Emergency Department, GCS= ISS= Injury Severity Scale, LNAA= large neutral amino acids, LOS= length of stay, MDZ= midazolam, Sedation Scale, RCRI= Revised Cardiac Risk Index, RCT= Randomized Clinical Trial, RM= Regression Therapeutic Intervention Scoring System [a] no clear measurement of delirium at ICU admission, [b] and GEE, a priori, [e] not clear if measured before delirium onset.

Building the Multivariable Model

Included[d]	APACHE III diagnosis (cardiac, respiratory, gastrointestinal, sepsis or other), age, sex, APACHE II, surgical admission, elective admission, cumulative dose of midazolam[e], dexmedetomidine[e], the use of vasopressors[e], dialysis[e] within first 48 hrs of admission.
Included	Age, history of stroke, APACHE II, serum cortisol level
Removed MV	Education, COPD, ASA class, additional narcotics, additional BZ
Removed[c]	Body mass index, gender, hypertension, coronary heart disease, DM , renal dysfunction, chronic smoking, alcoholism, habitual BZ use, habitual opiates use, previous surgical therapy, general anesthesia, perioperative use of scopolamine, duration of anesthesia, duration of surgery, intraoperative blood transfusion, intraoperative fluid infusion, type of surgery, patient controlled analgesia including epidural analgesia, mechanical ventilation
Included[d]	RASS (stable/change >2), sedatives (none, propofol, Midazolam), sedatives (None, propofol bolus, propofol continuous, midazolam bolus, midazolam continuous, both propofol and midazolam continuous), opiates (None, fentanyl, morphine, remifentanyl, alfentanil, epidural analgesia, others) all separately tested with gender, age, SAPS II, ICU site, medical/surgical ICU
Included	use alcohol, cognitive impairment, medical admission, psychoactive medication, endotracheal tube or tracheostomy, more than three perfusions, isolation, no visible daylight, no visit
Removed MV	living single at home, smoking, SAPS II, TISS, gastric tube, bladder catheter, no normal food, admission through transfer, physical restraints
Removed[c]	Age, gender, cardiac disease, pulmonary disease, APACHE II, arterial catheter, number vascular catheters, fever, admission through emergency department, open room ICU, no clock present or visible

Evaluation, ASA= Anesthesiologists Physical Status, B/A= Before/After, BZ = benzodiazepines, COPD= Glasgow Coma Scale, HAP/VAP= Hospital/ventilator associated pneumonia, ICU= Intensive Care Unit, MV= multivariable analysis, PCA= Principal Component Analysis, RASS= Richmond Agitation and Model, SAPS= Simplified Acute Physiology Score, SOFA= Sequential Organ Failure Assessment, TISS= [c]p-value univariable analysis before stepwise/block regression analysis [d]decided a priori [e]not decided

Table E2. Description of the multivariable statistical model used in included cohort

First Author	Year	Study Design	Outcome	Statistical Model
vd Boogaard	2012	Cohort	Incidence	Logistic RM Stepwise Backward
Veiga	2012	Cohort	Incidence	Logistic RM Block
Yoshitaka	2013	Cohort	Incidence	Logistic RM Block
Zaal	2013	B/A	Prevalence[a]	Logistic RM Block

AIS= Abbreviated Injury Scale, ADL= Activity Daily Living, APACHE= Acute Physiology and Chronic Health Chronic Obstructive Pulmonary Disease, DM= Diabetes Mellitus, ED= Emergency Department, GCS= ISS= Injury Severity Scale, LNAA= large neutral amino acids, LOS= length of stay, MDZ= midazolam, Sedation Scale, RCRI= Revised Cardiac Risk Index, RCT= Randomized Clinical Trial, RM= Regression Therapeutic Intervention Scoring System [a] no clear measurement of delirium at ICU admission, [b] and GEE, a priori, [e] not clear if measured before delirium onset.

Building the Multivariable Model

Included	Age, APACHE II, coma, admission category, infection, metabolic acidosis, morphine use, sedative use, urea concentration, urgent admission
Removed MV	Anemia, elevated hepatic enzymes, fever, hyperbilirubinemia, hypotension, hypocalcaemia, respiratory disease
Removed[c]	Alcohol abuse, dementia, epidural analgesia, hyperamylasemia, hyponatremia, use of dopamine, lorazepam use, hypertension
Included	Age, ASA Physical status, total RCRI, emergency surgery, hypertension, hyperlipidemia, ischemic heart disease, congestive heart disease, cerebrovascular disease, renal insufficiency, fresh frozen plasma, erythrocytes and troponin
Removed[c]	Gender, BMI, duration anesthesia, type anesthesia, temperature, COPD, High risk surgery, insulin therapy for DM, crystalloids, colloids
Included	Age, APACHEII, epidural analgesia[e], mechanical ventilation, operation duration, melatonin
Removed[c]	Gender, Charlson Comorbidity Index, Operation categories, intraoperative blood loss
Included[d]	Age, gender, APACHE II, Charlson co-morbidity index, highest SOFA[e], urgent admission, admitting discipline, Single room ICU with increased light

Evaluation, ASA= Anesthesiologists Physical Status, B/A= Before/After, BZ = benzodiazepines, COPD= Glasgow Coma Scale, HAP/VAP= Hospital/ventilator associated pneumonia, ICU= Intensive Care Unit, MV= multivariable analysis, PCA= Principal Component Analysis, RASS= Richmond Agitation and Model, SAPS= Simplified Acute Physiology Score, SOFA= Sequential Organ Failure Assessment, TISS= [c]p-value univariable analysis before stepwise/block regression analysis [d]decided a priori [e]not decided

Table E3. Methodological Assessment of included cohort studies

First Author	Year	Low Risk Selection Bias	Low Risk Perofrmance Bias	Outcome Clearly Defined	Blinding	Clear measure of exposure
Abelha	2012	1	1	1	n/a	1
Agarwal	2010	1	1	1	n/a	1
Aldemir	2001	1	0	1	n/a	0
		- Daily structured interview by trained clinicians and				
		- No test characteristics known of the				
Angles	2008	1	0	1	n/a	1
Colombo	2012	1	0	1	0	1
		- Before/after study without blinding.				
Dubois	2001	1	1	1	n/a	1
Girard	2012	1	0	1	n/a	1
Guillamondegui	2011	1	0	1	n/a	1
Heyman	2007	0	0	1	n/a	1
		- Retrospective Cohort with possibly selection bias				
		- DDS as measure of delirium (not preferred tool in				
Lin	2008	1	1	1	n/a	1
Morandi	2011	1	0	1	n/a	1
Morandi	2012	1	0	1	n/a	1
McNicoll	2003	1	0	1	n/a	1
		- In presentation of the results incident delirium is				
Ouimet	2007	1	0	1	n/a	1
Pandharipande	2006	1	0	1	n/a	1
Pandharipande	2008	1	0	1	n/a	1
Pandharipande	2009	1	0	1	n/a	1
		- No confidence intervals provided.				
Pisani	2007	1	0	1	n/a	1
Robinson	2009	1	0	1	n/a	1
		- No confidence intervals provided.				
Serafim	2012	1	0	1	n/a	1
Seymour	2012	1	0	1	n/a	1
Shehabi	2013	1	1	1	n/a	1
		- CAM-ICU in patients with RASS range -2 to +1,				

++ = high quality (6-7), + = acceptable quality (5), - = low quality (0-4), 1 = yes, 0 = no, ? = can't say,

Clear Outcome Assessment	Accurate statistical Analysis	Total Score	Quality Statement
1	1	7/7	++
1	1	7/7	++
0	1	4/7	-
only in doubt DSM-IV criteria.			
“daily structured interview.”			
1	1	6/7	++
1	1	5/7	+
1	1	7/7	++
1	1	6/7	++
1	1	6/7	++
0	1	4/7	-
due to missing data (137/333=41%).			
ICU patients).			
1	1	7/7	++
1	1	6/7	++
1	1	6/7	++
1	1	6/7	++
indistinguishable from prevalent delirium.			
1	1	6/7	++
1	1	6/7	++
1	1	6/7	++
1	1	6/7	++
1	1	6/7	++
1	1	6/7	++
1	1	6/7	++
1	1	6/7	++
0	1	6/7	++
whereas validated in RASS range -3 to +4.			

n/a = does not apply

Table E3. Methodological Assessment of included cohort studies *(continued)*

First Author	Year	Low Risk Selection Bias	Low Risk Perofrmance Bias	Outcome Clearly Defined	Blinding	Clear measure of exposure
Shi	2010	1	0	1	n/a	1
		- NuDesc as measure of delirium (not preferred tool				
Svenningsen	2013	1	0	1	0	0
		- Measure of exposure not well defined (used/day				
		- Both RASS and delirium assessment are subjective.				
		- Blinding should have been addressed.				
van Rompaey	2009	1	0	1	0	1
		- Several subjective measures noted so blinding				
van den Boogaard	2009	1	1	1	n/a	1
Veiga	2012	1	0	1	n/a	1
Yoshitaka	2013	1	0	1	n/a	1
Zaal	2013	1	0	1	0	1
		- Before/after study without blinding.				

++ = high quality (6-7), + = acceptable quality (5), - = low quality (0-4), 1 = yes, 0 = no, ? = can't say,

Clear Outcome Assessment	Accurate statistical Analysis	Total Score	Quality Statement
0	1	5/7	+
in ICU patients).			
1	1	4/7	-
of in time before delirium).			
1	1	5/7	+
should have been addressed.			
1	1	7/7	++
1	1	6/7	+
1	1	6/7	+
1	1	5/7	+

n/a = does not apply

Table E4. Methodological Assessment of included controlled trials

First Author	Year	Random Allocation	Concealment	Blinding	Successful Randomization	Similar treatment across groups
Pandharipande	2007	1	1	1	1	1
Riker	2009	1	1	1	1	1
Ruokonen	2009	1	?	1	1	1
		- No information provided on method used for				
van Rompaey	2012	1	1	1	0	0
		- Difference between two treatment groups at				
		- Difference in observation period between two				

++ = high quality (6-7), + = acceptable quality (5), - = low quality (0-4), 1 = yes, 0 = no, ? = can't say,

Outcome	% drop-out	ITT analysis	Comparable across sites	Total Score	Quality Statement
1	?	1	?	7/9	+
1	3/3%	1	?	8/9	++
1	25/16%	1	0	6/9	+
allocation or concealment.					
1	~90%	1	?	5/9	+
baseline (education level, professionally active).					
treatment groups.					

n/a = does not apply

Table E5. Effect Estimates of variables presented in final multivariable model

Determinant	Study	Quality	OR/HR	95%CI
Predisposing Variables				
Age	Angles - 2008	++	1.03	(1.0 - 1.1)
	Colombo - 2012	+	1.03[b]	(1.0 - 1.1)
	Serafim - 2012	++	1.04	(1.02-1.1)
	Shehabi - 2013	++	1.01	(1.00-1.03)
	Shi - 2010	+	2.6[d]	(1.4-4.9)
	Van den Boogaard - 2012	++	1.04	(1.03-1.06)
	Van Rompaey - 2012	+	1.03	(1.01-1.05)
	Veiga - 2012	++	1.05	(1.04-1.1)
	Yoshitaka - 2013	++	1.2	(1.02-1.4)
	Pandharipande - 2006	++	1.02[d]	(1.00-1.03)
	Pandharipande - 2009	++	>1[d]	n/a
	Abelha - 2012	++	9.3	(2.0 - 43.0)
Alcohol Use	Heyman - 2007	-	7.2[f]	(1.7-29.6)
	Heyman - 2007	-	2.3[bf]	(1.2-4.7)
	Ouimet - 2007	++	2.0	(1.3-3.3)
	Van Rompaey - 2009	+	3.2	(1.3-8.0)
Nicotine Use	Dubois - 2001	++	2.2[c]	(0.9-4.9)
	Van Rompaey - 2012	+	1.9	(1.1-3.5)
ASA-PS III/IV	Veiga - 2012	++	2.2	(1.3-4.0)
Cognitive Impairment	Robinson – 2009[a]	++	2.3[h]	(1.5-3.6)
Comorbidity	Robinson - 2009[a]	++	0.5	(0.4-0.8)
Congestive heart failure	Abelha - 2012	++	6.2	(2.0 – 19.3)
Dementia	McNicoll - 2003	++	1.3	(1.1-1.6)
	Pisani - 2007	++	6.3	(2.9-13.8)
	Van Rompaey - 2009	+	2.4	(1.2-4.8)
History of stroke	Shi - 2010	+	4.5	(1.2-16.5)
Hypertension	Dubois - 2001	++	2.6	(1.1-5.7)
	Ouimet - 2007	++	1.9	(1.3-2.6)
Benzodiazepines < ICU	Pisani - 2007	++	3.4	(1.6-7.0)

+ = acceptable quality, ++ = high quality, - = low quality. ACCP= American College of Chest Physicians, confidence interval, COPD= Chronic Obstructive Pulmonary Disease, hrs= hours, HR= Hazard Ratio, MV= Organ Failure Assessment, vs= versus, Y/N= Yes/No (binomial outcome). [a]Not in original paper, [b]Hazard [d]analyzed with GEE Markov on daily transitions, [f]Same study both results of logistic and cox regression

Description on how the determinant was measured
In years
In years
In years
In years
Every 10 years increase
In years
In years
In years
In years
In years
In years
Age ≥ 65 years
Diagnosis of alcohol dependence or harmful use (ICD10) (Y/N)
Diagnosis of alcohol dependence or harmful use (ICD10) (Y/N)
≥2 drinks daily/weekly consumption equivalent 26oz 40 proof alcohol
Daily use of more than 3 units each day
Current active smoking history (Y/N)
Current daily smoking history (Y/N)
American Society of Anesthesiologists Physical status III/IV vs ASA-PS I/II
OR outcome no delirium. Mini-Cog test 0-5(no cognitive impairment)
Charlson Comorbidity Index, per point increment, outcome NO delirium
Preadmission comorbidity in medical history
MBDRS ≥3 and IQCODE ≥3.31
IQCODE ≥3.3
Established diagnosis of dementia recorded in medical record
Preadmission comorbidity in medical history
Preadmission comorbidity in medical history
Preadmission comorbidity in medical history
(not further defined)

APACHE= Acute Physiology and Chronic Health Evaluation, CDC= centers for disease control, CI= mechanical ventilation, OR= odds ratio, SCCM= Society of Critical Care Medicine, SOFA= Sequental ratio obtained with Cox Regression, [c]Not statistically significant but effect estimate ≥1.5 or ≤0.5. model counted as 1.

Table E5. Effect Estimates of variables presented in final multivariable model *(continued)*

Determinant	Study	Quality	OR/HR	95%CI
Precipitating variables				
Acute Illness				
APACHE II	Heyman - 2007	-	1.2[f]	(1.1-1.3)
	Ouimet - 2007	++	1.05	(1.03-1.1)
	Heyman - 2007	-	1.1[bf]	(1.0-1.1)
	Serafim - 2012	++	1.1	(1.04-1.2)
	Shi - 2010	+	1.4	(1.2-1.6)
	Van den Boogaard - 2012	++	1.06	(1.03-2.0)
	Yoshitaka - 2013	++	1.8	(1.09-2.9)
	Morandi - 2012	++	1.1[d]	(1.03-1.18)
	Pandharipande - 2006	++	1.06[d]	(1.02-1.11)
	Pandharipande - 2009	++	n/a[d]	n/a
Anxiety	Ouimet - 2007	++	1.8	(1.04-3.4)
Blood transfusions	Angles - 2008	++	1.4	(1.0-1.9)
Coma	Agarwal - 2010	++	44.9[d]	(19-105.8)
	Angles - 2008	++	0.6	(0.3-1.1)
	Ouimet - 2007	++	3.7	(2.3-5.9)
	Van den Boogaard - 2012	++	1.7	(1.1-3.1)
	Van den Boogaard - 2012[a]	++	17.1	(5.9-77.1)
	Van den Boogaard - 2012[a]	++	14.9	(4.6-73.8)
Delirium previous day	Agarwal - 2010	++	26.5[d]	(11.9-58.9)
	Pandharipande - 2009	++	>1[d]	n/a
Emergency admission	Van den Boogaard - 2012	++	1.5	(1.1-2.3)
Emergency surgery	Abelha - 2012	++	59.7	(6.7-530.5)
	Serafim - 2012	++	8.1	(3.6-18.1)
	Veiga - 2012	++	2.7	(1.6-4.5)
Fever	Aldemir - 2001	-	14.3	(4.1-49.3)
FFP	Veiga - 2012	++	1.7	(1.3-2.2)
Heart rate	Guillamondegui - 2011	++	1.02	(1.00-1.04)
Hypotension	Aldemir - 2001	-	19.8	(5.3-74.3)
Infection	Aldemir - 2001	-	18.0	(3.5-90.8)
	Van den Boogaard - 2012	++	2.9	(2.0-4.8)
Use of MV	Guillamondegui - 2011	++	1.2	(1.1-1.3)
	Van Rompaey - 2009	+	8.1	(1.2-55.1)
	Yoshitaka - 2013	++	14.1[c]	(0.4-519.2)
Medical Admission	Van den Boogaard - 2012	++	1.4	(0.9-2.2)
	Van Rompaey - 2009	+	4.0	(1.5-11.0)

+ = acceptable quality, ++ = high quality, - = low quality. ACCP= American College of Chest Physicians, confidence interval, COPD= Chronic Obstructive Pulmonary Disease, hrs= hours, HR= Hazard Ratio, MV= Organ Failure Assessment, vs= versus, Y/N= Yes/No (binomial outcome). [a]Not in original paper, [b]Hazard [d]analyzed with GEE Markov on daily transitions, [f]Same study both results of logistic and cox regression

Description on how the determinant was measured
Per point increment
Per point increment
Per point increment
Only Acute Physiologic Score of APACHE II, per point increment,
Per point increment
Per point increment
Per point increment
Per point increment
Modified APACHE II by removing GCS component, per point increment
Per point increment
Self-reported anxiety when RASS≥-3
Total units (not further defined) during ICU, per unit increment
Coma on previous day vs normal
Glasgow Coma Scale at Emergency Department, per point increment
All types (iatrogenic, medical, multifactorial) during ICU admission (Y/N)
Iatrogenic (medication induced) coma first 24hrs vs no coma
Both (iatrogenic/miscellaneous) types of coma first 24hrs vs no coma
Miscellaneous coma first 24hrs vs no coma
Delirium on previous day vs normal
Delirium vs normal
Unplanned intensive care admission (Y/N)
(not further defined) (Y/N)
Surgery < 24 hrs after surgeon evaluation before SICU admission (Y/N)
(not further defined) (Y/N)
Body Temperature > 38°C, timing unclear (Y/N)
Fresh Frozen Plasma (FFP) Units administered during surgery (Y/N)
Pulse at Emergency Department
Symptomatic or systolic blood pressure <80 mmHg, timing unclear (Y/N)
Symptomatic infection, timing unclear (Y/N)
Infection with start antibiotics in first 24hrs (Y/N)
Number of ventilator days, per point increment
Endotracheal tube or tracheostomy (Y/N)
Postoperative use of mechanical ventilation (Y/N)
Medical admission category vs. surgical admission category
Medical admission category vs surgical admission category

APACHE= Acute Physiology and Chronic Health Evaluation, CDC= centers for disease control, CI= mechanical ventilation, OR= odds ratio, SCCM= Society of Critical Care Medicine, SOFA= Sequental ratio obtained with Cox Regression, [c]Not statistically significant but effect estimate ≥1.5 or ≤0.5. model counted as 1.

Table E5. Effect Estimates of variables presented in final multivariable model *(continued)*

Determinant	Study	Quality	OR/HR	95%CI
Precipitating variables				
Acute Illness				
Neurology admission	Van den Boogaard - 2012	++	4.0	(2.6-7.5)
Organ Failure	Angles - 2008	++	8.8	(1.7-45.1)
	Heyman - 2007	-	1.5	(1.2-1.7)
	Van Rompaey - 2012	+	1.09	(1.01-1.2)
Poly(trauma) patient	Heyman - 2007	-	14.5[f]	(3.3-64.9)
	Heyman - 2007	-	2.7[bf]	(1.4-5.5)
	Serafim - 2012	++	6.2	(4.1-6.5)
	Van den Boogaard - 2012	++	3.1	(1.7-6.8)
	Angles - 2008	++	1.1	(1.01-1.1)
RASS change >2	Svenningsen - 2013	-	5.2	(3.8-7.1)
Respiratory disease	Aldemir - 2001	-	30.6	(9.5-98.4)
	Heyman - 2007	-	8.0[f]	(2.7-24.1)
	Heyman - 2007	-	2.3[bf]	(1.3-4.1)
Sepsis	Lin - 2008	++	3.7	(1.03-12.9)
Interventions	Heyman - 2007	-	1.1[b]	(1.0-1.1)
Medication				
Analgosedatives	Colombo - 2012	+	2.1[b]	(2.2-4.0)
	Van Rompaey - 2009	+	3.3	(1.5-11.2)
Epidural analgesia	Dubois - 2001	++	3.5	(1.2-10.4)
	Yoshitaka - 2013	++	0.3[c]	(0.0-3.4)
H2-blockers	Pandharipande - 2008	++	1.5[cd]	(0.8-2.6)
Propofol	Seymour - 2012	++	3.2[cd]	(1.0-10.6)
	Svenningsen - 2013	-	1.5[c]	(0.4-1.0)
Benzodiazepines	Pandharipande - 2006	++	1.7[cd]	(0.9-3.2)
	Pandharipande - 2008	++	2.8[d]	(1.4-5.3)
	Pandharipande - 2006	++	1.2[d]	(1.1-1.4)
	Pandharipande - 2009	++	>1[d]	n/a
	Agarwal - 2010	++	6.8[d]	(3.1-15)
	Seymour - 2012	++	1166[d]	(16-82719)
	Seymour - 2012	++	2.5[cd]	(1.0-6.3)
	Serafim - 2012	++	2.3	(1.04-5)
	Van den Boogaard- 2012[a]	++	4.0	(2.8 to 7.4)
	Svenningsen - 2013	-	0.4[c]	(0.2-0.7)
>3 perfusors iv	Van Rompaey - 2009	+	2.7	(1.1-7.1)

+ = acceptable quality, ++ = high quality, - = low quality. ACCP= American College of Chest Physicians, confidence interval, COPD= Chronic Obstructive Pulmonary Disease, hrs= hours, HR= Hazard Ratio, MV= Organ Failure Assessment, vs= versus, Y/N= Yes/No (binomial outcome). [a]Not in original paper, [b]Hazard [d]analyzed with GEE Markov on daily transitions, [f]Same study both results of logistic and cox regression

Description on how the determinant was measured
Neurological admission category vs surgical admission category
Maximum Multiple Organ Failure Score during ICU, per point increment
Daily, Sequential Organ Failure Assessment, per point increment
Sequential Organ Failure Assessment, per point increment
At admission, not further defined (Y/N)
At admission, not further defined (Y/N)
(not further defined) (Y/N)
Admission category vs surgical admission category
Injury Severity Index (only > 8 included), per point increment
Score changed >2 levels since previous delirium assessment (Y/N)
COPD, cor pulmonale, pneumothorax, hemothorax at admission (Y/N)
HAP/VAP based on clinical signs, (blood) cultures (tracheal aspirate/ Bronchial lavage), criteria CDC and American Thoracic Society (Y/N)
On ICU admission, definition according to consensus ACCP+SCCM (Y/N)
Daily, therapeutic Intervention Scoring System, per point increment
Midazolam and opiate infusion (Y/N)
Use psychoactive medication (morphine, benzodiazepines) (Y/N)
In first 5 days of ICU admission (Y/N)
Postoperative use epidural analgesia (Y/N)
Histamine (H2-blockers) previous day (Y/N)
OR: 0(10^{th})-40.1(90^{th}) mcg/kg/min previous day
Propofol bolus vs no sedatives since previous delirium assessment (Y/N)
Midazolam previous day, per $\log_e$ mg increment
Midazolam previous day (Y/N)
Lorazepam previous day, per $\log_e$ mg increment
Lorazepam previous day, (Y/N)
Total dose previous 24hr in midazolam equivalents
OR: 0(10^{th})-2.4(90^{th}) mg/hr lorazepam equivalents previous day
OR: -0.19(10^{th})-0.25(90^{th}) mg/hr Δ lorazepam equivalents day - night
Benzodiazepine use first 24hours (Y/N)
Propofol, midazolam, lorazepam or combination in first 24hrs (Y/N)
MDZ continuous vs no sedatives since delirium assessment (Y/N)
More than 3 perfusions (Y/N)

APACHE= Acute Physiology and Chronic Health Evaluation, CDC= centers for disease control, CI= mechanical ventilation, OR= odds ratio, SCCM= Society of Critical Care Medicine, SOFA= Sequental ratio obtained with Cox Regression, [c]Not statistically significant but effect estimate ≥1.5 or ≤0.5. model counted as 1.

Table E5. Effect Estimates of variables presented in final multivariable model *(continued)*

Determinant	Study	Quality	OR/HR	95%CI
Precipitating variables				
Medication				
Opiates	Dubois - 2001	++	7.8	(1.8-34.4)
	Van den Boogaard - 2012	++	1.5	(0.8-3.1)
	Dubois - 2001	++	9.2	(2.2-39.0)
	Van den Boogaard - 2012	++	1.1	(0.8 to 1.8)
	Dubois - 2001	++	6.0	(1.4-25.4)
	Van den Boogaard - 2012	++	1.7	(1.1- 2.7)
	Pandharipande - 2008	++	1.9[cd]	(1.0-3.6)
	Pandharipande - 2008	++	0.4[d]	(0.2-0.8)
	Pandharipande - 2009	++	>1[cd]	n/a
	Agarwal - 2010	++	0.5[d]	0.4-0.6
	Svenningsen - 2013	-	1.5	(1.08-2.2)
Laboratory Values/Biomarkers				
Metabolic acidosis	Aldemir - 2001	-	4.5	(1.1-17.7)
	Pisani - 2007	++	2.1	(1.1-3.9)
	Van den Boogaard - 2012	++	1.3	(1.0- 2.0)
Anemia	Robinson - 2009[a]	++	1.1	(1.02-1.2)
	Aldemir - 2001	-	5.4	(1.6-17.8)
Bilirubine	Aldemir - 2001	-	8.7	(2.0-37.7)
	Dubois - 2001	++	1.2	(1.03-1.4)
Cortisol	Shi - 2010	+	3.4	(1.7-6.8)
Creatinine	Pisani - 2007	++	2.1	(1.1-4.0)
Hepatic enzymes	Aldemir - 2001	-	6.3	(1.2-32.2)
Hyperamylasemia	Aldemir - 2001	-	43.4	(4.2-442.7)
Hyperglycemia	Heyman - 2007	-	4.2[f]	(1.4-12.1)
	Heyman - 2007	-	3.1[bf]	(1.6-6.1)
Hypoalbuminemia	Lin - 2008	++	5.9	(1.2-28.8)
Hypocalciemia	Aldemir - 2001	-	30.9	(5.8-163.2)
Hyponatremia	Aldemir - 2001	-	8.2	(2.5-26.4)
Low MMP-9	Girard - 2012	++	0.4[d]	(0.2-0.8)
Low protein C	Girard - 2012	++	0.4[d]	(0.2-0.9)
Soluble TNF receptor-1	Girard - 2012	++	2.1[d]	(1.2-3.6)
Urea	Aldemir - 2001	-	4.6	(1.4-15.6)
	Van den Boogaard - 2012[a]	++	1.0	(1.0 to 1.1)
Tryptohan	Pandharipande - 2009	++	>1[d]	n/a
Tyrosine	Pandharipande - 2009	++	>1[d]	n/a

+ = acceptable quality, ++ = high quality, - = low quality. ACCP= American College of Chest Physicians, confidence interval, COPD= Chronic Obstructive Pulmonary Disease, hrs= hours, HR= Hazard Ratio, MV= Organ Failure Assessment, vs= versus, Y/N= Yes/No (binomial outcome). [a]Not in original paper, [b]Hazard [d]analyzed with GEE Markov on daily transitions, [f]Same study both results of logistic and cox regression

Description on how the determinant was measured
Morphine equivalents, mean daily dosage 0.01-7.1mg first 5 days ICU
Cumulative dosage first 24hrs Morphine 0.01-7.1mg
Morphine equivalents, mean daily dosage 7.2-18.6mg first 5 days ICU
Cumulative dosage first 24hrs Morphine 7.2-18.6mg
Morphine equivalents, mean daily dosage 18.7-331.6mg first 5 days
Cumulative dosage first 24hrs Morphine18.7-331.6mg
Fentanyl previous day (Y/N)
Morphine previous day (Y/N)
Fentanyl previous day (Y/N)
Total dose previous 24hr in fentanyl equivalents, per mg increment
Administration Alfentanil since previous delirium assessment (Y/N)
(not further defined), timing unclear (Y/N)
Arterial pH <7.35 at ICU admission (Y/N)
pH <7.35 with bicarbonate <24mmol/L first 24hrs (Y/N)
Preoperative, per % increment. OR outcome no delirium.
<25% hematocrit, timing unclear (Y/N)
Hyperbilirubinemia >10 mg/dl total bilirubin, timing unclear (Y/N)
per 10% increased days with abnormal level of first 5 ICU days
Serum cortisol first postoperative day, per µg/L increment
Serum Creatinine > 2mg/dL at ICU admission (Y/N)
↑ alanine aminotransferase/↑aspartate aminotransferase, (Y/N)
Serum amylase > 300 U/l, timing unclear (Y/N)
Blood glucose ≥ 130 mg/dl, timing unclear (Y/N)
Blood glucose ≥ 130 mg/dl, timing unclear (Y/N)
On ICU admission (not further defined)
Serum Calcium < 8 mg/dl, timing unclear (Y/N)
Serum Natrium <130 mmol/l, timing unclear (Y/N)
OR: 14.9(25^{th})-152.5(75^{th}) ng/mL
OR: 96.2(25^{th})-139.9(75^{th}) % of the pooled control plasma standard
OR: 2900(25^{th})-6302(75^{th}) pg/mL
Elevated serum urea nitrogen (>100 mg/dl), timing unclear (Y/N)
Serum urea, per mmol/L increment
Tryptohan/LNAA ratio, per point increment
Tyrosine/LNAA ratio, per point increment

APACHE= Acute Physiology and Chronic Health Evaluation, CDC= centers for disease control, CI= mechanical ventilation, OR= odds ratio, SCCM= Society of Critical Care Medicine, SOFA= Sequental ratio obtained with Cox Regression, [c]Not statistically significant but effect estimate ≥1.5 or ≤0.5. model counted as 1.

Table E5. Effect Estimates of variables presented in final multivariable model *(continued)*

Determinant	Study	Quality	OR/HR	95%CI
Environmental variables				
Isolation	Van Rompaey - 2009	+	2.9	(1.0-8.4)
Lack of visits	Van Rompaey - 2009	+	3.7	(1.8-7.9)
Lack of windows	Van Rompaey - 2009	+	2.4	(1.3-4.5)
Variables associated with reduced delirium occurence				
Dexmedetomidine	Pandharipande - 2007	++	<1	n/a
	Riker - 2009	++	<1	n/a
	Ruokonen - 2009	+	<1	n/a
	Shehabi - 2013	++	1.4[b]	(1.1-1.8)
	Pandharipande – 2009	++	>1[cd]	n/a
Earplugs	Van Rompaey - 2012	+	0.5[b]	(0.3-0.8)
Melatonin level	Yoshitaka - 2013	++	0.5	(0.3-0.99)
Methadone	Agarwal - 2010	++	0.7[d]	(0.5-0.9)
Pain	Ouimet - 2007	++	0.9	(0.8-0.97)
Reorientation strategy	Colombo - 2012	+	0.5[b]	(0.3-0.9)

+ = acceptable quality, ++ = high quality, - = low quality. ACCP= American College of Chest Physicians, confidence interval, COPD= Chronic Obstructive Pulmonary Disease, hrs= hours, HR= Hazard Ratio, MV= Organ Failure Assessment, vs= versus, Y/N= Yes/No (binomial outcome). [a]Not in original paper, [b]Hazard [d]analyzed with GEE Markov on daily transitions, [f]Same study both results of logistic and cox regression

Description on how the determinant was measured
(not further defined) (Y/N)
No visits from relatives (Y/N)
No visible daylight (Y/N)
RCT, Dexmedetomidine vs lorazepam sedation up to 120hrs
RCT, Dexmedetomidine vs midazolam sedation up to 30 days
RCT, Dexmedetomidine vs midazolam/propofol sedation up to 72hrs
Cumulative dexmedetomidine first 48hrs ICU, per mcg/day increment
Dexmedetomidine previous day (Y/N)
Earplugs vs sleeping without earplugs
Δ melatonin pg/mL (pre-operative-postoperative), per point increment
Total methadone administered previous 24hr, per mg increment
Measured with numeric Rating Scale, per point increment
Program including frequent reorientation and stimulation vs normal care

APACHE= Acute Physiology and Chronic Health Evaluation, CDC= centers for disease control, CI= mechanical ventilation, OR= odds ratio, SCCM= Society of Critical Care Medicine, SOFA= Sequental ratio obtained with Cox Regression, [c]Not statistically significant but effect estimate ≥1.5 or ≤0.5. model counted as 1.

Anticholinergic load at ICU admission and delirium

5

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ABSTRACT

Objective

Identifying modifiable risk factors for delirium is of pivotal importance to prevent delirium. Anticholinergic drugs may increase the risk of delirium in non-critically ill patients, but it is unclear whether these are also risk factors for delirium in Intensive Care Unit (ICU) patients. In this study the hypothesis was tested that anticholinergic drug exposure at ICU admission increases the risk to develop delirium during ICU stay.

Methods

In this prospective cohort study, all consecutive non-neurological patients, admitted for more than 24 hours to a mixed medical-surgical ICU of an university hospital, were included. The presence of delirium was daily evaluated using a validated algorithm based on routine Confusion Assessment Method for the ICU (CAM-ICU) assessments in daily practice, the initiation of delirium treatment, a chart review and the CAM-ICU applied by researchers. Anticholinergic drug exposure at ICU admission was assessed using the Anticholinergic Drug Scale (ADS).

Results

Among 1090 patients evaluated, 513 (48%) developed delirium. Taking competing events (death and discharge) into account in multivariable Cox Regression analysis, the subdistribution hazard ratio (SHR) was 1.13 (95% CI: 0.91-1.40) for ADS of 1 point and 1.35 (95% CI: 1.09-1.68) for ADS ≥2 points compared with an ADS score of 0 (no anticholinergic drug exposure).

Conclusions

Anticholinergic drug exposure seems to be associated with the onset of delirium in ICU patients.

INTRODUCTION

Delirium frequently complicates admission to the Intensive Care Unit (ICU).[1,2] The costs accompanying delirium are high,[3] mainly due to an increased length of stay both in the ICU and hospital.[1,4,5] More importantly, delirium seems to be associated with higher mortality and an increased risk of long-term cognitive impairment.[6,7]

Identifying modifiable risk factors for delirium is of pivotal importance to prevent this condition. Although numerous risk factors have been described in non-ICU patients,[8] only few factors have strong evidence in critically ill patients.[9] Medication with anticholinergic effects is presumed to be a precipitating factor based on the central cholinergic deficit hypothesis.[8,10] The presumed reduction in acetylcholine activity in delirium is supported by observations that the use of anticholinergic drugs is deliriogenic in non-ICU patients and because acetylcholine is involved in processes such as attention and arousal which are the most important disturbances in delirium.[2,10,11,12] However, there are very few studies on anticholinergic drugs and the risk of delirium in ICU patients.[13,14]

Anticholinergic effects might be stronger in older people due to aging-related changes in metabolism, reductions in cholinergic brain receptors and because of concurrent use of multiple medications with anticholinergic properties.[11,15-17] Besides age, it has been hypothesized that severe sepsis might interact with anticholinergic drugs.[10] Both anticholinergic drugs and sepsis may lead to activation of microglial cells in the brain. When microglia are already primed, for example because of aging, new stimuli may lead to an overactivation, which may lead to long-term cognitive impairment.

In this study we aimed to investigate whether anticholinergic drug exposure at ICU admission is a risk factor for the development of delirium and secondly to test the hypothesis that this association is influenced by age and severe sepsis.

METHODS

Study design and population

From January 2011 to June 2013, all adults consecutively admitted to the 32-bed mixed ICU of the University Medical Center Utrecht (UMCU), the Netherlands, for at least 24 hours, were prospectively evaluated. Patients with neurological illness and those with a disorder impairing delirium assessment such as post-anoxic encephalopathy, mental retardation or inability to speak Dutch or English were excluded. Additionally, we excluded patients with delirium at ICU admission, diagnosed by the admitting ICU physician and/or retrospectively by the use of haloperidol within one hour after ICU admission. The local ethical review board gave approval for a waiver to obtain informed consent (IRB number 010/056/c and 12/421/c).

Data collection

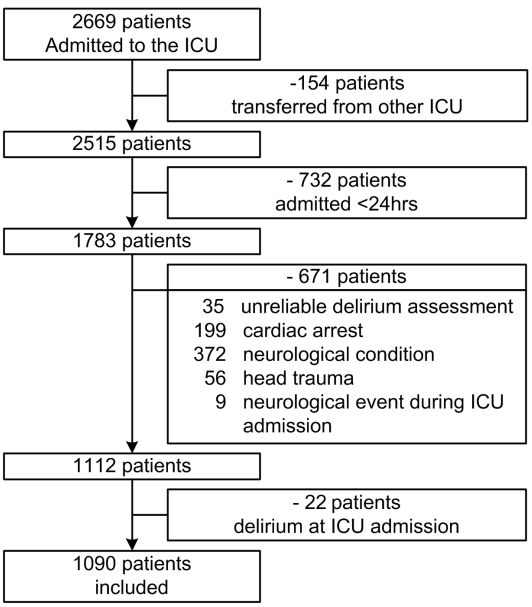
Medication use at ICU admission was retrieved from the medical record and referring letters combined with information given by the patient or his family. Each drug was assigned an anticholinergic score based on the Anticholinergic Drug Scale (ADS).[18] In this scale, the anticholinergic potential of drugs are rated in an ordinal fashion from 0 to 3: signifying no known anticholinergic activity (0), anti-cholinergic association by a serum assay study (1), some clinical evidence and anti-cholinergic association by a serum assay study (2) and marked anticholinergic activity (3). The individual scores of all the drugs prescribed to a patient at ICU admission were then summed to determine a total score for a particular patient.

Each day up until death or ICU discharge, patients were screened, between 09:00–11:00 AM, for delirium in the preceding day by a dedicated research team following a 5-step algorithm for daily mental status classification. This algorithm was developed and validated in the mixed-ICU of the UMCU, with interrater observer agreement ranging from 0.94-0.97, 0.75 sensitivity and 0.85 specificity.[19] With this flowchart, each patient was daily assigned a classification of the preceding day as: 1) coma, 2) delirium or 3) awake without delirium.

Demographics, co-morbidities, chronic medication use, ICU admission characteristics, and physiological measurements and vital signs, were collected daily by trained physicians dedicated to this patient cohort. When patients were readmitted to the ICU within 24 hours after ICU discharge, the two ICU admissions were merged

into one admission. Patient comorbidities were defined present when noted in the medical record or when patients used medication to treat the comorbidity, for example antidepressants in depression or insulin or oral anti-diabetics in diabetes mellitus. Alcohol abuse was considered present when patients used more than three units of alcohol per day, as documented in medical record or mentioned in (proxy) history. The presence of sepsis, severe sepsis and/or septic shock was classified using international sepsis definitions.[20-24]

Figure 1. Flowchart patient inclusion



hrs= hours, ICU= Intensive Care Unit.

Statistical analysis

All values were presented as the mean with standard deviation (SD), or median with the interquartile range (IQR). Differences between groups were assessed using the Chi Square test, Student's T-test or Mann-Whitney U test, where appropriate. To evaluate the risk of developing delirium during ICU admission dependent on the anticholinergic drug exposure at ICU admission, we performed multivariable competing risk Cox

proportional hazard analysis, as both the incidence of ICU discharge and death compete with the onset of delirium, and therefore act as competing events for delirium. Patients discharged from the ICU with palliative care were considered deceased during ICU admission. The competing risks analysis provided two measures of association: the cause-specific hazard ratio (CSHR), which estimates the direct effects of the anticholinergic drug exposure load on the different outcomes (delirium, ICU discharge and death), and the subdistribution hazard ratio (SHR) which describes in this study the instantaneous risk of developing delirium dependent on the anticholinergic load.[25] As we expected effect modification by age and severe sepsis, we performed stratified analysis in four subgroups of patients: aged < 65 years or ≥ 65 years, both with and without severe sepsis at ICU admission.

In all multivariable models, we adjusted for time-fixed covariables that were chosen a priori based on their expected associations with anticholinergic burden and delirium in the ICU after careful consideration of the literature.[9] Only variables with prevalence >10% were taken into account in multivariable analysis. The patient comorbidities included in the multivariable model were: cerebrovascular disease, depression, diabetes mellitus, hypertension, and current drinking status. Additionally, the following ICU admission characteristics were included in multivariable models: emergency admission (vs elective admission), surgery before admission and severe sepsis or septic shock at ICU admission. Lastly, in the multivariable analysis the Acute Physiology and Chronic Health Evaluation (APACHE) IV Score was included, as a measure of the severity of disease at ICU admission, and the maximum Sequential Organ Failure Assessment (SOFA) during ICU admission up until death, discharge or delirium (whichever occurred first), as a measure of the evolution of disease severity after ICU admission.[26,27] To avoid overcorrection a modified SOFA score without the central nervous system component, was used to assess daily severity of illness during ICU admission.[26]

All statistical tests were performed against 2-sided alternatives and p-vales <0.05 were defined as statistical significant. SPSS 20 (IBM, New York, USA) and R version 3.0.1 were used to perform the statistical analysis. The R-package "cmprsk" was used to plot cumulative incidence of delirium in the presence of competing risks.[25,28]

RESULTS

A total of 2669 patients were screened of whom 1579 were excluded, leaving 1090 included patients (Figure 1). In 513 (47%) patients, delirium occurred during admission. The characteristics of the included patients are presented in Table 1. Patients developing delirium during their ICU admission were on average older and had more often severe sepsis or septic shock at ICU admission compared with patients who did not develop delirium. Patient with delirium had a longer length of stay in the ICU and higher mortality at the ICU, with more frequent use of mechanical ventilation, than those without delirium.

Table 1. Patient demographics and clinical characteristics

Characteristic	Delirium n=513		No delirium n=577		p-value
Age in years, mean (SD)	63	(15)	58	(16)	<0.001
Male, n (%)	328	(64%)	328	(57%)	0.02
Comorbidity[a] at hospital admission					
Assisted Living, n (%)	6	(1%)	14	(2%)	0.17
Dementia, n (%)	3	(0.6%)	1	(0.2%)	0.35
Cerebrovascular disease, n (%)	63	(12%)	52	(9%)	0.10
Alcohol abuses, n (%)	31	(6%)	14	(2%)	0.004
Hypertension, n (%)	184	(36%)	191	(33%)	0.37
Diabetes Mellitus, n (%)	104	(20%)	112	(19%)	0.78
Depression, n (%)	40	(8%)	44	(8%)	0.99
Parkinson, n (%)	1	(0.2%)	0		0.47
No. of medication classes[a], median (IQR)	4	(2-5)	3	(1-5)	<0.001
Elective ICU admission, n (%)	129	(25%)	191	(33%)	0.005
ICU admission type					0.70
Medical admission, n (%)	222	(43%)[b]	259	(45%)	
Surgical admission, n (%)	253	(49%)[b]	282	(49%)	
Trauma admission, n (%)	38	(7%)[b]	36	(6%)	
APACHE IV score, mean (SD)	80	(26)	68	(28)	<0.001
Severe Sepsis at ICU admission, n (%)	201	(39%)	106	(18%)	<0.001
Mechanical ventilated during ICU, n (%)	496	(97%)	519	(90%)	<0.001
Maximum SOFA score, median (IQR)	8	(6-10)	5	(3-8)	<0.001
Length of ICU stay, median (IQR)	9	(5-19)	3	(2-5)	<0.001
Death at ICU, n (%)	77	(15%)	62	(11%)	0.04

APACHE= Acute Physiology and Chronic Health Evaluation, ICU= Intensive Care Unit, IQR= Interquartile range, No= number, SD= standard deviation, SOFA= Sequential Organ Failure Assessment. [a]at hospital admission, [b]percentages do not count up to 100% due to rounding.

With delirium developing in 254/485 (52%) of the patients aged ≥ 65 years, delirium was more common compared with 43% (259/605) in those aged < 65 years (p=0.002). Patients who fulfilled the criteria for severe sepsis developed delirium more often (65%, 201/307) than patients without severe sepsis (40%, 312/783, p=<0.001). Within the four subgroups for stratified analysis and definitions as above, the incidence of delirium was highest (p<0.001) in the older patients with severe sepsis (73%, 106/146), followed by younger patients with severe sepsis (59%, 95/161), older patients without severe sepsis (44%, 148/339) and younger patients without severe sepsis (37%, 164/444).

At ICU admission, patients who developed delirium had higher ADS scores (median 1, IQR0-2) compared with those who did not develop delirium (median 0, IQR 0-1), p < 0.01) (Table 2). With a prescription proportion of 17% in the whole study population, furosemide was the most commonly used anticholinergic drug, followed by prednisolone (12%), temazepam (7%) and oxazepam (7%). Table 2 shows the exposure

Table 2. Anticholinergic drug exposure at ICU admission

	All patients n=1090		**Delirium n=513**		**No Delirium n=577**	
Anticholinergic Drug Scale[c]						
Score = 0, n (%)	512	(47%)	217	(42%)[a]	295	(51%)
Score = 1, n (%)	284	(26%)	140	(27%)[a]	144	(25%)
Score ≥ 2, n (%)	294	(27%)	156	(30%)[a]	138	(24%)
Top 10 of medication with anticholinergic properties[b]						
Furosemide, *Rank*, n (%)	*1.*	189, (17%)	*1.*	106,(21%)	*1.*	83, (14%)[c]
Prednisolone, *Rank*, n (%)	*2.*	127, (12%)	*2.*	55, (11%)	*2.*	72, (12%)
Temazepam, *Rank*, n (%)	*3.*	73, (7%)	*3.*	34, (7%)	*3.*	39, (7%)
Oxazepam, *Rank*, n (%)	*4.*	71, (7%)	*4.*	34, (7%)	*4 .*	37, (6%)
Digoxine, *Rank*, n (%)	*5.*	46, (4%)	*5.*	26, (5%)	*7.*	20, (3%)
Oxycodon, *Rank*, n (%)	*6.*	43, (4%)	*9.*	16, (3%)	*5.*	27, (5%)
Amitryptiline, *Rank*, n (%)	*7.*	38, (3%)	*7.*	16, (3%)	*6.*	22, (4%)
Dipyridamol, *Rank*, n (%)	*8.*	35, (3%)	*8.*	16, (3%)	*8.*	19, (3%)
Nifedipine, *Rank*, n (%)	*9.*	30, (3%)	*6.*	17, (3%)	*12.*	13, (2%)
Isosorbidedinitrate,*Rank,*n(%)	*10.*	28, (3%)	*11.*	15, (3%)	*11.*	13, (2%)
Tramadol, *Rank*, n (%)	*11.*	27, (2%)	*10.*	16, (3%)	*14.*	11, (2%)
Codeïne, *Rank*, n (%)	*12.*	25, (2%)	*15.*	11, (2%)	*9.*	14, (2%)
Paroxetine, *Rank,* n(%)	*13.*	23, (2%)	*17.*	9, (2%)	*10.*	14, (2%)

[a]percentages do not count up to 100% due to rounding, [b]According to Anticholinergic Drug Scale, [c]statistical significant with p<0.05.

to anticholinergic drug at ICU admission by delirium status during ICU admission. Furosemide was the only drug with a significantly different prescription proportion, with 21% in the patients who developed delirium and 14% in the patients without delirium during ICU stay (p=0.008).

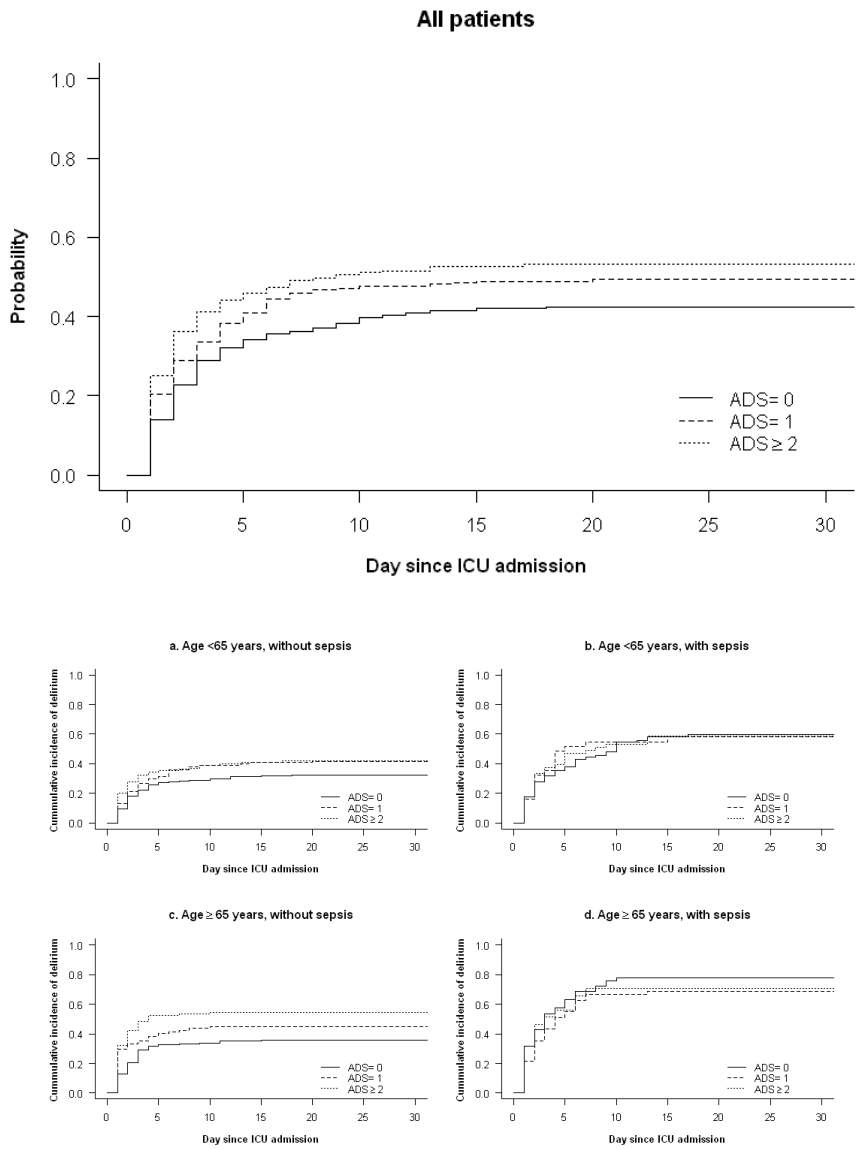
Relative to an ADS score of 0, and after adjusting for competing events and covariables, an ADS score of 1 point was not associated with a higher risk of delirium (SHR=1.13, 95% CI: 0.91-1.40), in contrast to an ADS score ≥2 points (SHR=1.35, 95% CI: 1.09-1.68) (Table 3, Figure 2). The results of the stratified analyses are also shown in Table 3 and in Figure 2. The association of an ADS score ≥2 with delirium onset was strongest in patients aged ≥65 years without severe sepsis at ICU admission (SHR: 2.14, 95% CI: 1.42-3.21).

Table 3. Anticholinergic drug exposure[a] and delirium onset[b,c]

	ADS = 0 (n=512)		ADS = 1 (n=284)		ADS ≥ 2 (n=294)	
Cause Specific Hazard Ratios						
Adjusted CSHR Delirium	1.00	(ref)	1.12	(0.90-1.39)	1.35	(1.09-1.67)[d]
Adjusted CSHR Death	1.00	(ref)	0.96	(0.49-1.85)	1.15	(0.60-2.19)
Adjusted CSHR Discharge	1.00	(ref)	1.08	(0.87-1.35)	0.87	(0.69-1.10)
Subdistributional Hazard Ratios for developing delirium						
Adjusted SHR	1.00	(ref)	1.13	(0.91-1.40)	1.35	(1.09-1.68)[d]
Age <65 years, no sepsis[e] (n=444, delirium = 164)	1.00	(ref)	1.17	(0.80-1.71)	1.28	(0.86-1.90)
Age <65 years, sepsis[e] (n=161, delirium = 95)	1.00	(ref)	1.06	(0.59-1.89)	1.18	(0.69-2.01)
Age ≥65 years, no sepsis[e] (n=339, delirium = 148)	1.00	(ref)	1.42	(0.93-2.17)	2.14	(1.42-3.21)[c]
Age ≥65 years, sepsis[e] (n=146, delirium = 106)	1.00	(ref)	0.78	(0.49-1.26)	0.86	(0.53-1.42)

CSHR= Cause Specific Hazard Ratio, ICU= Intensive Care Unit, SHR= subdistributional hazard ratio. [a]measured with the anticholinergic drug scale (ADS), [b]Using competing risk cox proportional hazard analysis, [c]Adjusted for age, gender, Acute Physiology and Chronic Health Evaluation IV Score, elective ICU admission (vs emergency), surgery before ICU admission, severe sepsis at ICU admission (not in stratified analysis), modified maximum Sequential Organ Failure Assessment Score, depression, hypertension, diabetes mellitus, cerebrovascular disease, current drinking status, [d]statistical significant with p-value <0.05, [e]severe sepsis at ICU admission according to international sepsis definitions.[20-24]

Figure 2. Cumulative incidence of delirium and anticholinergic drug exposure (stratified for age and severe sepsis at ICU admission in a t/m d)



Only in the subgroup of patients ≥ 65 years, without severe sepsis at ICU admission, a statistical significant association was found between ADS ≥ 2 and delirium relative to ADS = 0. ADS = Anticholinergic Drug Scale, ICU = Intensive Care Unit.

DISCUSSION

This is the first study in ICU patients on anticholinergic drug exposure and delirium. We found that higher anticholinergic drug exposure at ICU admission increases the risk of delirium.

In the 1980s, a relationship between serum anticholinergic activity, anticholinergic drug exposure and postoperative delirium was observed.[14,29,30] Due to the small sample sizes (n=25[14,29] and n=29[31]) no adjustments were made for confounding. More recently, exposure to anticholinergic drugs and the risk of developing delirium the next day was studied, showing no association.[13] However, this study only discriminated between the use or non-use of presumed anticholinergic drugs without using an anticholinergic drug scale to define anticholinergic burden. Outside the ICU setting more investigations have been performed on anticholinergic burden and delirium. Serum ACH activity has been associated with delirium in postoperative[29,30] and medical patients,[11,32] providing a biological mechanism for the hypothesis that anticholinergic drug increase the risk of delirium. However, results of studies on anticholinergic drug exposure in itself being a risk factor for delirium in non-ICU patients yielded inconsistent results. Non-ICU patients with delirium were found to use more medication with anticholinergic properties than patients without delirium, or patients whose delirium has resolved.[11,30,32-35] However, in other studies no association was observed.[36-38] possibly as a result of low exposure to anticholinergic drugs.[11,36,38] In respectively postoperative, palliative care and acute stroke patients, studies confirmed that a higher anticholinergic drug load was associated with delirium.[14,39,40]

To date, there is no consensus which scale best represents anticholinergic load. Several scales have been developed, but these define anticholinergic activity differently; some use anticholinergic serum activity in combination with expert opinion,[18] others also include clinical information.[41-43] Consequently, the scales differ in the number of included drugs. Currently, the Anticholinergic Drug Scale (ADS) is widely used which assesses anticholinergic burden of a drug based on both anticholinergic serum activity and clinical evidence.[44] The ADS may be superior to other scales because it uses a serum radioreceptor assay to quantify drug induced muscarinic blockade as a measure of an individual's level of anticholinergic activity.[31,45,46] It is thought that the ADS reflect the cumulative antimuscarinic burden of all substances present in a person's serum, including medication, drug metabolites and possibly endogeneous substances.

Assessment of anticholinergic drug exposure with the use of anticholinergic drug scales has also limitations. Firstly, it is only a quantitative measure and it may not accurately represent true anticholinergic effects. Secondly, using these scales the exposure is based on the use or not of drugs with allotted anticholinergic properties. However, the variation in the risk of a drug having anticholinergic effects may also depend on individual pharmacological characteristics of the drug or its metabolites, such as a higher plasma concentration at a given dose (because of increased bioavailability or decreased clearance), an increased brain access (because of age and disease related changes in blood-brain barrier), or increased sensitivity at the receptor level (because of change in the binding affinity to the muscarinic receptor or displacement from the receptor by other drugs).[44] This could be an explanation for the larger effect of anticholinergic burden in older people in our study group.

With our stratified analysis we explored the hypothesis that anticholinergic drug exposure influences delirium onset differently in the presence of sepsis or with higher age. As expected, the incidence of delirium in our cohort was highest in older patients with severe sepsis.[10] The underlying mechanism for this association may be that peripherally produced pro-inflammatory cytokines enter the brain, leading to a neuro-inflammatory state with neurotoxic effects.[10,47,48] It is presumed that the cholinergic neurotransmitter system inhibits this neuro-inflammatory state.[10] The finding that higher anticholinergic drug load was an independent risk factors in older patients without severe sepsis was therefore unexpected. However, to our knowledge, this is the first study to prospectively evaluate this sepsis-anticholinergic-interaction hypothesis in a cohort of critically ill patients and more research is necessary to further explore the interaction between age, sepsis and anticholinergic drug load.

Strengths of our investigation include the large sample size, the prospective data collection, the extensive adjustment for important confounders and incorporation of competing events in our statistical analysis. Further, we used a reliable and thorough ascertainment of delirium based on a validated algorithm for daily classification of mental status including at least two delirium assessments per day. Limitations include the lack of confirmation of drugs used at ICU admission. Since adherence is a common problem we cannot be sure whether drugs retrieved from the medical records and referring letters were actually taken. Further, we did not include information on time of use, frequency or dose. Although we adjusted extensively we cannot exclude residual confounding due to unmeasured confounders. The prevalence of dementia in our cohort

was 0.4% which precluded inclusion of this variable in multivariable analysis. We did not perform a structural assessment of cognition at ICU admission.

CONCLUSION

Exposure to drugs with anticholinergic effects seems to increase the risk of delirium in ICU patients. As delirium is difficult to treat and associated with negative outcomes, prevention is of paramount importance. Our results indicate that evaluating anticholinergic drug exposure at ICU admission may have efficacy in the prevention of delirium during critical illness.

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Benzodiazepine-associated delirium in critically ill adults

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ABSTRACT

Objective

The association between benzodiazepine administration and the risk of delirium in the ICU remains unclear. Prior investigations have failed to account for the evolution of disease severity prior to delirium onset, for competing events that may preclude delirium detection (such as coma, discharge or death), or for an adequate number of patients receiving midazolam. In this study the association between benzodiazepine use and delirium was evaluated.

Methods

In a cohort of consecutive critically ill adults admitted over a 2.5 years period, daily mental status was classified as either awake without delirium, delirium, or coma. In a first-order Markov model, multivariable, multinomial logistic regression analysis was used that included 5 possible outcomes the next day (i.e., awake without delirium, delirium, coma, ICU discharge and death) to quantify the association between benzodiazepine use and delirium occurrence the following day.

Results

Among 1112 patients, 9867 daily transitions occurred. Administration of benzodiazepines in a patient awake without delirium was associated with an increased probability of delirium the next day (OR: 1.04, 95% CI: 1.03-1.05). When the method of benzodiazepine administration was considered, the transition to delirium was found to be driven by continuous IV infusion (OR: 1.04, 95% CI: 1.03-1.06) rather than intermittent bolus only (OR: 0.97, 95% CI: 0.88-1.06) use.

Conclusions

Benzodiazepine administration increases the risk for delirium occurrence in critically ill adults, although this association is less pronounced than previously reported and seems to be limited to continuous IV infusion.

INTRODUCTION

Delirium is common during critical illness and is associated with substantial morbidity both during and after the Intensive Care Unit (ICU) stay.[1-4] Avoidance of medications that may cause or prolong delirium is strongly recommended in practice guidelines.[5-8] These recommendations are primarily based on the results from observational cohort studies.[5-8] However, outside of the setting of a randomized controlled trial, the ability to characterize the association between medication exposure and delirium occurrence in the ICU is challenging.[9]

Benzodiazepines are frequently administered to maintain patient comfort and safety in the ICU.[10] Compared to other medications that may cause delirium, the relationship between benzodiazepine exposure and delirium occurrence is more complex given that benzodiazepine-induced coma precludes delirium recognition, that level of wakefulness influences the ability to recognize delirium, and that delirium that is detected in a sedated patient, but rapidly resolves with daily awakening, may not be clinically significant.[11-13]

While a number of investigations have found a positive relationship between benzodiazepine use and delirium occurrence in critically ill adults,[14-20] other reports have failed to demonstrate this same association.[2,21-26] Given the time-varying nature by which disease severity, benzodiazepine administration, and delirium occurrence may oscillate over the course of the ICU stay, it is crucial to use time-dependent multivariable analysis methods when investigating this relationship.[9] Although five previous studies in this field have employed such statistical techniques,[2,14,16,19,20] important methodological limitations still remain. A single Confusion Assessment Method for the ICU (CAM-ICU) assessment was used to characterize delirium occurrence over an entire 24 hour period despite the frequent transitory nature of delirium.[2,14,16,19,20] In addition, these studies have made the false assumption that the incidence of delirium is not precluded by the occurrence of coma, ICU discharge or death and thus have potentially overestimated the benzodiazepine-associated delirium risk.[2,14,16,19,20,27,28] A focus on patients receiving lorazepam limits the extrapolation of these results to patients administered midazolam, a far more frequently used benzodiazepine in the ICU, given the substantial pharmacodynamic and pharmacogenomics differences between these two benzodiazepines in the critically ill.[29,30] None of the studies considered the method of benzodiazepine administration in their analysis

[i.e., continuous IV infusion versus intermittent (oral or IV)], despite evidence suggesting that continuous IV benzodiazepine use therapy may be associated with a greater incidence of delirium.[31,32]

The aim of this study was to determine whether the administration of a benzodiazepine is an independent risk factor for the transition from an awake, non-delirious state to delirium in critically ill adults. Secondly, the association between delirium and continuous versus intermittent benzodiazepine use was explored.

METHODS

Study design and patients

From January 2011 through June 2013, all consecutive adults admitted for at least 24 hours to the 32-bed mixed-ICU of the University Medical Center Utrecht were considered inclusion. A well-established institutional protocol was in place throughout the study period that advocated sedation be targeted to a light level, daily sedation interruption, and the assessment of all patients for delirium using the CAM-ICU at least twice daily. Patients with acute neurological disease or other disorders precluding delirium assessment were excluded. The local Institutional Review Board waived the need for informed consent (IRB #010/056/c and #12/421/c) given the non-interventional nature of the investigation.

Mental status classification and outcome

For each day in the ICU, the mental status of each patient was assessed by study investigators using a previously published, validated protocol.[33] The transition from being awake (i.e., not comatose) without delirium on any day of the ICU admission (day t) to delirium the next day (day t+1) was studied as the primary outcome. Patient wakefulness was evaluated every three hours using the Richmond Agitation and Sedation Scale (RASS) where a RASS ≤ -4 denoted coma.[34] The presence of delirium during each 24 hour period was determined using a previously validated, 5-step algorithm (inter-observer agreement: 0.94-0.97, sensitivity: 0.75, specificity: 0.85).[33] This algorithm incorporated a review by a study investigator of all CAM-ICU scores documented by the bedside nurse, whether delirium treatment had been initiated by the ICU physician, a chart review, and an additional CAM-ICU assessment by the investigator for any patient

not yet classified using prior steps.[33] The daily mental status for each patient was then classified as: 1) awake without delirium, 2) delirium, or 3) coma [33]. For the outcome the next day (day t+1) ICU discharge and death were added, resulting in five possible outcome categories (Supplementary data Figure E1).

Data collection

Medication data, including dose, route and time of administration were retrieved from the electronic patient data management system. All administered benzodiazepines were converted into equivalent doses of midazolam (MDZE) (Supplementary data Table E1). The dose of any benzodiazepine administered via the enteral route was reduced by 50% given the reduced bioavailability associated with this route in critically ill patients.[35]

Demographics, the presence of co-morbidities, ICU admission characteristics and daily physiological measurements and vital signs were prospectively collected by trained physicians. Daily severity of disease was assessed using the modified Sequential Organ Failure Assessment (mSOFA) excluding the neurological component to avoid overcorrection.[36] A trend imputation for missing covariables was performed because of the availability of longitudinal data prior and following each observation day.[37]

Statistical analysis

Within a first-order Markov model, multinomial logistic regression was used. Discharged alive from the ICU [971/9867 (10%)] and death [144/9867 (1%) were combined into one category given that each represented few of the total daily transitions and neither were the outcome of interest.

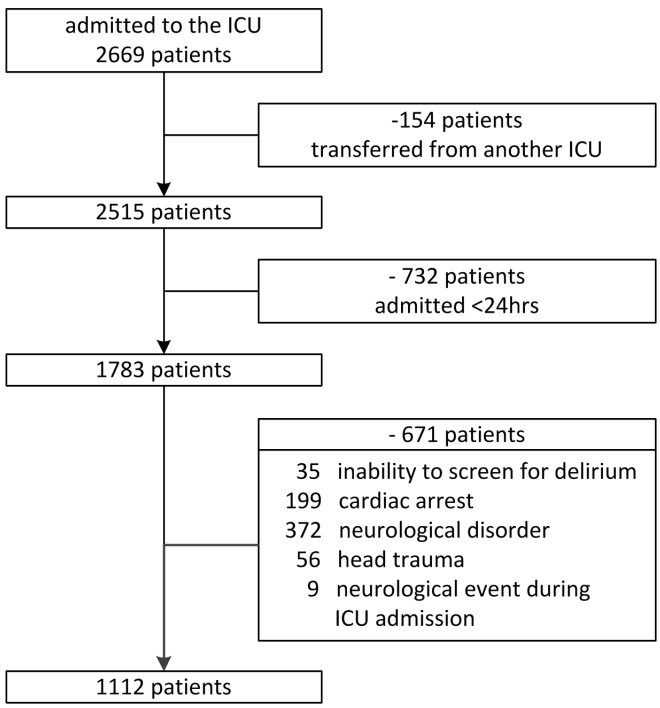
The primary exposure to benzodiazepines was modelled using an interaction term of benzodiazepines per 5 milligrams MDZE on day t and the mental status on day t. Differentiating between intermittent (i.e., either oral or IV) and continuous IV infusion benzodiazepine administration led to the inclusion of two, not mutually exclusive, interaction terms in the statistical model.

A thorough review of the literature was conducted to identify covariables that might influence the presence of delirium, the use of a benzodiazepine or their resulting pharmacodynamic response.[5,17,29,38] Only covariables with an absolute prevalence ≥ 10% were eligible for inclusion into the multivariable analysis. In total, 8 variables measured at ICU admission and 8 time-varying variables measured daily were included in the model (Supplementary data Table E2).

Two planned sensitivity analyses were performed. Firstly, to account for the fact that benzodiazepine therapy is sometimes initiated to treat the prodromal symptoms of delirium and that disease severity often increases after the onset of (i.e., reverse causation) we used benzodiazepine exposure and mSOFA on day t-1 instead of day t to explore the association of benzodiazepine use with delirium on day t+1. To explore a possible carry-over effect of benzodiazepine beyond the first-order Markov assumption, we only included days up until delirium, ICU discharge or death on day t+1 (whichever occurred first) in a second sensitivity analysis.

SPSS 20 (IBM, New York, USA) and R 3.0.1 (www.r-project.org) were used to perform the statistical analysis. All statistical tests were performed against 2-sided alternatives and p-values < 0.05 were defined as statistically significant.

Figure 1. Flowchart patient inclusion



hrs= hours, ICU= Intensive Care Unit.

RESULTS

Patients and observation days

Among 2669 patients admitted to the ICU during the study period, 1112 were included in the analysis (Figure 1). These patients had an average age of 60 years, were mostly male (60%) and had an average Acute Physiology and Chronic Health Evaluation (APACHE) IV Score of 74 (Table 1).

Delirium occurred in 538 (48%) of the 1112 patients and was present on 2672 (27%) of the 9867 observation days (Table 2). Patients were exposed to a benzodiazepine on 48% of the observation days with median daily MDZE dose of 7 (IQR 3-66) mg. Among days where a benzodiazepine was administered, midazolam (53%) and oxazepam (28%) use were common; lorazepam use was rare (1%).

Table 1. Characteristics of study population (n=1112)

Age, mean (SD)	60	(16)
Male, n (%)	672	(60)
Charlson comorbidity index [39], median (IQR)	6	(0-10)
Body mass index, mean (SD)	26	(6)
Psychoactive medication, n (%)[a]	212	(19)
Smoking, n (%)[a]	90	(8)
Alcohol consumption, n (%)[a]	45	(4)
Dementia, n (%)[a]	4	(0.4)
Hypertension, n (%)[a]	384	(35)
Planned admission, n (%)	322	(29)
Admission category		
Medical, n (%)	493	(44)
Surgical, n (%)	544	(49)
Trauma , n (%)	75	(7)
APACHE IV Score [40], mean (SD)	74	(28)
Length of ICU stay (days), median (IQR)	5	(2-10)
Maximum mSOFA [36], median (IQR)[b]	7	(4-10)
Mechanical ventilation required, n (%)[b]	1034	(93)
Delirium, n (%)[b]	535	(48)
Benzodiazepine use, n (%)[b]	814	(73)
Days of benzodiazepine use, median (IQR)[b]	1	(0-4)

APACHE = Acute Physiology and Chronic Health Evaluation, ICU = Intensive Care Unit, IQR = interquartile range, mSOFA = modified Sequential Organ Failure Assessment, SD=standard deviation.
[a]present at the time of hospital admission, [b]during ICU stay.

Table 2. Characteristics of individual ICU days (n=9867) by mental status on day t

Characteristic on day t	All patients (n=9867)	
Characteristics of benzodiazepine use		
Use of any benzodiazepine, n (%)	4716	(48)
Dose (if any) in mg, median (IQR)[a]	6.9	(2.5-65.9)
Use of midazolam, n (%)[b]	2513	(53)
Other benzozodiazepine, n(%)[b]	2574	(55)
Use of oxazepam, n (%)[b]	1323	(28)
Use of lorazepam, n (%)[b]	55	(1)
Use of intermittent benzodiazepine, n (%)	4009	(41)
Dose (if any) in mg, median (IQR)[a]	4.1	(1.9-8.3)
Use of continuous IV benzodiazepine, n (%)	1904	(19)
Dose (if any) in mg, median (IQR)[a]	99.0	(29.4-212.0)
Characteristics of covariables		
mSOFA, median (IQR)	5	(3-7)
Metabolic acidosis, n (%)	1354	(14)
Severe sepsis or septic shock, n (%)	2458	(25)
Use of mechanical ventilation, n (%)	7706	(78)
Use of propofol, n (%)	1312	(13)
Use of an opioid(s), n (%)	4686	(47)
Use of an alpha-2-agonist, n (%)	1072	(11)

BZ = benzodiazepines, hrs = hours, ICU = Intensive Care Unit, IQR=Interquartile Range, mg=milligrams, [a]in midazolam equivalents, [b]use of benzodiazepine on day t is not mutually exclusive so percentages do

		Mental status day t			
Awake without delirium (n=5299)		**Delirium (n=2672)**		**Coma (n=1896)**	
2253	(43)	1241	(46)	1222	(64)
3.8	(1.9-8.3)	6.4	(3.0-29.9)	125.0	(33.3-254.8)
646	(29)	687	(55)	1180	(97)
1772	(79)	710	(57)	92	(8)
857	(38)	395	(32)	71	(6)
37	(2)	14	(1)	4	(0.3)
2122	(40)	1129	(42)	758	(40)
3.5	(1.9-6.6)	5.0	(2.0-9.9)	7.5	(4.6-14.0)
366	(7)	443	(17)	1095	(58)
50.0	(16.2-111.7)	50.2	(17.8-120.0)	142.7	(60.0-268.5)
3	(2-6)	5	(3-8)	8	(6-11)
522	(10)	290	(11)	542	(29)
674	(13)	822	(31)	962	(51)
3738	(71)	2162	(81)	1806	(95)
518	(10)	367	(14)	427	(23)
2048	(39)	1296	(49)	1342	(71)
359	(7)	521	(19)	192	(10)

mSOFA=modified Sequential Organ Failure Assessment (without central nervous component).
not count up to 100%.

Risk of transitioning to delirium and benzodiazepine use

Among the 5299 observation days that patients were awake without delirium, 562 (11%) transitions to delirium the next day occurred (Figure 2). In the primary analysis, the odds ratio (OR) of the transition from awake without delirium towards delirium was 1.04 (95% Confidence Interval (CI): 1.03-1.05) per 5 mg MDZE administered (Table 3).

The method by which benzodiazepines were administered affected the odds of transitioning to delirium. When administered as a continuous IV infusion to an ICU patient who was awake without delirium, the odds for delirium the next day (for every 5 mg MDZE administered) was nearly identical to that for all benzodiazepine exposure days (OR: 1.04, 95% CI: 1.03-1.06) (Table 3). The absolute, dose-related risk of delirium occurrence (from a state of being awake without delirium) with the daily administration of a continuous infusion of IV midazolam is plotted in Figure 3. In contrast, intermittent administration of benzodiazepines was not associated with delirium the following day (OR: 0.97, 95% CI: 0.88-1.06).

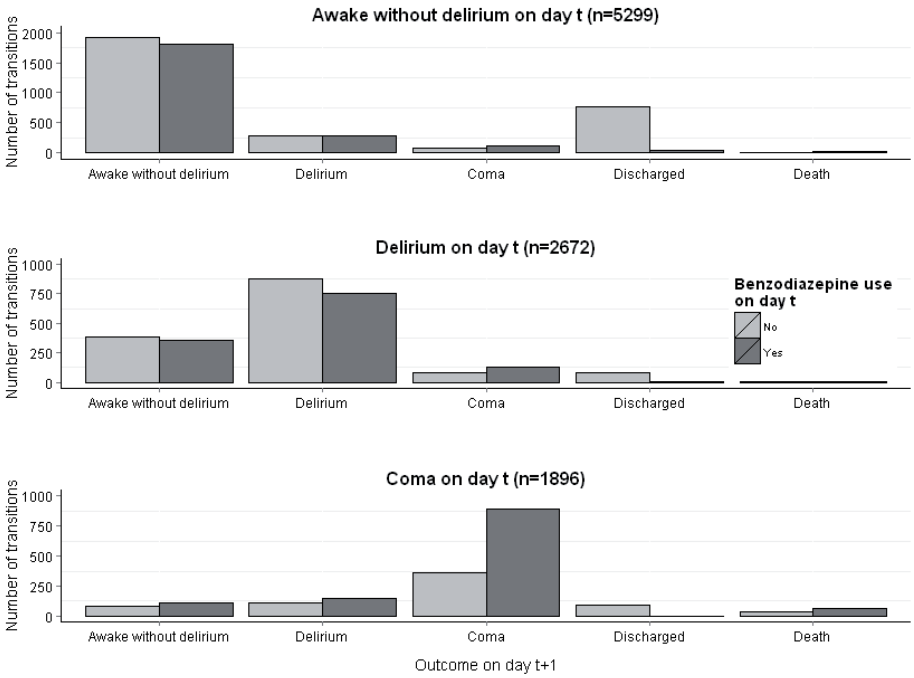
The results of the sensitivity analyses are shown in the Supplementary Data Table E3. Overall, benzodiazepine administration was not associated with an increased risk for a transition to delirium two days after the benzodiazepine exposure (OR: 1.00, (95% CI: 0.99-1.02) unless the benzodiazepine had been continuously infused (OR: 1.02, 95% 1.00-1.03). With the inclusion of only the daily transitions until the first day of delirium, ICU discharge or death (885 patients, 3616 observation days), the findings were similar when compared to the primary analysis with OR benzodiazepine administration of 1.03 (95% CI:1.02-1.05), OR for bolus administration of 1.04 (95% CI: 0.92-1.17) and OR for continuous administered benzodiazepines of 1.03, (95% CI: 1.01-1.05).

Table 3. Primary analysis on benzodiazepines and delirium transition

Primary analysis for all benzodiazepines				
Mental status *day t*	**Mental status** *day t+1*	**Exposure**	**Adjusted Odds Ratio[a,b,c]**	
Awake, no delirium	Awake, no delirium	No		*reference*
Awake, no delirium	Delirium	Yes	1.037	(1.025-1.050)
Awake, no delirium	Delirium	Bolus	0.965	(0.883-1.055)
Awake, no delirium	Delirium	Continuous	1.044	(1.029-1.058)

[a]per 5 mg midazolam equivalents, [b]adjusted for time-fixed covariables: admission category (medical, surgical, trauma), age, Acute Physiology and Chronic Health Evaluation (APACHE) IV Score, Body Mass Index, Charlson Comorbidity Index, hypertension, elective admission (vs. emergency admission), use of a psychoactive medication(s) prior to hospital admission, [c]adjusted for time-varying covariables on day t: day of ICU admission, metabolic acidosis, modified Sequential Organ Failure Assessment score (without neurological component), presence of severe sepsis or septic shock, use of mechanical ventilation, use of an alpha-2-agonist, use of an opioid, use of propofol.

Figure 2. Daily transitions according to the administration of any benzodiazepines (n=9867)



For each mental status on day t a barplot is shown with the number of transitions towards the 5 different outcome categories on day t + 1 according to benzodiazepine use, none (light grey) and yes (dark grey).

DISCUSSION

This investigation provides clinicians with a more accurate estimate of the risk between benzodiazepine use and delirium occurrence in critically ill adults than those previously published on this subject. As little as 5 mg of midazolam administered in a 24 hour period to a critically ill patient who is both coma-an d delirium-free, will increase the odds that this patient will develop delirium the next day by 4%. Although, the risk between benzodiazepine use and delirium occurrence we report is less strong than previously published, and may not exist with intermittent benzodiazepine use,

the fact that this risk is additive (i.e., 10 mg of midazolam per day will increase the odds of delirium the next day by 8%), makes the results of our analysis important to ICU clinicians when they are making sedative prescribing decisions.

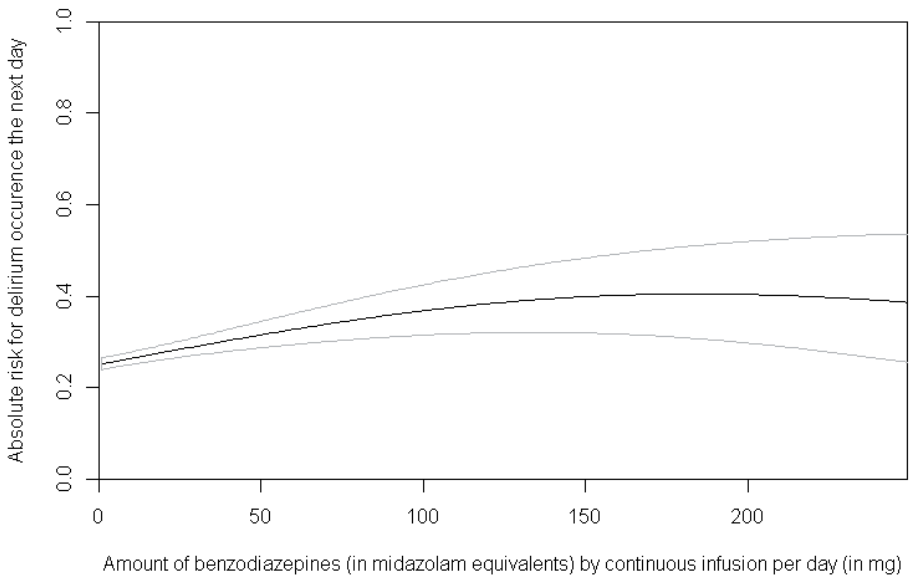
Given that benzodiazepines were administered to almost three quarters of our study population, reduced prescription of benzodiazepines could have large implications for the burden of delirium in critically ill patients. The avoidance of continuous infusions of benzodiazepines is possible for most ICU days: first, alternatives exist for benzodiazepines such as sedation with dexmedetomidine which seems to be protective of developing delirium.[5,38] Second, a goal for an individual level of sedation should be sought, aiming for light sedation. Finally, our results support attempting using intermittent boluses of benzodiazepines before the use of continuous sedative infusions.

There are unique and novel aspects of our analysis. The size of our cohort is the largest evaluated to date (1112 critically ill adults were evaluated over 9786 ICU days), a large proportion of patients were exposed to midazolam (the most commonly used benzodiazepine in the ICU), the daily mental status of each patient was classified using a validated delirium assessment protocol that evaluated all patients at least twice daily, benzodiazepine exposure was dichotomized between intermittent only and continuous IV administration strategies, the time-varying nature of both disease severity and delirium were considered, and all possible competing events for delirium (i.e., coma, ICU discharge, and death) were incorporated. Using sensitivity analyses, we carefully investigated the role of potential factors that could have affected the delirium risk with benzodiazepine exposure we report. Neither reverse causation nor a benzodiazepine carry-over effect were found to influence delirium risk although it should be noted ruling out these effects completely would require more frequent mental status evaluations which is very resource and time consuming (e.g. necessity of nightly mental status classification).

Our analysis has several potential limitations. Results from a single-center analysis may not be generalizable to centers having patients with differing underlying risk factors for delirium (e.g. severity of illness) or where the use of delirium reduction strategies (e.g., early mobilization) differ.[38,41] That said, the case-mix of patients and sedative use patterns in our cohort are similar to that of other studies in this area.[42,43] Unlike other published analyses, the proportion of benzodiazepine use accounted for by midazolam was high. When replicating our primary analysis on only midazolam exposure (instead

of all benzodiazepine exposure) our results where almost similar to the primary analysis with OR: 1.04 (95%CI: 10.3-1.05) on all benzodiazepine use, OR: 1.06 (95% CI: 0.95-1.18) for bolus administration and OR 1.04 (95% CI: 1.02-1.05) for administration by continuous IV infusion. These results indicates that the use of midazolam in our cohort explains to a large extent the association found between benzodiazepine use and delirium.

Figure 3. Relation between continuous infusion of benzodiazepines and delirium



Among patients awake and without delirium who were administered a continuous IV benzodiazepine infusion for all or part of a 24 hour period, the absolute risk is plotted for delirium occurring the next day. 95% Confidence Interval is plotted in grey.

The association between lorazepam use and delirium occurrence remains unclear. The infrequent use of lorazepam in our ICU may be a result of ICU sedation practices differences between Europe and North America. Within the first-order Markov model correlation within patient observations were ignored and thus the probability of daily transition was assumed to be independent of patient history beyond the prior day (Markov assumption). While a recently published systematic review of the published literature was used to generate the covariables included in the multivariable analyses,

it is possible, as in any observational study, that other unmeasured covariables could have influenced the reported results.[38] Although with the algorithm used for mental status classification over a 24 hour period patients the risk of misclassification was minimized, it remains possible that some of the delirium detected in the cohort may have been rapidly reversible and not clinically significant.[13]

CONCLUSION

Benzodiazepine administration appears to be associated with the risk of delirium. Whereas intermittent administration of benzodiazepines to patients who are awake without delirium appears not be a risk factor for delirium, continuous IV infusion does increase the risk for delirium. The use of continuous IV administration of benzodiazepines should therefore be considered a modifiable risk factor for the development of delirium and its minimized. Although we used robust statistical techniques to explore the relationship, large randomized controlled trials are needed to further determine the absolute risk of sedation with benzodiazepines on delirium.

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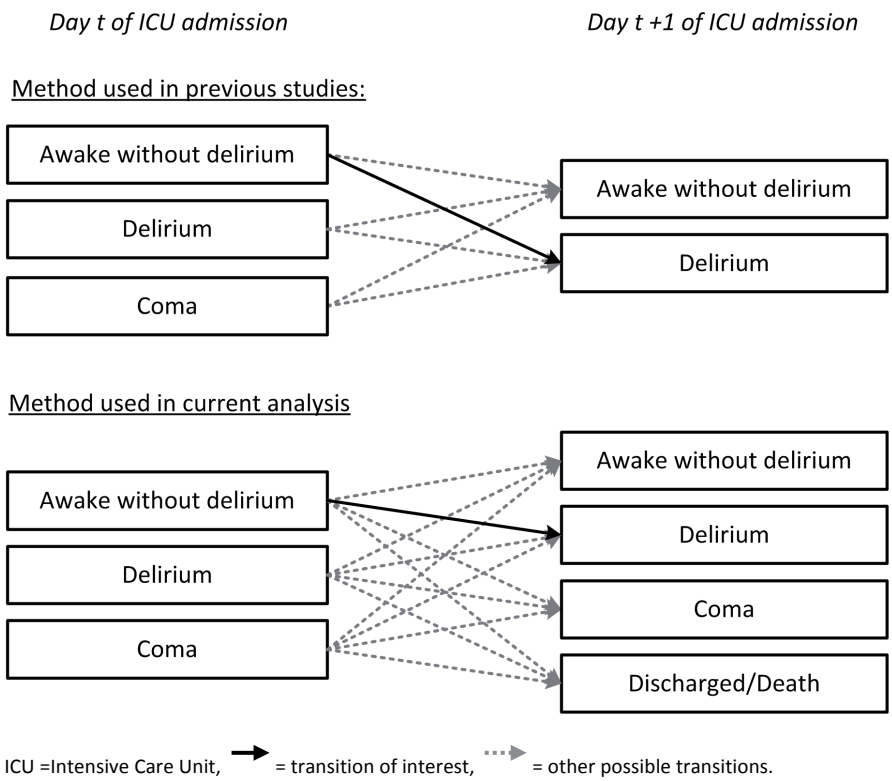
SUPPLEMENTARY DATA

Figure E1. Transition matrix



ICU =Intensive Care Unit, → = transition of interest, ⇢ = other possible transitions.

Table E1. Conversion of benzodiazepines to midazolam equivalents

Medication	Conversion factor
Midazolam	* 1.00
Lorazepam	* 7.14
Oxazepam	* 0.57
Temazepam	* 0.71
Zopiclone	* 1.10

Table E2. Covariables considered for multivariable analysis

Covariable	Day	Measure	Range	Included
Time-fixed variables				
Admission category	0	Categorical	Medical	●
	0		Surgical	●
	0		Trauma	●
Age	0	Continuous	18- ∞	●
APACHE IV Score[40]	0	Continuous	0 - 220	●
Body mass index	0	Continuous	0 - ∞	●
Charlson Comorbidity Index[39]	0	Continuous	0-37	●
Current alcohol use [a]	0	Binomial	(Y/N)	
Dementia[b]	0	Binomial	(Y/N)	
Hypertension[c]	0	Binomial	(Y/N)	●
Planned admission	0	Binomial	(Y/N)	●
Psychoactive medication use[d]	0	Binomial	(Y/N)	●
Time-varying variables				
Metabolic acidosis[e]	X	Binomial	(Y/N)	●
Day of ICU admission	X	Continuous	0 - ∞	●
mSOFA[36f]	X	Continuous	0-20	●
Severe sepsis/septic shock[g]	X	Binomial	(Y/N)	●
Use of mechanical ventilation	X	Binomial	(Y/N)	●
Use of an alpha-2-agonist	X	Binomial	(Y/N)	●
Use of an opioid	X	Binomial	(Y/N)	●
Use of propofol	X	Binomial	(Y/N)	●

APACHE = Acute Physiology and Chronic Health Evaluation, SOFA = Sequential Organ Failure Assessment, Y/N = Yes/No. [a]>3 units of alcohol per day, as documented in the medical records or mentioned in the (proxy) history at the time of ICU admission, [b]by (proxy) interview at the time of ICU admission or described in the medical records as diagnosed by a geriatrician or neurologist, [c]presence of hypertension or use of an antihypertensive medication(s) documented in the medical record prior hospital admission, [d]documented use of an antipsychotic (i.e., aripiprazole, bromperidol, chlorpromazine, chlorprothixene, clozapine, flufenazine, flupentixol, fluspirilene, haloperidol, olanzapine, paliperidone, penfluridol, perfenazine, periciazine, pimozide, pipamperon, quetiapine, risperidone, sertindole, sulpiride, tiapride, zuclopentixole); an antiparkinson (ie., apomorphine, biperidene, bromocriptine, dexetimide, entacapon, levodopa/benserazide, levodopa/carbidopa, levodopa/carbidopa/entacapon, orfenadrine, pergolide, pramipexole, rasagiline, ropinirole, rotigotine, selegiline, tolcapon, trihexyfenidyl) and/or a benzodiazepine (i.e., alprazolam, bromazepam, brotizolam, chlordiazepoxide, chloralhydrate, clobazam, clorazepam, diazepam, flunitrazepam, flurazepam, loprazolam, lorazepam, lormetazepam, midazolam, nitrazepam, oxazepam, prazepam, temazepam, zolpidem, zopiclone) medication before hospital admission, [e]with pH in daily arterial blood gas of ≤ 7.35, [f]modified Sequential Organ Failure Assessment (without central nervous component), [g]according to international sepsis definitions.[44-47]

Table E3. Results of sensitivity analyses

Mental status	Outcome	Benzodiazepine	Odds ratio[a]
Day t	Day t+1		Adjusted
1. Reverse causation (n=1112 patients, n=9867 days)[b]			
Awake, no delirium	Awake, no delirium	No	*reference*
Awake, no delirium	Delirium	Yes	1.002 (0.990-1.015)
Awake, no delirium	Delirium	Bolus	0.823 (0.744-0.910)
Awake, no delirium	Delirium	Continuous	1.017 (1.003-1.032)[d]
2. Possible carry-over effect of sedation (n=885 patients, n=3616 days)[c]			
Awake, no delirium	Awake, no delirium	No	*reference*
Awake, no delirium	Delirium	Yes	1.031 (1.016-1.046)[d]
Awake, no delirium	Delirium	Bolus	1.039 (0.920-1.173)
Awake, no delirium	Delirium	Continuous	1.031 (1.013-1.050)[d]

ND=No delirium. [a]per 5 mg midazolam equivalent administered, [b]With mSOFA day t-1 and benzodiazepine exposure day t-1, [c]Only days until either delirium, ICU discharge or death on day t+1 (whichever occurred first), [d]statistical significant with p-value <0.05.

Intensive care unit environment may affect the course of delirium

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ABSTRACT

Objective

Delirium is a common disorder in Intensive Care Unit (ICU) patients. It is unclear whether ICU environment affects delirium. We investigated the influence of ICU environment on the number of delirium days during ICU admission.

Methods

In this prospective before-after study, ICU delirium was compared between a conventional ICU with wards, and a single-room ICU with, among others, improved daylight exposure. We included patients admitted for more than 24 hours between March and June 2009 (ICU with wards) or between June and September 2010 (single-room ICU). Patients who remained unresponsive throughout ICU admission were excluded. The presence of delirium in the preceding 24 hours was assessed daily with the Confusion Assessment Method for the ICU (CAM-ICU) by research physicians combined with evaluation of medical and nursing charts. The number of delirium days was investigated with Poisson regression analysis.

Results

We included 55 patients (449 observation days) in the ICU with wards and 75 patients (468 observation days) in the single-room ICU. After adjusting for confounding, the number of delirium days decreased with 0.4 days (95% Confidence Interval: 0.1-0.7) in the single-room ICU (p=0.005). The incidence of delirium during ICU stay was similar in the ICU with wards (51%) and in the single-room ICU (45%, p=0.53).

Conclusions

This study is the first to show that ICU environment may influence the course of delirium in ICU patients.

INTRODUCTION

Delirium is a common condition in Intensive Care Unit (ICU) patients,[1,2] characterized by a disturbance of consciousness and attention with a change in cognition and fluctuating course.[3] Delirium in the ICU is associated with complications and adverse outcomes including prolonged hospital stay[4,5] and increased morbidity and mortality.[6-8]

In non-ICU patients, non-pharmacological strategies could prevent delirium.[9-11] These include proactive geriatric consultation[9] and education of medical and nursing staff with special attention for known risk factors.[10,11] In ICU patients, non-pharmacological measures have hardly been studied in relation to delirium.[12] Still, the ICU environment with continuous light and noise, around the clock personnel and lack of orientation points is assumed to play a role in the development of delirium.[12-15] A previous study in ICU patients suggested that isolation and the absence of daylight were associated with an increased risk of delirium.[13] However, this study may have been biased as isolation and bed assignment may have been dependent on disease characteristics.

The ICU design can ameliorate healthcare outcomes, and lead to improved patients' sleep and a reduced frequency of hospital-acquired infections and medical errors by influencing circadian rhythm, the immune response and patients' and staffs behavior.[16] The ICU of our institution recently moved to a new location, providing a unique opportunity to study the effects of a changed ICU environment on the course of delirium.

The aim of this study was to investigate the influence of ICU environment on the number of delirium days.

METHODS

Design and study population

This prospective, before-after study was performed in the 32-bed mixed ICU of the University Medical Center Utrecht (UMCU), the Netherlands. Both in the ICU with wards and in the single-room ICU, the ICU has been divided into three units with 11 beds. All three units are equal in staffing, admission criteria, and facilities. A waiver of informed consent was obtained from the local Medical Ethics Committee.

We included all patients admitted for more than 24 hours of one out of the three ICU units between March and June 2009 (ICU with wards) or between June and September 2010 (single-room). We excluded patients who were unable to speak Dutch and English, and those who remained unresponsive (defined as a Richmond Agitation and Sedation Scale17 (RASS) < -3 and/or a Glasgow Coma Scale score18 (GCS) ≤ 8) throughout ICU admission.

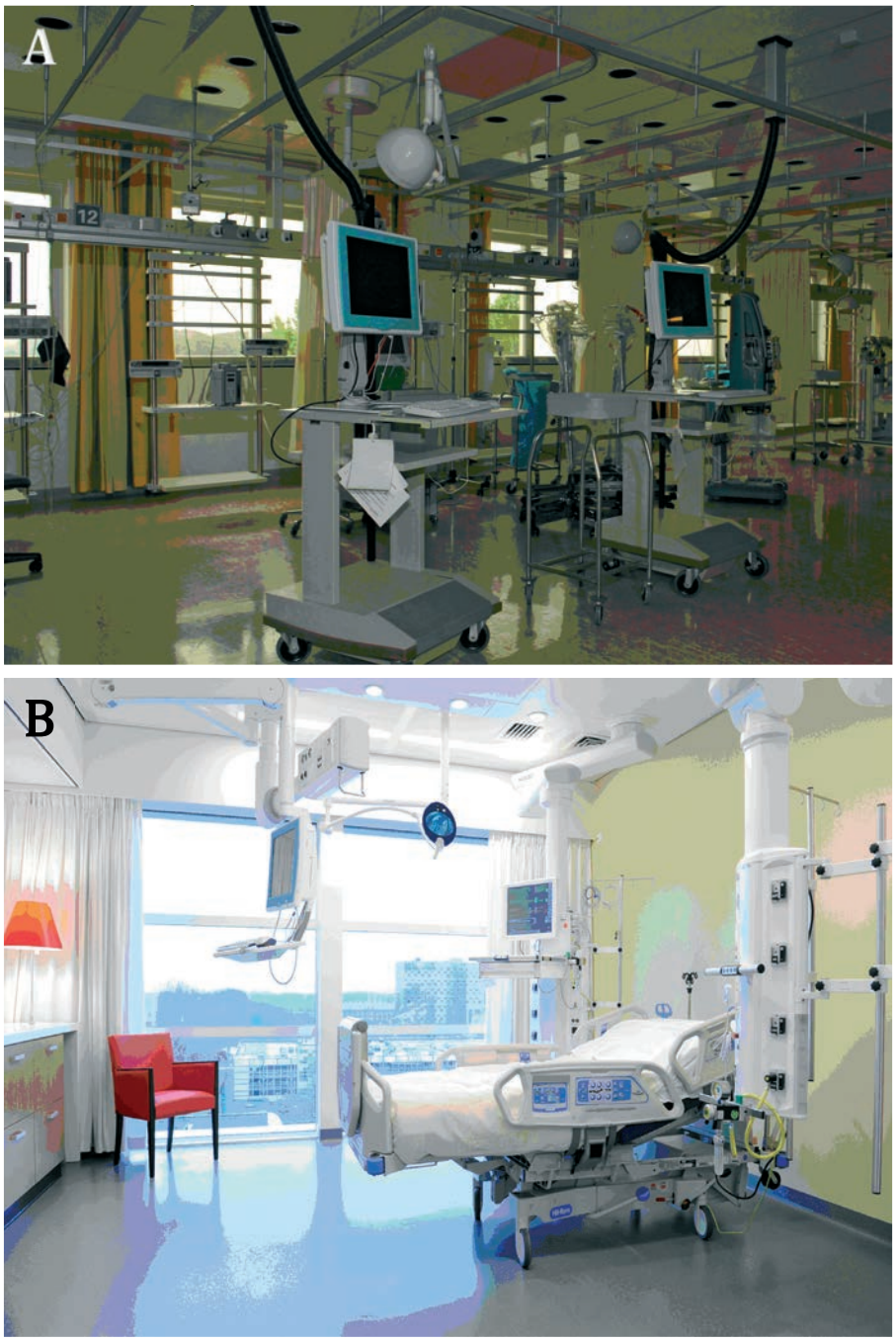
Intervention

ICU delirium, medication use and light intensities were compared between an ICU with wards and a single-room ICU. Until March 2010, patients were admitted to a mixed ICU, divided over three large wards with 11, 11 and 10 beds, and only curtains to separate patients from each other, see figure 1A. In March 2010, the ICU of the UMCU moved to a new location, set up as a patient centered environment. The new ICU was again divided over three wards with 11, 11 and 10 beds. All patients have separate rooms designed to reduce noise and make patients feel at home, using soft warm colors and with a view providing orientation and sufficient daylight. Patients are not exposed to unnecessary and excessive noise owing to the use of remote control monitors both inside and outside the patient rooms, noise-absorbent materials, glass sliding doors separating patient rooms from the corridors and improved alarm systems that filter and selectively send alarms to the nurses' cell phones. More information about the new ICU can be seen in figure 1B and our recent publication.[19] The transition to the single-room ICU was a multicomponent intervention. Other factors did not differ between the two study periods. Importantly, the policy for family visits remained a 24 hours open regimen and the doctor-patient and nurse-patient ratios were not altered. Teaching, practice and protocols on sedation, analgesia and delirium were not changed between study periods either.

Data collection

Data was collected prospectively, on a daily basis, 7 days a week. Standard demographic data were registered at inclusion. Co-morbidity at hospital admission was registered with the Charlson Co-morbidity Index.[20] Severity of illness at ICU admission was assessed using the Acute Physiology and Chronic Health Evaluation version (APACHE) II score.[21] Severity of illness during ICU admission was estimated daily with the Sequential Organ Failure (SOFA) score.[22,23] We further recorded daily the use of physical restraints at any moment during the preceding day, defined from 10 AM-10 AM

Figure 1. Wards (old setting, A) and single room (new setting, B) ICU



DELIRIUM ASSESSMENT

Delirium in the preceding day was assessed daily, 7 days a week, by two research physicians (IJZ and CFS) who received theoretical and bedside training by a neurologist-intensivist (AJCS). This classification of mental status, was as follows: (1) awake and not delirious during the preceding day, or (2) delirious at any moment during the preceding day, or (3) always unresponsive during the preceding day. The research physicians administered the Dutch version of the Confusion Assessment Method for the ICU[24] (CAM-ICU) at a predefined time, between 10 and 12 AM. If the patient was inaccessible, the evaluation was repeated between 3 and 5 PM.

Delirium often has a fluctuating course. To minimize the influence of this fluctuation the research physicians inspected the medical- and nursing charts, including the results of the twice-daily CAM-ICU screening by trained bedside ICU nurses.[25] In case of doubt, a neurologist or psychiatrist was consulted who had the decisive vote with regard to the classification of mental status. The number of delirium days was counted cumulatively during ICU admission, hence without taking different periods of delirium into account. The Delirium Severity Index (DSI) was used to register daily the severity of delirium,[26] based on the highest absolute RASS score in the preceding day. To determine inter-observer variability in the mental status classification, the two research physicians and neurologist-intensivist evaluated 36 patients simultaneously, where every observer was blinded to other observers' conclusions.

MEDICATION USE

Medication use was recorded with a computerized patient data monitoring system. For this study, we collected data on the use of medication that is mentioned in our protocols on sedation, analgesia and delirium, i.e. propofol, midazolam, oxazepam, temazepam, zopiclon, fentanyl, morphine, clonidine, haloperidol and quetiapine. During the study period, dexmedetomidine was not available in the Netherlands. In the statistical analyses, benzodiazepines dosages were converted in diazepam equivalents and opioids dosages into fentanyl equivalents.[27,28]

LIGHT INTENSITY

Light intensities were measured in September 2009 (ICU with wards) and in September 2010 (single-room ICU) with a light sensor (OSD15-E photodiode). The light sensor was attached 1 meter from a randomly assigned patient's head to measure light intensity in

30-seconds intervals. After three days, the light sensor was moved to another, randomly assigned, patient. This cycle was repeated six times in both the old and the new setting. The Royal Netherlands Meteorological Institute (KNMI) headquarters is located in De Bilt, the Netherlands, just 2700 meters north of the UMCU. For the days of our light measurements we consulted the KNMI database and retrieved the daily observations of the weather station in De Bilt.[29] In this database the daily sunshine duration is calculated according to an algorithm developed and published by the KNMI.[30] The covering of the sky by clouds is recorded in a graded scale from 0, indicating clear weather, to 9, completely over clouded.

Statistical analysis

The primary outcome was the number of delirium days during ICU admission. Secondary outcomes were the occurrence rate and severity of delirium.

The student's t-test was used to study independent samples of continuous, normally distributed data and the Mann-Whitney U test for continuous, skewed data. The chi-square test was used to analyze categorical data. With Poisson regression analysis, we compared the cumulative number of delirium days during ICU admission between the two settings, adjusted for the following confounding variables: age, gender, APACHE II, Charlson Co-morbidity index, highest SOFA score during ICU admission, admission type (urgent versus elective) and admitting discipline (in four categories: 1. medicine, 2. general surgery, 3. cardiology or cardiothoracic surgery, 4. neurology or neurosurgery). We used logistic regression analysis to study the association between the two settings and the occurrence of delirium, adjusted for the possible confounders mentioned above. We used linear regression analysis to compare the severity of delirium, based on the cumulative DSI per patient divided by the total number of delirium days for the particular patient, adjusting for the same covariates. We tested for multicollinearity in our multivariable regression analyses. Inter-observer variability was expressed as κ-score.

We computed total light intensity over 24 hour by summing the measurements of the 30-seconds intervals. Dividing this total light intensity by the number of measurements provides a mean light intensity over 24 hours. Similarly, we calculated the mean light intensity during the day (07.00 AM to 10.00 PM) and the night (10.00 PM to 07.00 AM).

All statistical analyses were performed using SPSS 17.0 ®, SPSS inc., Chicago, Illinois, USA. A two-sided p-value < 0.05 was considered statistically significant. Variance inflation factors (VIF) ≥ 10 and tolerance values (1/VIF) < 0.1 were considered as values indicating problems of multicollinearity.

Table 1. Characteristics of the study population

	Old ICU (n=55)		New ICU (n=75)		p-value
Age, mean (SD)	59.9	(15.5)	58.2	(18.3)	0.57
Male gender, n (%)	36	(66%)	44	(59%)	0.47
APACHE II, mean (SD)	16.3	(9.7)	18.5	(6.5)	0.13
CCI, median (IQR)	0	(0-2)	1	(0-3)	0.03
SOFA max, mean (SD)	6.7	(4.4)	6.5	(3.8)	0.81
Admitting discipline, n (%)					0.02
General medicine	14	(26%)	22	(29%)	
General surgical	4	(7%)	15	(20%)	
Cardiovascular[a]	27	(49%)	18	(24%)	
Neurological[b]	10	(18%)	20	(27%)	
Admission type, n (%)					0.01
Urgent	33	(60%)	62	(83%)	
Elective	22	(40%)	13	(17%)	
ICU LOS; days, median (IQR)	5	(2-10)	4	(3-8)	0.56
Mechanical ventilation, n (%)	52	(95%)	63	(84%)	0.06
Days of MV,median (IQR)	2	(1-8)	2	(1-5)	0.24
Mortality, n (%)	2	(4%)	7	(9%)	0.72

APACHE= Acute Physiology and Chronic Health Evaluation, CCI= Charlson Co-morbidity Index, ICU= Intensive Care Unit, IQR= Inter Quartile Range, LOS=Length of Stay, MV= Mechanical Ventilation, SD= Standard Deviation, SOFA= Sequential Organ Failure Assessment. [a]including cardiothoracic surgery, bincluding neurosurgery.

RESULTS

In the ICU with wards, 65 patients were eligible of whom 10 remained unresponsive. In the single-room ICU, a total of 91 patients were evaluated. We excluded 16 patients: one because the patient did not speak/understand Dutch or English sufficiently to apply the CAM-ICU and 15 others because they remained unresponsive throughout ICU admission. Therefore, our study population included 55 patients in the ICU with wards (449 observation days) and 75 patients in the single-room ICU (468 observation days). Baseline characteristics of the study population are shown in Table 1. Admitting discipline differed between groups (p=0.02), with more cardiovascular admissions in the ICU with wards. In the single-room ICU, there were more urgent admissions (p=0.01) with higher co-morbidity (p=0.03).

Table 2. Main outcomes and multivariable regression analysis

Delirious patients[a]	**Old ICU (n=28)**	**New ICU (n=34)**	**p-value**
Number of delirium days, median (IQR)	3 (2-5)	2 (1-3)	0.04
Adjusted Δ delirium days, (95% CI)[b]	*Reference*	-0.4 (-0.7 to -0.1)	0.005
Mean DSI per delirium day, mean (SD)	2.3 (0.7)	2.5 (0.8)	0.34
Adjusted Δ DSI, (95% CI)[b]	*Reference*	0.3 (-0.2 to 0.7)	0.22
Days spent comatose, median (IQR)	4 (0-5)	1 (1-4)	0.33
Mortality, n (%)	1 (4%)	3 (9%)	0.72
All patients	**Old ICU (n=55)**	**New ICU (n=75)**	**p-value**
Crude incidence of delirium, n (%)[a]	28 (51%)	34 (45%)	0.53
Adjusted OR (95%CI) for delirium[a,b]	*Reference*	0.6 (0.3-1.6)	0.53
Mean RASS, mean (SD)	-1.1 (1.1)	-1.3 (1.4)	0.55
Days spent comatose, median (IQR)	0 (0-4)	0 (0-2)	0.94

CI= Confidence interval, DSI= Delirium Severity Index, ICU= Intensive Care Unit, IQR= Inter Quartile Range, OR= Odds Ratio, RASS= Richmond Agitation and Sedation Score, SD= Standard Deviation. [a]assessed with review of medical and nursing charts and the Confusion Assessment Method for use in the Intensive Care Unit (CAM-ICU), [b]models adjusted for age, gender, APACHE II, Charlson Co-morbidity index, highest SOFA score, admission type and admitting discipline.

The mean κ for agreement between the three observers (O1, O2 and O3) on the mental status classification was 0.91 (κ O1-2: 0.91, κ O1-3: 0.91, κ O2-3: 0.91). When delirium occurred, the median number of days with delirium was 3 days (IQR 2 - 5) in the ICU with wards and 2 days (IQR 1 - 3) in the single-room ICU (p=0.04). When we adjusted for confounding with Poisson regression analysis, the average number of delirium days was 0.4 days (95% CI 0.1 - 0.7) less in the single-room ICU than in the ICU with wards (p=0.005), Table 2. The risk of multicollinearity was considered low with no VIF or tolerance value meeting the thresholds. Overall, delirium occurred in 28 (51%) patients in the ICU with wards versus 34 (45%) patients in the single-room ICU (adjusted odds ratio (OR) 0.6, 95% Confidence Interval (CI) 0.3 - 1.6, p=0.53), Table 2.

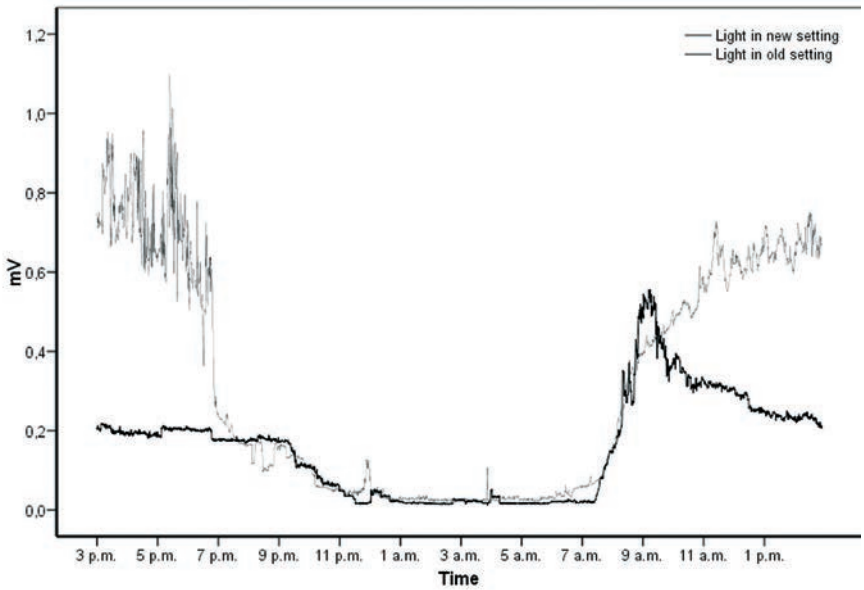
The severity of delirium, assessed with the mean daily DSI, was not different between the two environments, Table 2. There was no difference in proportion of patients that was physically restrained during any moment in their ICU admission nor in the number of days patients were physically restrained (data not shown). As shown in Table 3, we found no relationship between ICU environment and the use of propofol, benzodiazepines, opioids, clonidine or haloperidol. None of the included patients received quetiapine.

Table 3. Haloperidol, sedatives and analgesics use during ICU admission

	Old ICU (n=55)		New ICU (n=75)	
Haloperidol				
- No. using haloperidol, n (%)	16	(21%)	20	(27%)
- per patient/mg/day, median (IQR)	4	(2-6)	3	(2-5)
Propofol				
- No. using propofol, n (%)	34	(62%)	41	(55%)
- per patient/mg/day, median (IQR)	1304	(664-2910)	1360	(588-2923)
Opioids				
- No. using opioids, n (%)	47	(85%)	59	(79%)
- per patient/mg/day, median (IQR)[a]	0.13	(0.06-0.28)	0.16	(0.05-0.38)
Benzodiazepines				
- No. using benzodiazepines, n (%)	35	(64%)	43	(47%)
- per patient/mg/day, median (IQR)[b]	13	(7-69)	35	(7-96)
Clonidine				
- No. using clonidine, n (%)	12	(22%)	20	(27%)
- per patient/mg/day, median (IQR)	262	(82-508)	259	(145-437)

ICU = Intensive Care Unit, IQR=Inter Quartile Range, No.=number, mg=milligram. [a]in fentanyl equivalents, [b]in diazepam equivalents, [c]statistical significant difference with p-value<0.05.

Figure 2. Light intensities in the ICU with wards (old) and single rooms (new)



On the days of our light measurements we found no difference (p=0.70) in hours of sunshine with median (IQR) of 1.0 (0.2-4.0) hours in the ward-like ICU and 2.5 (0-5.2) hours in the single room ICU. Also, there was no difference (p=0.94) in the covering of the sky by clouds with in the ward-like ICU a median (IQR) cloudiness off 6.0 (5.5-8.0) and in the single-room ICU off 6.0 (6.0-6.5). A total of 103,680 light intensity measurements were performed. Overall, median light intensity in the ICU with wards was 0.31 V/minute (IQR 0.24 - 0.38) and in the single-room ICU 0.52 V/minute (IQR 0.39 - 0.74, p<0.001). During the day, median light intensity was particularly lower in the ICU with wards (0.42 V/minute, IQR 0.35 - 0.55) than in the single-room ICU (0.81 V/minute, IQR 0.60 - 1.17, p<0.001, figure 2). However during the night, light intensity was similar with median (IQR) light intensity of 0.05 V/minute (IQR 0.04 - 0.10) in the ICU with wards and 0.05 V/minute (0.03 - 0.09) in the single-room ICU, p=0.52.

DISCUSSION

In summary, this study suggests that a change in ICU environment can decrease the number of delirium days during ICU admission. In an ICU with all single rooms, we found that patients spent fewer days with delirium than in a conventional ICU with wards. Reducing the duration of delirium is of pivotal importance to ICU patients as each additional day with delirium in the ICU has been found to be associated with a 10% increased risk of death.[6,31]

Since the development of ICUs in the 1950s, the main focus of Intensive Care Medicine was the survival of the patients, while less attention was paid to the environment in which this was established. However, the nursing environment, and especially excessive noise or light, appeared to influence several healthcare outcomes.[16] Post-surgical patients with a view on a natural scene had a shorter hospital stay than patients with windows facing a brick wall.[32] Studies focusing on ICU environment and patient outcomes are however sparse.[15,33] This is the first study comparing different ICU environments and delirium in intensive care patients.

Strengths of this study include the seven days a week assessments by research physicians with high interobserver agreement, which ensured good quality of the evaluations. Delirium often has a fluctuating course. Using both CAM-ICU assessments and chart evaluations we tried to minimize the influence of fluctuation of the symptoms on our daily mental status classification. Because of the strict follow-up, there were no missing data. The study populations included a wide spectrum of diseases and conditions representing a typical mixed-type adult ICU, ensuring generalization of the results. Although the sample size of our study population (n=130) was relatively small, the number of observation days was high (n=917).

This study has also some limitations. Most important is the before-after study design and the possibility that other factors than ICU environment have changed over time and influenced our findings. Between the two settings there were however no changes in doctor-patient or nurse-patient ratios, nor in practice or protocols on sedation, analgesia and delirium. We further adjusted for all differences in patient characteristics between the two ICU settings. A source of bias may be that the two research physicians were aware of the change in ICU environment and the aim of the study. Theoretically, blinding would overcome this limitation, but this is impossible to apply in a study on the effects of ICU environment. Because of high specificity of the CAM-ICU performed

in daily practice by bedside nurses,[25] who were not aware of the aim of the study, their CAM-ICU screening was taken into account in the daily mental status classification. Up until now it is unclear how to quantify the severity of delirium, therefore there is no golden standard for rating the severity of delirium. Without a golden standard it is not possible to validate severity instruments. In our study we made use of the DSI, which, also, has not been validated yet. The use of the Charlson Co-morbidity Index in studies regarding delirium is limited because it does not register relevant co-morbidity for delirium, such as cognitive decline, drug or alcohol abuse and other psychiatric disorders. We have used a multicomponent intervention. However, our results could be subject to confounding by non-environmental factors or any other environmental change. The use of specific medication or physical restraints, undertreated pain and the duration of mechanical ventilation are possible risk factors for the development of delirium.[7,13,34,35] In our study population, the duration of mechanical ventilation and the use of psychoactive medication, opioids and physical restraints were not different between the two settings. Unfortunately, we did not register pain in our study. However, possible differences in pain may be related to the changes in the ICU environment, as shown in patients after cholecystectomy.[32] Differences in pain between the two settings may therefore be one of the intermediate factors. In our study we have measured light intensities as one part of the multicomponent intervention. In the literature light levels are generally expressed in either Volts or Lux. Whereas Lux is correlated to the light perceived by the human eye, a photodiode (measuring light in Volts) is much more sensitive. Therefore, linear conversion from Volts to Lux is only possible within the visible spectrum. In both the ICU with wards and the single-room ICU, we measured light beyond the visible spectrum, hampering conversion to Lux. Unfortunately, in our study we did not incorporate measurement of other environmental factors, such as noise levels. Finally, we used Poisson regression to analyze differences in the number of days with delirium and did not include the time-varying nature of delirium. We cannot exclude potential immortal time bias, as the sickest patients are most likely to die early during critical illness with less opportunity to develop delirium.[36] However, in the two settings there was no difference in mortality, nor in the occurrence rate of delirium in the patients who died. Therefore, the risk of immortal time bias in our data was considered low.

CONCLUSION

This study is the first to assess the influence of ICU environment on delirium in the ICU. Our study suggests that environmental factors can influence the number of days with delirium during ICU admission, broadening the evidence for the effectiveness of non-pharmacological measures in the treatment of delirium. Future research should focus on single interventions in the ICU environment to determine the influence of ICU environmental factors on delirium. As the ICU environment appears to influence the course of delirium, non-pharmacological anti-delirium measures deserve more attention in Intensive Care Medicine.

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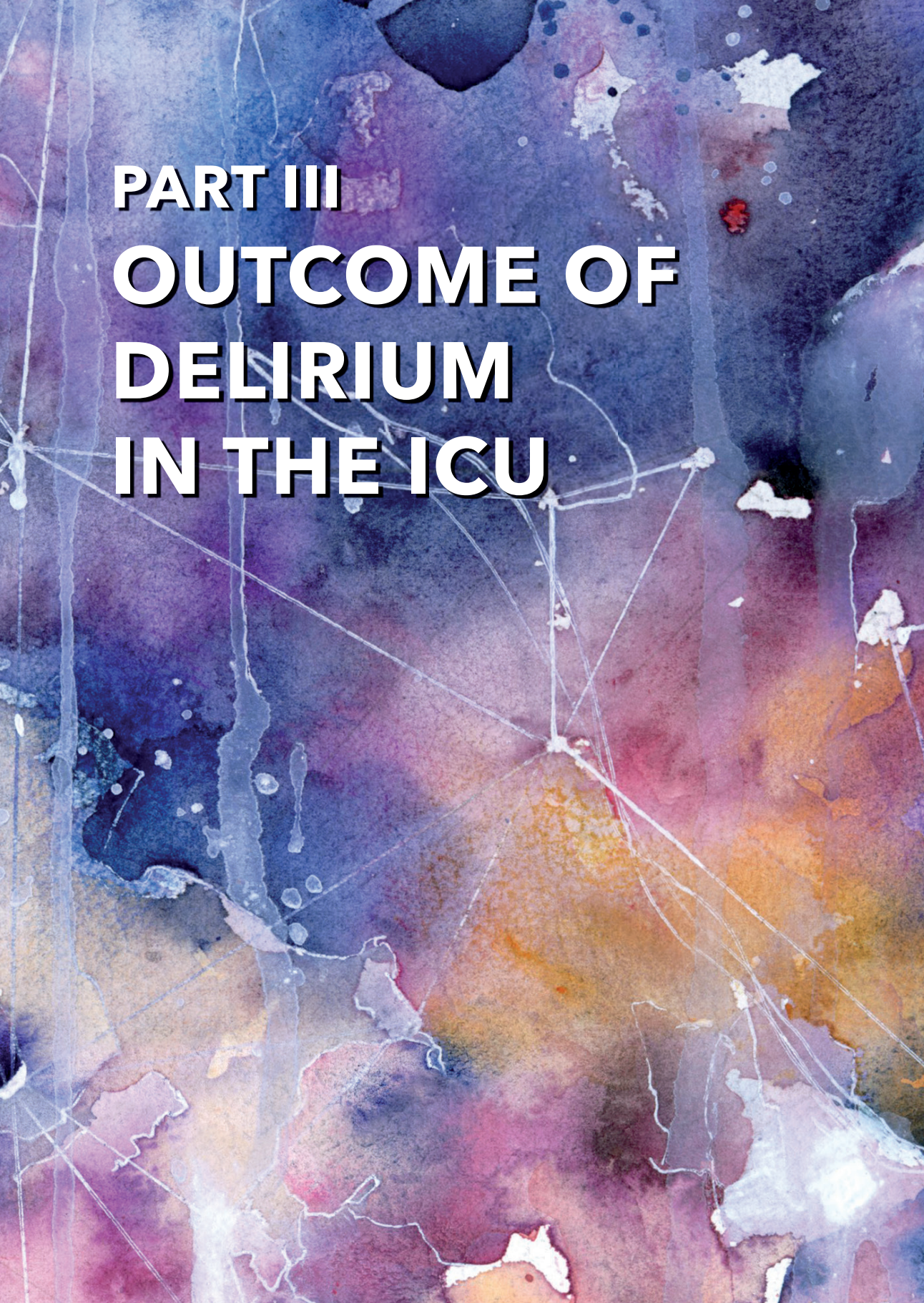

PART III
OUTCOME OF DELIRIUM IN THE ICU

The attributable mortality of delirium in critically ill patients: a prospective cohort study

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ABSTRACT

Objective

Previous studies have reported that delirium increases the risk of death in critically ill patients by up to three-fold, but failed to adjust for confounding caused by time-varying disease severity and did not model competing events that occur during intensive care unit (ICU) admissions. We determined the attributable mortality caused by delirium in critically ill patients.

Methods

Over a 30-month period, all consecutive adults admitted to a 32-bed mixed ICU in the Netherlands for at least 24 hours were included in this prospective cohort study. Delirium evaluations were performed daily using a validated protocol that included a Confusion Assessment Method for the ICU (CAM-ICU) assessment by trained observers. Logistic regression and competing risks survival analyses was used to adjust for baseline variables, and a marginal structural model analysis to adjust for confounding by evolution of disease severity prior to delirium onset.

Results

Among 1112 evaluated patients, 558 (50%) subjects developed at least one episode of delirium, with a median (interquartile range) duration of 3 (2 to 7) days. Crude mortality was 94/558 (17%) in patients with delirium compared to 40/554 (7%) in patients without delirium ($p<0.001$). Delirium was significantly associated with mortality in the multivariable logistic regression analysis (odds ratio 1.77; 95% confidence interval (CI) 1.15 to 2.72) and survival analysis (subdistribution hazard ratio (SHR) 2.08; 95% CI 1.40 to 3.09). However, the association disappeared when we adjusted for time-varying confounders in the marginal structural model (SHR 1.19; 95% CI 0.75 to 1.89). Using this approach, only 7.2% (95% CI -7.5 to 19.5%) of deaths in the ICU were attributable to delirium, with an absolute mortality increase of 0.9% (95% CI -0.9 to 2.3%) by day 30 in patients with delirium. In post-hoc analyses, however, delirium that persisted for ≥2 days remained associated with a 2.0% (95% CI 1.2 to 2.8%) absolute mortality increase. Furthermore, competing risk analysis showed that delirium of any duration was associated with a significantly reduced rate of discharge from the ICU (cause-specific hazard ratio 0.65; 95% CI 0.55 to 0.76).

Conclusions

Overall, delirium prolongs ICU admission but does not cause death in critically ill patients. Future studies should focus on episodes of persistent delirium and its long-term sequelae rather than on acute mortality.

INTRODUCTION

Delirium is a common complication of critical illness, occurring in 30-60% of intensive care unit (ICU) patients.[1-5] Although most studies have identified delirium as an independent predictor of death in the ICU,[6-14] several others found no association with mortality.[15-17] These inconsistencies have been explained by differences in case-mix, tools used for delirium assessment, and study design.[18] Deficiencies in modelling methodology and residual confounding may, however, provide an alternative explanation. In particular, none of the previous studies have adequately adjusted for disease progression prior to the start of delirium, nor for competing events (such as discharge) that may preclude observation of ICU mortality. It remains therefore unclear whether delirium is merely a marker of poor prognosis or causally linked to mortality in the ICU.

We aimed to estimate the proportion of deaths that can be attributed to delirium in a large cohort of critically ill patients by performing a marginal structural model (MSM) analysis from the field of causal inference. Such analysis can overcome bias that results from the evolution of disease severity until the onset of delirium as well as for more traditional sources of bias.[19,20] To aid in the interpretation of our findings, we compared the results of the MSM analysis with standard statistical regression methods.

METHODS

Study population

We prospectively evaluated consecutive adults admitted for at least 24 hours to the 32-bed mixed ICU of the University Medical Center Utrecht, the Netherlands, between January 2011 and June 2013. We excluded patients with acute or premorbid neurological

disease at baseline, patients in whom delirium assessments could not be performed due to a language barrier, and patients transferred from or to another ICU. The local ethical review board gave approval for an opt-out consent method (IRB number 10-056/12-421) whereby participants and family members were notified of the study by a brochure that was provided at ICU admission with an attached opt-out card.

Delirium

In addition to a twice daily completion of the Confusion Assessment Method for the ICU (CAM-ICU) by nurses, a research team dedicated to this study classified the mental status of patients daily until ICU discharge, using a validated flowchart.[21] Patients were categorized as either (1) comatose (2) sedated, (3) awake and delirious, or (4) awake and non-delirious. First, the level of consciousness was assessed using the Richmond Agitation–Sedation Scale (RASS). Patients with maximum scores of –5 or -4 during the entire 24h observation period could not be assessed for delirium and were classified as either comatose or sedated.[22] A sedated state was defined as the continuous administration of propofol at a rate > 1 mg/kg per h and/or midazolam in a dose > 50 mg per day or equivalent (other benzodiazepines; dexmedetomidine was not used our ICU during the study period), either at the time of assessment or at any time in the 48 hours before assessment. All other cases with RASS scores -5 or -4 were classified as comatose. The remaining patients were assessed for delirium with the use of the CAM-ICU as well as inspection of medical notes and nursing charts by the research team. These patients were classified as delirious when they tested positive on the CAM-ICU and/or when there was a description of fluctuation in the level of consciousness, agitation, disorientation or hallucinations. Furthermore, because haloperidol and quetiapine were exclusively used for the treatment of delirium during the study period, patients were also classified as delirious on the day of initiation of either of these drugs. In case of doubt, a neurologist (AS) was consulted, who cast the decisive vote with respect to mental status classification. This procedure ad a sensitivity of 0.75 (0.47-0.92), specificity of 0.85 (0.68-0.94) and an excellent interrater agreement (Fleiss' kappa 0.94). To enable our primary analysis we dichotomized the mental status by reclassifying sedated patients as non-delirious, and comatose patients (without sedation) as delirious (Supplementary data Figure E1). The clinical team responsible for the patients was unaware of the results of the delirium assessments made by the study team.

Covariables and outcome

In all multivariable models, we adjusted for covariables that were chosen a priori based on their expected associations with delirium and mortality after careful consideration of the literature. These covariables included age, gender, history of dementia, history of alcohol abuse, Charlson comorbidity index, acute physiology and chronic health evaluation (APACHE) IV score, admission type, re-admission status, and presence of sepsis on admission to the ICU.[23] These are all time-fixed variables, representing the risk of delirium at baseline. However, because the risk of delirium onset is likely to vary over the course of ICU admission depending on the evolution of disease severity, we also incorporated time-dependent variables in our primary analysis (Figure 1). These included daily measurements of the sequential organ failure assessment (SOFA) score, sepsis status, core temperature, mechanical ventilation status, use of sedative and analgesic medications, and plasma sodium, urea, pH and haematocrit levels.[1,6,7,15,17,24-38] Several physiological and laboratory variables (i.e., temperature, sodium, pH, urea, and haemoglobin) were transformed in order to account for their non-linear relation with delirium or mortality. We transformed these variables using the cut-offs from the APACHE IV model (if applicable, i.e. temperature, sodium, urea, haemoglobin) or based on literature (pH).[39] Data were prospectively collected as part of a large cohort study by observers dedicated to this study and regularly checked for data integrity.[40] For daily observations, 3.1% of data were missing (range 0-6.9% for individual variables). Because of the availability of longitudinal data prior to each observation day for each patient, we performed a trend imputation for missing covariables.[41] There were no missing data in baseline variables, daily mental status classifications or the outcome. ICU ICU mortality was the primary outcome of interest in all analyses.

Statistical analysis

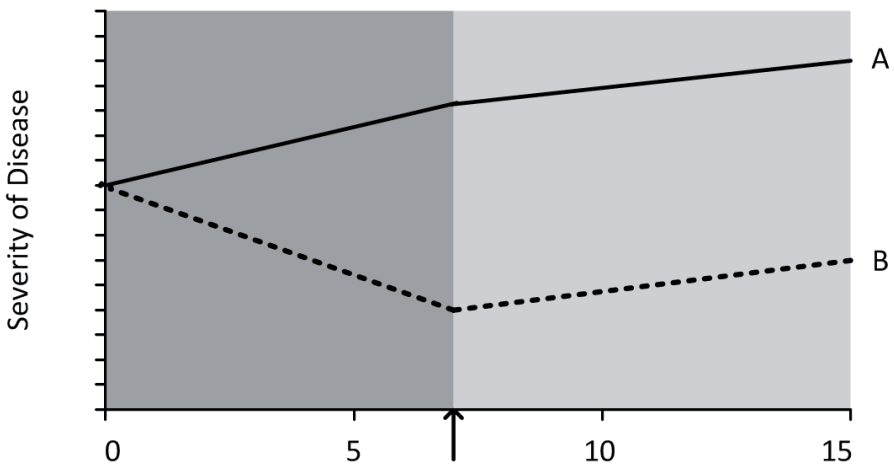
To obtain first estimates of the association between delirium and mortality in our cohort, and to be able to compare our results with previous literature, we performed a multivariable logistic regression analysis, adjusting for a priori selected baseline confounders. To comply with existing literature, we assumed that patients who develop delirium are at increased risk for the entire duration of their ICU stay, even if they develop delirium not before several days after admission. The resulting bias can be overcome by using a Cox proportional hazards analysis and with inclusion of delirium as a time-dependent variable.[42] In this type of analysis, however, one should additionally

account for informative censoring of the survival time by considering discharge as a competing risk for mortality, because patients who are discharged from the ICU alive are in a different health state compared to patients who remain admitted beyond that time point.[43] A competing risks analysis provides two measures of association: the cause-specific hazard ratio (CSHR), which estimates in this case the direct effects of delirium on outcome (both ICU discharge and death), and the subdistribution hazard ratio (SHR) which describes the instantaneous risk of dying from delirium given that the subject has not died from delirium.[44] The SHR is, therefore, a summary measure of all separate cause-specific hazards and can be used to calculate the cumulative incidence of the outcome of interest (i.e., death in this study). The Fine and Gray model can be used to directly model the effect of covariables on the cumulative incidence function.

Although the above methods can adjust for baseline confounders, the time-varying nature of delirium onset and informative censoring caused by ICU discharge, a limitation of these methods is that neither can adjust for other, potentially important, sources of confounding. Firstly, the severity of disease on the day of ICU admission may not be representative of the health state at the time of delirium onset, which typically occurs later on during ICU stay (Figure 1). As delirium preferentially develops in the more severely ill,[25] bias occurs when such changes in disease severity are not adjusted for during the analysis. Secondly, bias might occur when (1) a time-dependent covariable is not only a risk factor for death, but also predicts subsequent delirium, and (2) delirium status at a previous time point predicts the risk factor.[45] For instance, severely agitated patients with delirium may eventually be treated with sedatives, whereas sedative use itself is a known risk factor for delirium.[25] An MSM analysis addresses these limitations by adjusting for the changes in disease severity prior to delirium onset, while preventing bias.[19,20] It enables assessment of what the ICU mortality would have been in a hypothetical population in which all patients remained delirium-free, and is therefore called a counterfactual analysis.

To accomplish such a counterfactual analysis, we performed two steps. Firstly, we modelled the daily probability of acquiring delirium in the ICU using a multivariable logistic regression analysis that included both baseline and daily patient characteristics. Based on these estimated daily probabilities, we calculated stabilized patient-specific weights (so-called inversed probability weights, IPWs) that represent the cumulative

Figure 1. Evolution of disease severity prior to onset of delirium in two hypothetical patients



This figure shows the changes in the severity of disease in two hypothetical patients admitted to the intensive care unit (ICU). Both patients have similar disease severities at admission, but the condition of patient A worsens and of patient B improves. As delirium preferentially develops in more severely ill patients confounding occurs when disease severity after baseline is not adjusted for in the analysis. Logistic regression and survival analysis adjusts for baseline variables at t=0 only. A marginal structural model adjusts for changes in disease severity until the onset of delirium (dark grey), but not thereafter (light grey).

risk of acquiring delirium per patient. Because adjustment for time-varying variables measured after the start of delirium may result in bias, we used lagged values from the preceding day to predict delirium on each day.[46] We adjusted for lagged values of the SOFA score two days before to acknowledge that the SOFA score measured within 24 hours before the onset of delirium may have been influenced by an insidious onset of delirium. Secondly, we performed an IPW-weighted Cox regression analysis with competing endpoints (death and discharge alive) and estimated both the daily hazard and cumulative risk of death. To aid in the interpretation of the results, we computed the population attributable fraction which indicates the percentage of patients that have died from delirium.

Table 1.Patient characteristics by delirium status

Characteristic	Never delirium (N=554)		Ever delirium (N=558)		*p*-value
Age (years)	61	(49-69)	64	(54-74)	<0.001
Male gender	316	(57%)	356	(64%)	0.02
Caucasian race	535	(97%)	534	(96%)	0.29
Current alcohol abuse[a]	12	(2%)	33	(6%)	<0.001
Charlson comorbidity index	5.4	(0.0-10.2)	7.1	(1.0-11.4)	<0.001
Prior ICU admission[b]	83	(15%)	91	(16%)	0.54
Admission type					0.26
medical	253	(46%)	266	(48%)	
elective surgery	165	(30%)	142	(25%)	
emergency surgery	136	(24%)	150	(27%)	
Medical specialty					<0.001
general surgery	213	(38%)	211	(38%)	
cardiology and cardiothoracic surgery	165	(30%)	170	(30%)	
Internal medicine	105	(19%)	131	(23%)	
Other	71	(13%)	46	(9%)	
Sepsis at admission	190	(34%)	306	(55%)	<0.001
APACHE IV score	63	(48-81)	79	(62-97)	<0.001
Length of stay (days)	3	(2-5)	9	(5-18)	<0.001
Mechanical ventilation	470	(85%)	510	(91%)	<0.001
ICU case fatality	40	(7%)	94	(17%)	<0.001

Continuous variables are expressed as medians (inter-quartile range); categorical variables as absolute numbers (%).APACHE = Acute Physiology and Chronic Health Evaluation, ICU = intensive care unit. [a]Defined as alcohol consumption of >40 gram alcohol/day, [b]Defined as prior ICU admission during current hospitalization.

We performed several post-hoc sensitivity analyses (Supplementary data Figure E1). Firstly, instead of categorizing sedated patients as non-delirious, we reclassified these patients based on the first-available valid delirium assessment following the cessation of sedation, using backward imputation. Secondly, we applied a more rigorous definition of delirium by considering patients as being delirious only when they had been classified as delirious on at least two consecutive days. Thirdly, to assess possible effect modification by the underlying condition, we performed subgroup analyses in patients with sepsis only, and stratified by APACHE IV score.

All analyses were performed using SAS 9.2 (Cary, NC) and R 2.14 (www.r-project.org). We used the R-package "IPW" for the MSM analysis.[47] P-values less than 0.05

were considered to be statistically significant. We used robust estimators (Huber sandwich) to calculate confidence intervals for the hazard ratios resulting from the MSM analyses,[48] and used bootstrapping to estimate the confidence intervals for the attributable mortality.

RESULTS

During the 2.5-year study period, 2854 critically ill patients were admitted to our ICU of whom 1112 met the inclusion criteria (Figure 2). The average length of stay was 8.9 days, amounting to a total of 9867 observation days. Delirium was observed on 2524 (26%) of these days. However, to obtain a dichotomous exposure variable for use in the regression analyses, we additionally reclassified 537 coma days to days with delirium and 1371 sedation days to days without delirium. After this, 558 (50%) patients had at least one episode of delirium. The median time to onset of delirium was 2.0 days (IQR 1.0-4.0 days) and the median duration of a delirium episode was 3.0 days (IQR 2.0-7.0 days).

Table 1 shows patients characteristics by delirium status. There were no missing data in baseline variables, daily mental status classifications or the outcome. For daily observations, 3.1% of data were missing overall (range 0-6.9% for individual variables). Patients with delirium had significantly greater severity of disease on admission, were older, and were more likely to be male. Crude mortality was 94/558 (17%) in patients with delirium compared to 40/554 (7%) for those without delirium ($p<0.001$).

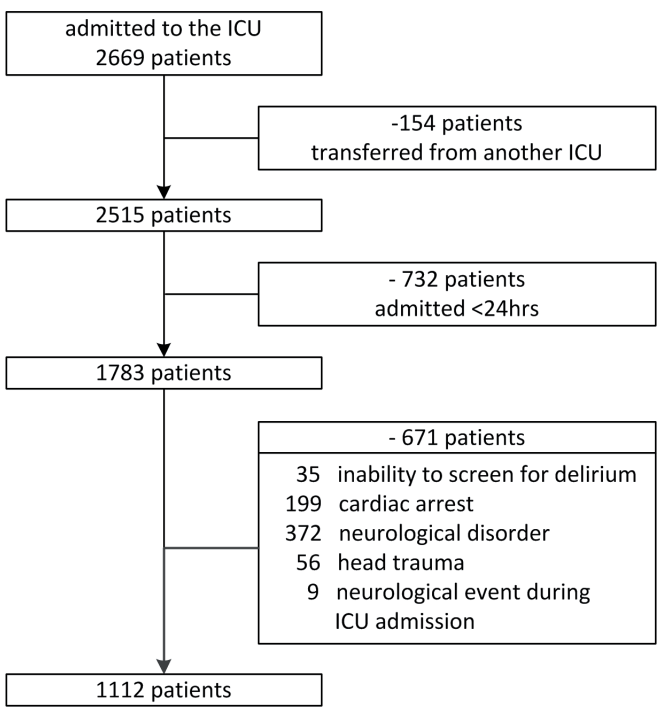
Regression analysis

Table 2 shows the results of the regression models. Delirium was significantly associated with mortality by logistic regression analysis (crude odds ratio (OR) 2.60; 95% confidence interval (CI) 1.76-3.85; adjusted OR 1.77; 95% CI 1.15-2.72). In time-dependent, cause-specific survival analysis, however, delirium had no direct effect on the daily risk of death (CSHR 0.64; 95% CI 0.39-1.03) but did result in a lower daily probability of being discharged from the ICU (CSHR 0.53; 95% CI 0.46-0.61). Consequently, patients with delirium remained longer at risk of dying in the ICU, resulting in a combined hazard of death for patients with delirium that was significantly increased (SHR 2.08; 95% CI 1.40-3.09). In contrast, once we adjusted for the evolution of disease severity prior to

onset of delirium in the MSM analysis, delirium was no longer associated with ICU death (SHR 1.19; 95% CI 0.75–1.89). Figure 3 shows the effect of delirium on the cumulative risk of death over time. By day 30, the population-attributable fraction of ICU mortality due to delirium was 7.2% (95% CI -7.5–19.5%), corresponding to an absolute case fatality of 0.9% (95% CI -0.9–2.3%).

Supplementary date Table E1 provides the results of the post-hoc analyses using alternative delirium definitions. The sensitivity analysis using backward imputation for patients in whom delirium assessments were obscured by the use of sedation yielded similar estimations. However, the sensitivity analysis using a delirium definition that required the derangement to persist for ≥2 consecutive days yielded a stronger overall association with mortality than our primary analysis (SHR 1.67, 95% CI 1.13-2.47; 30-day absolute risk difference in mortality 2.0%, 95% CI 1.2-2.8%).

Figure 2. Flowchart of patient inclusion



hrs= hours, ICU = Intensive Care Unit.

In this case, cause-specific analysis also showed that increased mortality was mediated through a prolonged length of stay in the ICU rather than by a direct effect on the daily risk of death. No signs of effect modification were found in the subgroup of patients presenting with sepsis, nor in relation to the severity of illness at the time of ICU admission (Table E2).

Table 2. Effect estimates for the association between delirium and ICU mortality using various statistical approaches

	Logistic regression	Competing risks survival regression	Marginal structural model[h]
Adjustment for:			
- Baseline covariables	✓	✓	✓
- Time-varying onset of delirium	×	✓	✓
- Competing risks (death, discharge)	×	✓	✓
- Evolution of disease prior to delirium onset[a]	×	×	✓
Effect estimate:[bc]			
Crude	2.60 (1.76-3.85)	3.14 (2.32-5.04)	3.14 (2.32-5.04)[ef]
Adjusted[d]	1.77 (1.15-2.72)	2.08 (1.40-3.09)	1.19 (0.75-1.89)[g]

[a]Logistic regression and survival analysis can also be used to correct for evolution of disease severity, however over-adjustment and collider-stratification bias might occur. The marginal structural model prevents these biases.[19b] The logistic regression analysis gives an odds ratio whereas the survival analysis and marginal structural model provide a subdistribution hazard ratio, [c]Delirium was included as a time-dependent variable in the competing risks survival regression and marginal structural models, [d]The multivariable analysis was adjusted for baseline variables (age, gender, Charlson co-morbidity index, acute physiology and chronic health evaluation (APACHE) IV score, admission type, and sepsis on admission). The marginal structural model was furthermore adjusted to time-varying variables: sequential organ failure assessment (SOFA) score, sepsis status, temperature, sodium, urea concentration, acidosis, haematocrit, mechanical ventilation and sedative and analgesic medications, [e]The crude subdistribution hazard ratio of the marginal structural model was calculated assuming the weights to be equal to 1 and is therefore equal to the estimation of the competing risks survival analysis, [f]The adjusted cause-specific hazard ratios of the competing risks survival regression were 0.64 (0.39-1.03) and 0.53 (0.46-0.61) for mortality and discharge, respectively, [g]The adjusted cause-specific hazard ratios of the marginal structural model analysis were 0.38 (0.22-0.65) and 0.65 (0.55-0.76) for mortality and discharge, respectively, [h]The inversed probability weights (IPW) estimates were: mean 0.974 (range 0.127-8.51) and median 0.894 (IQR 0.731-1.072).

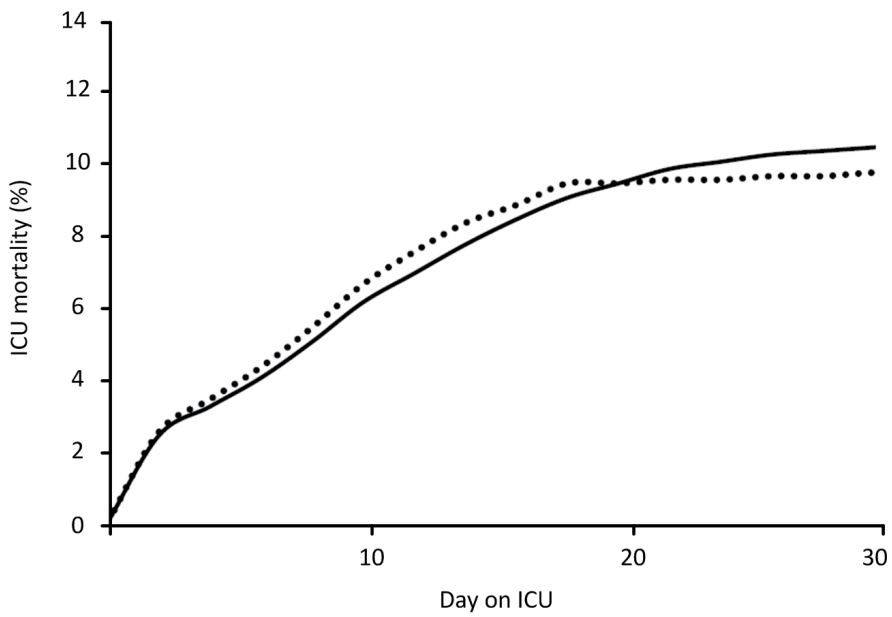
DISCUSSION

We estimated the mortality due to delirium in critically ill patients while taking into account bias caused by time-varying disease severity until the onset of delirium and by the competing risk of discharge. Using this approach, the population attributable ICU mortality was estimated at 7.2% by day 30, implying that absolute case fatality can be reduced by no more than 0.9% if we were able to completely prevent delirium in all patients.

Our findings confirm the estimates of a two to three-fold increased case fatality rate associated with delirium that were reported in previous studies when we adjusted for baseline variables only.[6-8,10,11,14-16,42,49,50] However, as we added complexity to our analyses and adjusted for changes in disease severity prior to the onset of delirium, we found no association between delirium (of any duration) and ICU mortality, which is consistent with a recent meta-analysis of clinical trials that also showed that delirium was not associated with short-term mortality.[51] However, results of post-hoc sensitivity analyses suggest that patients who develop an episode of delirium that persists for more than two days were exposed to an overall increased risk of death in the ICU. Although this finding needs further confirmation, it gives support to recent reports suggesting a fundamental distinction between rapidly reversible, sedation-related delirium and severe, persistent delirium in the ICU.[52] In pre-specified subgroup analyses, the presence of sepsis and severity of illness at baseline was not associated with an increased mortality rate in patients with delirium. Although sepsis is often associated with delirium, it is unknown whether this so-called septic encephalopathy really is different from other entities of delirium. Our results indicate that sepsis-associated delirium is similar to other forms of delirium regarding mortality. In any case, however, all cause-specific analyses indicated that delirium does not directly affect case fatality rates, but rather that any increase in overall mortality is mediated through a more protracted length of ICU stay, exposing patients longer to a fixed daily risk of dying (e.g., due to nosocomial infections, drawbacks of prolonged sedation and/or mechanical ventilation, and other 'general' ICU complications). Indeed, the average length of stay of patients without delirium was 4.0 days, as compared to 8.8 and 16.5 days for patients with either a short or persistent episode of delirium, respectively. The effect of delirium on the length of stay is plausible because patients with delirium are typically less likely to interact with their environment (hampering early mobilization), may have an increased incidence of complications (e.g., due to self-removal of catheters or tubes), and often receive medication with sedative effects.[15,49,53,54]

Many authors have addressed the association of delirium and mortality, but only in a few studies multivariable analyses have been performed to adjust for severity of disease at baseline.[6,8,10] To avoid immortal time bias (i.e. bias due to the time-varying nature of delirium), others have incorporated the time of delirium onset in their analyses.[7,42] However, we considered it crucial to also incorporate the evolution of disease severity prior to the development of a delirium episode into our analyses as critically ill patients may show either rapid deterioration or reversal of organ dysfunction, both of which are likely to significantly impact the risk of delirium onset over time. Although standard regression models can be used for this purpose, their use may result in the elimination of any potential effects of delirium on mortality if a time-varying confounder is also an intermediate factor in the causal pathway that leads up to delirium, as well as to the collider-stratification bias that occurs when disease severity on a given day is influenced by the presence of delirium at a prior point in time.[46,55] The MSM analysis that we used is not affected by these problems.

Figure 3. Cumulative incidence of observed and estimated ICU mortality



This figure represents the expected mortality in the whole cohort estimated by the cumulative incidence function in the absence and presence of delirium. We adjusted for informative censoring using a competing risks analysis and for evolution of disease using a marginal structural method. The exact procedures are explained in the methods section.

We acknowledge some limitations of our study design. Firstly, management of delirium is largely pragmatic and may vary between centres, which may limit the generalizability of our findings, in addition to the single centre design. Yet, both our case-mix and the results of our initial logistic and survival regression analyses were in line with previous literature. Secondly, as is true for all observational studies, we cannot rule out the possibility that unobserved confounding might still have occurred, even after accounting for a relatively large number of covariables. Furthermore, delirium can be the first symptom of an impending complication, such as ICU-acquired sepsis.[56,57] When this happens, any mortality due to this sepsis event may then be falsely attributed to delirium, since an MSM analysis (deliberately) adjusts for the evolution of disease severity up until the onset of delirium. The true association of delirium with mortality might therefore be even lower than we report.

In addition to these methodological concerns, there also remains an important issue with respect to the way our study (or, for that matter, any study in this domain) deals with the classification of unobserved days due to coma or sedation. Because delirium assessment in unresponsive patients is impossible and the statistical methods that we used required a dichotomous classification of subjects, we re-categorized patient-days on which delirium could not be observed due to coma and/or sedation. No universally accepted methods for such reallocation exist and, in fact, many previous authors did not describe exactly how these days were dealt with. We chose to categorize patients who remained comatose (RASS <-3) for more than 48 hours after cessation of sedation as delirious, because we felt that coma represents a state of severe 'brain failure' that forms a continuum with delirium. This approach is similar to what has been done in previous studies.[58,59] However, in contrast to these authors, we chose to categorize patients who were unresponsive due to continuous sedation (or those who were within 48 hours of stopping a sedative infusion) as non-delirious because we felt that doing otherwise would introduce bias against surgical patients who remain frequently sedated for at least the first hours of their stay.[52] Furthermore, we assumed that most patients with true delirium would be detected after cessation of sedation after all, which would result in only a minor error with respect to the timing of delirium onset (rather than risking a major error of misclassifying patients as delirious when in fact they were receiving sedation for an unrelated but legitimate reason). In our sensitivity analyses we addressed any possible misclassification error with respect to timing of delirium onset in sedated patients by using a first valid observation carried backward approach and found very similar results.

Despite the fact that we did not find an association between delirium and increased ICU mortality, delirium remains an important clinical syndrome in critically ill patients and should be prevented or treated whenever possible.[60] Delirium is very distressing to both patients and their relatives,[61] it generates significant costs,[62] may have severe long-term consequences such as cognitive impairment[63] and could cause long-term mortality.[42] These latter studies might however have suffered from the same bias, i.e., failing to adjust for the evolution of disease severity prior to delirium onset. Most importantly, sensitivity analyses indicated that episodes of severe, persistent delirium may still be associated with an increased risk of death in the ICU by day 30, despite our overall finding of no association with delirium of any duration. The possible causal mechanisms for this association are incompletely understood, but may include autonomic dysregulation causing hypotension and subsequent organ failure, immune-modulatory effects causing increased susceptibility to infections, and excessive stress responses causing increased corticosteroid production.[5,64-69] Notwithstanding, the absolute risk increase of 2.0% following the onset of persistent delirium would translate into a number needed to treat of more than 50, even if we were able to effectively prevent this complication by an intervention of some sort. Furthermore, since this finding was based on post-hoc analyses, these observations need to be confirmed in other cohorts of critically ill patients.

CONCLUSION

To our knowledge, this is the first study to estimate delirium-associated mortality in critically ill patients using a counterfactual analysis that incorporates correction for variations in disease severity prior to delirium onset. Using this approach, the absolute attributable short-term mortality associated with a delirium episode in the ICU (of any duration) was much lower than previously suggested. Future studies should focus on episodes of persistent delirium and its long-term sequelae rather than on acute mortality.

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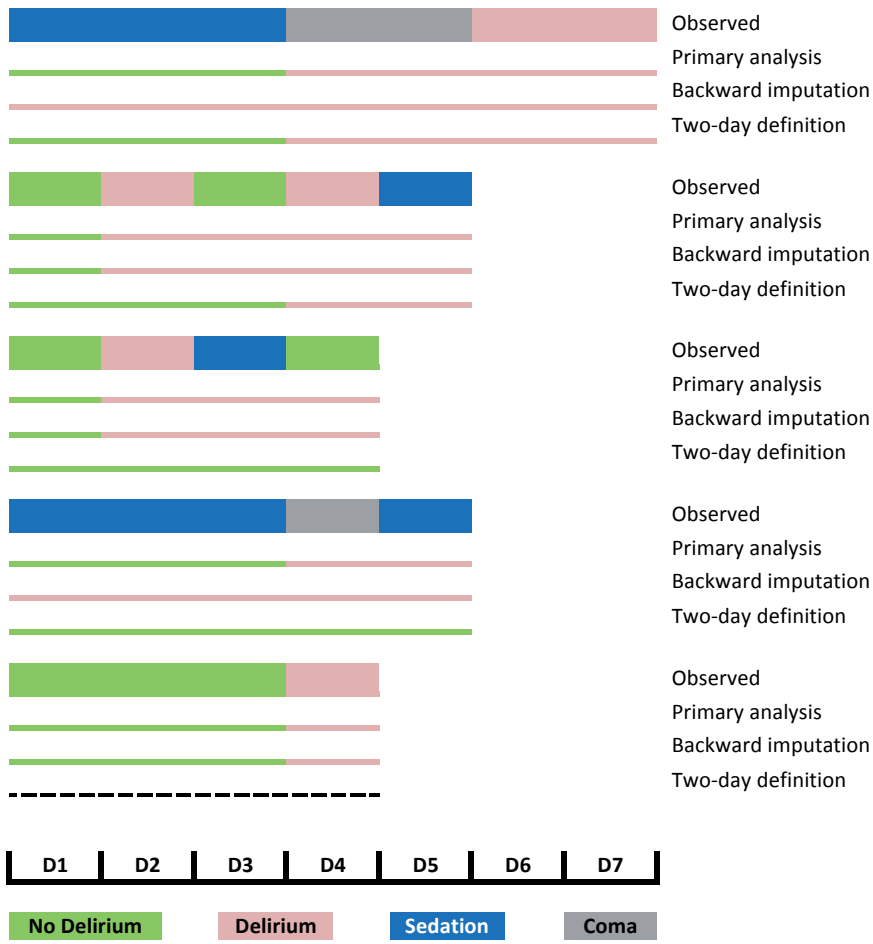
SUPPLEMENTARY DATA

Figure E1. Reclassification of sedation and coma days in the various sensitivity analyses



This figure shows the reclassification of sedation and coma days in six hypothetical patients using various definitions of delirium. 'Observed' denotes the original scoring. The dotted line denotes the exclusion of the patient from that particular analysis. D1 – D7 = ICU observation Day 1 to Day 7.

Table E1. Estimates of delirium-associated ICU mortality using various definitions of delirium

Primary analysis

Whole cohort (n=1112)	
1. Logistic regression	1.77 (1.15-2.72)
2. Competing risks survival regression	2.08 (1.40-3.09)
3. Marginal structural model	1.19 (0.75-1.89)

Sensitivity analyses

Backward imputation of sedation days (n=1112)[a]	
1. Logistic regression	1.77 (1.15-2.72)
2. Competing risks survival regression	1.74 (1.16-2.61)
3. Marginal structural model	0.86 (0.56-1.33)
Observed delirium for at least 2 days (n=1095)[b]	
1. Logistic regression	2.02 (1.34-3.03)
2. Competing risks survival regression	2.15 (1.50-3.09)
3. Marginal structural model	1.67 (1.13-2.47)

All models were adjusted for baseline variables (age, gender, Charlson co-morbidity index, acute physiology and chronic health evaluation (APACHE) IV score, admission type, and sepsis on admission). The marginal structural model was furthermore adjusted to time-varying variables: sequential organ failure assessment (SOFA) score, sepsis status, temperature, sodium, urea concentration, acidosis, hematocrit, mechanical ventilation and sedative and analgesic medications. The logistic regression analysis returns the odds ratio (OR) and the survival analysis and marginal structural model return the subdistribution (SHR) hazard ratios. Delirium was included as a time-dependent variable in the competing risks survival regression and marginal structural models. [a]Sedated patients were reclassified based on the first available valid delirium assessment following the cessation of sedation, using backward imputation, [b]Patients were classified as being exposed when they had at least two consecutive days of positive CAM-ICU screening. These patients were compared to all other patients. Patients with one day of delirium before discharge or death were excluded. Patients having delirium before sedation or coma and awakening with delirium were classified as delirious.

Table E2. Estimates of delirium-associated intensive care unit mortality in subgroups

Statistical model	Sepsis[a] (n=496)	No sepsis[a] (n=616)
1. Logistic regression	1.95 (1.31-2.90)	3.27 (1.62-6.62)
2. Competing risks survival regression	1.52 (0.95-2.42)	3.64 (1.91-6.94)
3. Marginal structural model	1.32 (0.81-2.17)	1.44 (0.68-3.03)
	APACHE > 80 (n=414)	**APACHE <80 (n=698)**
1. Logistic regression	1.44 (0.83-2.48)	2.00 (0.98-4.05)
2. Competing risks survival regression	1.78 (1.10-2.87)	2.37 (1.24-4.52)
3. Marginal structural model	1.51 (0.91-2.51)	1.38 (0.67-2.86)

All models were adjusted for baseline variables (age, gender, Charlson co-morbidity index, acute physiology and chronic health evaluation (APACHE) IV score, admission type, and sepsis on admission). The marginal structural model was furthermore adjusted to time-varying variables: sequential organ failure assessment (SOFA) score, sepsis status, temperature, sodium, urea concentration, acidosis, hematocrit, mechanical ventilation and sedative and analgesic medications. The logistic regression analysis returns the odds ratio (OR) and the survival analysis and marginal structural model return the subdistribution (SHR) hazard ratios. Delirium was included as a time-dependent variable in the competing risks survival regression and marginal structural models. [a]At ICU admission.

PART IV

Summary and General Discussion

9

In part based on:

Irene J. Zaal, Arjen J.C. Slooter
Light levels of sedation and DSM-5 criteria for delirium.
INTENSIVE CARE MEDICINE 2014; 40(2):300-301

John W. Devlin, Irene J. Zaal, Arjen J.C. Slooter
Clarifying the confusion surrounding drug-associated delirium in the ICU
CRITICAL CARE MEDICINE 2014;42(6):1565-66.

SUMMARY

In this thesis we have examined risk factors for delirium in the intensive care unit (ICU) and the association between delirium and mortality during ICU admission. With this focus, the studies described in this thesis aimed to contribute to a better understanding of the causation of this complex syndrome and to guide design of future research as well as prevention and treatment strategies.

Chapter 2 provides a literature overview of delirium, deliberating on the incidence, diagnosis, pathophysiology and management of delirium in critically ill patients. As there were still many gaps in the knowledge of delirium in the ICU, a large, observational cohort study at the ICU of the University Medical Center Utrecht (UMCU) was conducted. This large patient cohort, consisting of 1112 consecutively admitted adults without neurological comorbidity, provided us with the clinical data for chapter 3, 5, 6 and 8.

First, in chapter 3 a description of the patient cohort was presented, including the newly developed and validated algorithm to daily classify a patient's mental status in the past 24 hours, which was used during the study period. In the algorithm the Confusion Assessment Method for the ICU (CAM-ICU) by bedside nurses, the start of delirium treatment by ICU physicians, a chart review and a CAM-ICU assessment by researchers was incorporated, to classify patients as: 1) coma, 2) delirium, 3) awake without delirium during the preceding day. The algorithm showed excellent test characteristics when compared to a team of delirium experts who used the Diagnostic Statistical Manual (DSM) for Psychiatric Disorders, revised version IV, with sensitivity 0.75, specificity 0.83 and high inter-observer agreement with Fleiss' kappa ranging from 0.94-0.97. In our cohort, delirium was common with an incidence of 48%. Of the patients that developed delirium, in 43% the delirium episode lasted one day compared to the remaining delirious patients with either prolonged delirium or multiple episodes of delirium.

The systematic review in chapter 4 identified that the evidence supporting determinants for being risk factors for delirium in the ICU was sparse. Among 33 studies included in this systematic review, for only 11 risk factors a moderate or strong level of evidence was identified. Subsequently, the search for iatrogenic, modifiable, risk factors continued in chapter 5, 6 and 7.

In chapter 5, it was shown that a higher anticholinergic drug exposure at ICU admission affected the incidence of delirium. Moreover, the association of higher

anticholinergic load and delirium onset was modified by age and the presence of sepsis; only in patients aged 65 years or older without severe sepsis at ICU admission the anticholinergic drug load was associated with an instanteneous risk of delirium onset.

For many years it has been believed that the administration of benzodiazepines provoke delirium in the ICU. However the evidence supporting this statement was inconsistent (chapter 4). Benzodiazepines are frequently used in patients admitted to the ICU for patient comfort and safety. In chapter 6, we showed an overall association between benzodiazepines and the transition from a non-comatose, non-delirious state towards delirium the next day. Our study is the first to appropriately differentiate between continuous infusion and intermittent administration of benzodiazepines and to account for the events that preclude delirium to be diagnosed (competing events), such as coma, ICU discharge or death. The association found seemed to be driven by continuous IV infusion of benzodiazepines and was not present for intermittent, bolus administration of benzodiazepines.

In chapter 7, a before-after design was used to study the relationship between two different ICU environments and the incidence and duration of delirium. It is believed that the ICU environment can be hazardous for the patient, with little privacy, a lack of natural daylight and continuous noise. In the ICU of the UMCU there was the unique opportunity to study the effects of the ICU environment, as the ICU moved from a ward-like ICU setting to a completely new build ICU with single-rooms. A difference in delirium duration was found, although the incidence proportion was similar between the two environments. This finding implicates that environmental factors are not the most important precipitating factors for the onset of delirium, but that they can attribute to the duration of delirium.

The remaining chapter of this thesis, chapter 8, concentrates on the short term mortality during ICU admission and delirium. This is important as previous investigations on this association did not account for the time-varying nature of disease severity and the competing event for death during ICU admission, namely, ICU discharge. We found that delirium itself did not attribute to death during ICU admission. However, patients with delirium are less likely to be discharged, exposing them, on average for longer period of time to the ICU with an everyday risk of dying. When specifying prolonged delirium (more than two days) this prolonged delirium did have a direct effect on attributable mortality. This is important as this prolonged delirium is common and may have a different prognosis than one-day delirium.

GENERAL DISCUSSION

While in this thesis risk factors for delirium were identified and the association between delirium and ICU mortality was explored, uncertainties about this complex syndrome remain. To study such a heterogeneous syndrome as delirium in a very heterogeneous patient population of critically ill patients, many assumptions have been made (see Table 1). Some of these assumptions have been challenged in this thesis, others will be discussed in the following sections.

Table 1. Common assumptions made in ICU delirium research

I	The delirium diagnosis can be reliably made as a dichotomous condition, independent of the assessor and the condition of the assessed patients
II	The incidence of delirium during ICU admission is not precluded by the incidence of different events (competing events)
III	Delirium has consistent features across the wide range of critically ill patients
IV	Delirium has similar consequences independent of its etiology

Delirium definition and diagnosis

Some conditions in ICU patients are clearly dichotomous, such as the presence or absence of endotracheal intubation. However, establishing the diagnosis of delirium is not so straightforward (assumption I). Delirium is a behavioral syndrome, which is always a manifestation of an underlying encephalopathy. For years it has been discussed whether delirium is a condition that exists as a separate entity to critical illness per se. There is the fundamental issue of what delirium 'really' means. In the end, this question considers the definition that is used to diagnose delirium. Delirium is being defined by the criteria of the Diagnostic Statistical Manual of Mental Disorders (DSM). In this thesis the revised fourth edition of the DSM (DSM-IV-R) has been used as the reference standard for delirium definition and diagnosis (Table 2).[1] Recently, the American Psychiatric Association adjusted the criteria for delirium in its fifth edition (DSM-5).[2] Compared to the DSM-IV-R, less emphasis has been put on a disturbance of consciousness (Table 2).

Despite the version of the DSM used, the criteria of the DSM are open to interpretation, and dependent on the skills and perspective of the assessor (assumption I). The assessor needs to have knowledge of the 'normal' behavior of the individual to

be able to recognize 'fluctuation', 'change' or 'disturbance'.[3] In the ICU, the aspects of neuropsychiatric examination are particularly difficult as the condition and treatment of the assessed patients often hampers delirium assessment (assumption I). Neuropsychiatric examination is to a large extent dependent on the use of language, but many ICU patients are unable to speak because of endotracheal intubation. Also, patients in the ICU often receive sedatives or analgesics impairing their attention span and level of consciousness. As many ICU patients are admitted after surgery or in an acute setting requiring immediate organ support, diagnosing delirium at ICU admission or gathering information about the baseline behavior or cognition is similarly challenging.

When looking at Table 2, in both editions of the DSM, a patient at a light level of sedation may fulfil the criteria for delirium. Also, in recent publications it has been argued that sedation confounds reliable detection of delirium when using current assessment tools.[4-6] For example, a low Richmond Agitation and Sedation Score (RASS) increases the likelihood to screen positive on the CAM-ICU and the Intensive Care Delirium Screening Checklist (ICDSC).[6-8] Both the CAM-ICU and the ICDSC were validated against the DSM-IV-R criteria and developed to be more applicable in the mechanically ventilated, critically ill patients. Both screening tools are recommended by the guidelines on pain, agitation and delirium of the Society of Critical Care Medicine.[9] It appears that the CAM-ICU has higher sensitivity compared to the ICDSC,[10] and in the ICU of the University Medical Center Utrecht (UMCU) the CAM-ICU was therefore chosen to be implemented in clinical practice. The delirium screening methods perform well in a research setting when compared to a reference team of delirium experts applying the DSM-IV-R criteria. Nevertheless, they failed to provide a reasonable negative predictive value when used in daily, routine practice.[11] The DSM criteria and DSM-IV-R-based screening tools seem therefore not to be that tailored to intubated, critically ill patients. Recently, a promising new approach for objective delirium detection was provided in postoperative patients after cardiothoracic surgery, using a limited number of electroencephalogram (EEG) electrodes.[12] Unfortunately, this method is not (yet) suitable for ICU patients because of different patient characteristics and the possible inference of sedation on the EEG signals.

Table 2. Criteria for delirium according to the Diagnostic and Statistical Manual (DSM)

Fourth, revised edition (DSM-IV-R)	
A.	Disturbance of consciousness (i.e., reduced clarity of awareness of the environment) with reduced ability to focus, sustain or shift attention.
B.	A change in cognition (such as memory deficit, disorientation, language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established, or evolving dementia.
C.	The disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
D.	There is evidence from the history, physical examination, or laboratory findings that the disturbance is caused by the direct physiological consequences of a general medical condition.

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of Mental Disorders; sedation effects are underlined

Fifth edition (DSM-5)

A. Disturbance in attention (i.e. reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).

B. The disturbance develops over a short period of time (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of the day.

C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuospatial ability, or perception).

D. The disturbances in criteria A and C are not explained by another pre existing, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as coma.

E. There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiologic consequence of another medical condition, substance intoxication or withdrawal (i.e. because of a drug of abuse medication), or exposure to a toxin, or is because of multiple etiologies.

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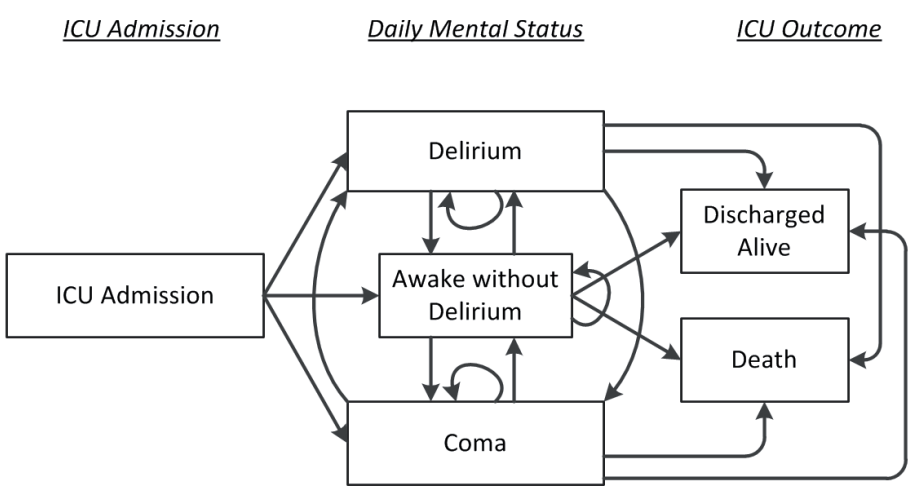
In chapter 3 of this thesis we validated an algorithm to make the daily mental status classification. Because of the limitations of the current screening methods, as listed above, we thought it was necessary for our research to use an additional method on top of the routine CAM-ICU screening in clinical practice. By incorporating the start of delirium treatment, a chart review and a CAM-ICU assessment by the researchers in our algorithm, the risk of missing any delirium was minimized.

The administration of sedatives and analgesics is common in critically ill patients to provide patient comfort and safety. Comatose status, for example due to deep sedation, precludes any delirium assessment according to the DSM-IV-R and DSM-5 criteria and thus the presence of delirium. The presence of coma on a particular day can therefore be considered a competing event for delirium (assumption II, figure 1). Also, when a patient without delirium so far, is being discharged or dies the next day, it is not possible anymore to develop delirium during the ICU admission. The two ICU outcome events of being discharged or death are also competing events of ICU delirium (assumption II, figure 1). When studying delirium it is therefore a necessity to account for these competing events in the statistical analyses to prevent overestimation of the risk of interest. In this thesis we used competing risk proportional hazard regression analysis (Chapter 5 and 8) and first-order Markov modelling within a multinomial logistic regression analysis (Chapter 6) to incorporate these competing events.

Figure 1. The possibilities of patients' daily mental status and ICU outcome



Clinical features, subtyping and outcome of delirium

In an effort to define and diagnose delirium one has to make the assumption that delirium has similar clinical features across the wide range of critically ill patients (assumption III). It seems plausible that different pathophysiological pathways, induced by a wide variety of factors, end up in a final common pathway of encephalopathy that presents as the behavioral syndrome of delirium. However, patients with delirium may differ in clinical presentation, and treatment response.[13] The identification of subtypes is a mechanism by which this variety can be accommodated within the unitary syndrome of delirium.[13] This subtyping can be performed by different approaches.

Motoric subtyping of delirium in critically ill patients

Most studies on subtyping delirium are based on different psychomotor features.[13] The, easy to recognize, hyperactive delirium, is characterized by agitation and psychomotor restlessness. Hypoactive delirium is marked by a slowing or lack of movement and apathy. In mixed delirium, patients alternate between hyper- and hypoactive expressions. The motor subtypes give the impression to be useful outside the ICU. However, their use has not been validated in the ICU and classifications made in the ICU in earlier investigations were mainly based on brief observations, which may not capture the usual fluctuations in delirium over time.[14,15] In previous studies in ICU patients the purely hyperactive form was found to be rare, with a frequency of 1% (ranging from 0-2%).[14,15] In our patient cohort of 1112 patients its frequency was even less. In 513 of the patients experiencing delirium a total of 790 delirium episodes occurred with a median (inter quartile range, IQR) duration of 2 (1-4) days. Of these 790 delirium episodes only 1 (0.1%) was purely hyperactive. ICU specific syndromes, such as ICU acquired weakness, and ICU specific symptoms, such as patient discomfort due to endotracheal intubation, could affect the subtyping of delirium based on motoric features. However, the difficulty with motoric subtyping of delirium in the ICU appears to be driven by the confounding effect of coma and sedation. Thus, coma and sedation not only affect the diagnosis of delirium, as explained above, but also influence the subtyping of delirium in motoric subtypes. It seems therefore that the use of motoric subtyping in critically ill patients is limited.

Subtyping of delirium in critically ill patients by delirium severity

Another approach to subtype delirium is based on delirium severity. One way could be to quantify the degree of hyperactive or hypoactive delirium, such as done in the Delirium Severity Index (DSI).[16] We used this approach in chapter 7 to evaluate differences in delirium severity between two different ICU environments. However, until now, no severity score for ICU delirium has been validated, as no universal criteria for the severity have been determined. With the absence of a reference standard, we decided not to use the DSI in subsequent studies.

One could also argue that the length of delirium refers to delirium severity or different etiology. In chapter 3 we described that 43% of the patients experiencing delirium during their ICU admission developed only a single, one-day episode, compared to 57% with either a prolonged (≥2 consecutive days) episode of delirium or multiple episodes of delirium. In many studies. impaired patient outcomes appear to be associated with delirium duration as opposed to simply the presence versus absence of delirium.[17-20] In a recent study, patients with rapidly reversible, sedation-related delirium (delirium that abates shortly after sedative interruption) had fewer ventilator days and hospital days and were more likely to be discharged home compared to those with persistent delirium (delirium that persists despite a short period of sedative interruption).[21] Moreover, in the same study, the patients with persistent delirium showed increases 1-year mortality.[21] In Chapter 8, a sensitivity analysis on delirium that persisted ≥2 consecutive days showed a population-attributable fraction of ICU mortality on day 30 due to delirium of 2.0% (95% confidence interval (CI): 1.2-2.8%), whereas the primary analysis on all delirium, revealed no population-attributable fraction of delirium on ICU mortality on day 30 (7.2%, 95% CI:-7.5–19.5%). Both studies suggest differences in patient outcomes between different subtypes of delirium (assumption IV), with prolonged delirium having more impact on patient outcomes than a short episode of delirium, or rapidly reversible delirium.

FUTURE PERSPECTIVES

Delirium subtyping in critically ill patients

With no adverse consequence on patient outcomes with short delirium, maybe we should not be that concerned of a single-day episode of delirium. With many patients

in the ICU encountering this short delirium, it seems to be more important to focus our attention to patients with prolonged delirium and treat any underlying condition. In chapter 3 we describe the difference in baseline characteristics between these two entities of delirium. Patients who developed one single-day delirium episode were younger and had a lower comorbidity score in general, but more cardiovascular risk factors such as hypertension and active smoking, and were more often admitted postoperatively when compared to patients with either prolonged or multiple delirium episode(s). The difference in etiology and possible prediction of short and prolonged delirium is important as one can only distinguish the two retrospectively, whereas the clinician needs a prospective view to be able to prevent or treat this delirium subtype.

Delirium in critically ill patients usually results from a multitude of factors including inflammation, multi-organ failure, metabolic disturbances and medication effects. The interaction of different etiologies makes it difficult to identify to which factor delirium can be attributed. Though, subtyping delirium based on etiology would would ease treatment strategies. Future studies should aim to further unravel the complex etiology of delirium in the ICU.

In identifying possible risk factors for delirium in critically ill patients

In chapter 4, 5, 6 and 7 we aimed to identify risk factors for delirium that are iatrogenic (i.e. consequence of medical treatment or advice) and modifiable (i.e. that can be influenced). In the search for possible risk factors for delirium many questions remain. As many factors attributing to delirium in critically ill patients cannot be influenced, it is crucial to focus on those factors that are modifiable, and even more on modifiable factors that are iatrogenic. After all, as medical professionals we vow to do no harm to our patients.

Identifying medication that is deliriogenic can be important when alternatives for these medication exist. Traditionally, sedation is often provided to mechanically ventilated patients, and these patients have been treated with benzodiazepines, propofol and opioids.[9,22] The use of non-benzodiazepine sedatives are associated with improved ICU patient outcomes, including a shortened duration of mechanical ventilation, ICU and hospital length of stay and decreased incidence of long-term cognitive dysfunction, compared to the use of benzodiazepines.[23-25] For example, the use of dexmedetomidine, a potent alpha-2-adrenergic receptor agonist, was found to decrease the number of delirium days, compared to either sedation with lorazepam, midazolam or morphine (chapter 2).[23-25]

In this thesis a high anticholinergic drug load at ICU admission was identified as a risk factor, but it is still not known to what extent a daily anticholinergic drug load attributes to the transition from non-comatose, non-delirious state towards delirium the next day. Also, the evidence for opioids and/or pain as risk factors for delirium is inconsistent. Most critically ill patients will experience pain during their ICU stay, but many are unable to self-report because of an altered level of consciousness or endotracheal intubation. Opioids are used to treat pain, however they influence patients' level of consciousness and therefore interfere with the diagnostic criteria for delirium themselves. Further research on this subject should evaluate the association of pain and opioids with delirium, using a standardized protocol for pain monitoring (using self-reported pain and behavioral pain scales in patients unable to self-report), preemptive analgesics in invasive and potential painful procedures and standardized pain treatment.

Although this thesis identified risk factors, it remains to be studied whether diminished exposure to these risk factors, by risk reduction strategies, results in less delirium and improved patients outcomes. Moreover, when deliriogenic medication is stopped, it may be unclear whether a delirious patient will benefit from ceasing the deliriogenic drug or will deteriorate because of worsening of the underlying condition for which this medication had been started. Future intervention studies are needed to evaluate the impact of risk reduction strategies.

As delirium was studied in this thesis as one entity, it could be that for different etiologic subtypes of delirium the effects of the risk factors are larger or smaller. Chapter 5 provides an example, with the largest association of anticholinergic drug load with delirium onset found in the subgroup of patients aged 65 years or over, without severe sepsis at ICU admission. Future research should evaluate the influence of age, inflammation (sepsis) and anticholinergic drug separately from each other and combined to further evaluate the hypothesis that sepsis and older age attenuate the cholinergic system.[26]

Other future perspectives for delirium research in critically ill patients

This thesis has focused on the population based risk factors for delirium in critically ill patients. For example, in general, the daily administration of continuous IV benzodiazepines increases the risk of delirium the next day in a general critically ill patient. This thesis does not provide answers to a clinician who wants to know whether in a particular patient the continuous infusion of benzodiazepine will impose delirium

the next day. Preferably, for every patient the risk for developing delirium should be known and made available by prediction models (daily or at ICU admission). Ideally even, the same (statistical) framework can be used to identify which factors maintain delirium, providing the clinician with the etiologic fraction of the different risk factors and supplying him/her with specific targets for treatment strategies. Hence, for a better understanding of delirium and treatment options, it is also important to know which factors cause the delirious patients transitioning from a delirious state to an awake state without delirium.

Further research should explore differences in patients' outcome between patients with delirium of short duration and those with prolonged delirium, but also evaluate patients with recurrent episodes. In chapter 3 of this thesis we found that in 28% of the patients with delirium during ICU stay, another episode of delirium develops. Using similar techniques as used in chapter 8 of this thesis, differences in patient outcomes and ICU mortality should be explored between patients with prolonged or multiple episodes of delirium and those patients where delirium occurred only once during ICU admission in a one day episode. It is also of interest to know which factors make an individual more prone to this recurrence of delirium. It could be plausible, as in other psychiatric diseases such as affective disorders, that the likelihood of subsequent episodes increases with every new episode.[27] Joint frailty models can be applied to model recurrent delirium episodes taking into account this individual degree of vulnerability (frailty) for developing delirium, and the competing events of recurrent delirium episodes (coma, ICU discharge and death).

CONCLUSIONS

To study the etiology of delirium in ICU patients, we incorporated different statistical methods to account for competing events, the time varying nature of delirium and the evolution of disease during ICU admission. The work presented in this thesis can be considered an important step forward to characterize the epidemiology of delirium in critically ill patients. However, we are still far from thorough comprehension of this complex syndrome and from knowing to what extent risk reduction strategies for delirium delay onset, decrease duration or most importantly, improve patient outcomes.

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Nederlandse Samenvatting

SAMENVATTING

Delirium, ook wel delier genoemd, is een plotseling optredende verwardheid die gekenmerkt wordt door een aandachtsstoornis. Andere symptomen zijn hallucinaties, waanbeelden, onrust, agressie of slaperigheid. Per definitie wordt delirium veroorzaakt door een onderliggende lichamelijke ziekte, bijvoorbeeld een infectie. De plotselinge verwardheid van een delirium is tijdelijk, al kan de duur van de periode wisselen van enkele uren tot dagen of, in enkele gevallen, zelfs maanden. Omdat patiënten die op een Intensive Care (IC) liggen ernstig ziek zijn, werd delirium vroeger als onvermijdelijk gezien. Daarnaast werd verondersteld dat een delirium volledig verdwijnt bij verbetering van de lichamelijke conditie van de patiënt. Uit onderzoek blijkt echter dat het doormaken van een delirium tijdens een verblijf op de IC is gerelateerd met complicaties en negatieve uitkomsten voor de patiënt zoals een langere opnameduur in het ziekenhuis of verminderd cognitief functioneren na ontslag uit het ziekenhuis. Het is dus belangrijk om delirium te herkennen en om het optreden van delirium te voorkomen.

Delirium kan alleen worden voorkomen als we kunnen doorgronden waarom het delirium ontstaat. Uit eerdere onderzoeken weten we dat iedere patiënt delirium kan ontwikkelen, maar dat sommige patiënten er meer vatbaar voor zijn dan anderen doordat zij bepaalde risicofactoren hebben. Een aantal van die risicofactoren zijn niet te veranderen, zoals een hogere leeftijd of het hebben van geheugenstoornissen. Andere factoren kunnen wel worden beïnvloedt, zoals het vermijden van bepaalde medicijnen die delirium kunnen uitlokken. Het doel van dit proefschrift was om risicofactoren voor delirium te identificeren en om de relatie van delirium met het overlijden tijdens een IC-opname nader te evalueren. In de volgende alinea's worden de resultaten van de verschillende onderzoeken besproken.

In hoofdstuk 2 van dit proefschrift wordt een algemene inleiding over delirium gegeven, waarbij de meetinstrumenten voor screening en diagnostiek en het voorkomen en de behandeling van delirium op de IC worden besproken. Het evalueren van de aanwezigheid van een delirium op de IC wordt bemoeilijkt doordat veel mensen niet kunnen communiceren; veel patiënten zijn in een (kunstmatig) coma of worden beademd waarbij er een beademingsbuis langs de stembanden wordt geschoven waardoor men niet kan spreken. Om het vaststellen van delirium makkelijker te maken zijn er

verschillende screeningsmethoden ontwikkeld waarbij door middel van vragenlijsten zowel de aandacht en het bewustzijn van de patiënt, alswel de inhoud en vorm van zijn/haar gedachten worden getoetst. Met de hulp van deze vragenlijsten wordt delirium veel beter herkend, met name als deze screening wordt gedaan door mensen die veel ervaring hebben met delirante patiënten. Echter, als de screening wordt toegepast in de dagelijkse praktijk wordt in 50% van de evaluaties het aanwezige delirium niet herkend. Daarnaast is de screening slechts een korte momentopname, terwijl de symptomen van delirium sterk kunnen wisselen gedurende de dag. In hoofdstuk 3 wordt een algoritme gepresenteerd dat gevolgd kan worden om, in 5 stappen, elke patiënt op de IC in te kunnen delen als: 'wakker en niet delirant', 'delirant' of 'in coma' tijdens de afgelopen 24 uur. Met deze classificatie kan een delirium dat ergens op de dag aanwezig was goed worden vastgesteld: in 75% van de gevallen dat delirium aanwezig was (beoordeeld door een delirium expert-team bestaande uit een psychiater, neuroloog en geriater) werd dit ook vastgesteld door het algoritme (sensitiviteit), en in 83% van de gevallen dat delirium niet aanwezig was (ook beoordeeld door het delirium expert team) werd ook geen delirium vastgesteld door het algoritme. Gedurende een periode van 2.5 jaar zijn alle patiënten die langer dan 24 uur opgenomen waren op de IC van het Universitair Medisch Centrum (UMC) Utrecht en die geen neurologische afwijkingen hadden dagelijks geclassificeerd op de aanwezigheid van delirium. De hoofdstukken 3, 5, 6 en 8 zijn gebaseerd op deze patiëntengroep die uiteindelijk 1112 IC-patiënten omvat. In 48% van deze patiënten trad delirium op tijdens de IC-opname. In 43% van de delirante patiënten trad delirium slechts eenmaal op, met een duur van maximaal 1 dag. Deze laatste groep van delirante patiënten had andere karakteristieken (zoals een lagere leeftijd) in vergelijking met delirante patiënten die meerdere delirium episodes hadden en/of waarbij het delirium langer dan 1 dag duurde.

Deel 2 van dit proefschrift richt zich op het identificeren van risicofactoren voor delirium op de IC. Allereerst biedt hoofdstuk 4 een literatuuroverzicht waarin de bewijslast van mogelijke risicofactoren voor delirium in de IC-patiënt is samengevat. In 33 artikelen werd voor slechts 11 factoren een sterke of middelmatige bewijslast gevonden dat zij delirium op de IC uitlokken. Derhalve is de zoektocht naar de beïnvloedbare risico factoren gecontinueerd in de hoofdstukken 5, 6 en 7. Mogelijk is een verstoring van neurotransmittersystemen in de hersenen, met name in het cholinerge systeem, een onderliggend mechanisme voor het ontstaan van delirium. Het cholinerge systeem is betrokken bij leer- en geheugenprocessen, welke beide gestoord

zijn tijdens delirium. Medicijnen met een anticholinerge werking geven een blokkade van cholinerge receptoren in het brein waardoor er een tekort aan acetylcholine ontstaat. In hoofdstuk 5 laten we zien dat een patiënt die bij opname op de IC meer medicijnen gebruikt met anticholinerge (bij)werking een hogere kans heeft om delirium tijdens de IC-opname te ontwikkelen. Deze relatie tussen anticholinerge medicijnen en delirium lijkt te worden beïnvloed door leeftijd en de aanwezigheid van een ernstige sepsis (bloedvergiftiging). Hoewel de patiënten van 65 jaar en ouder die een ernstige sepsis hebben bij IC-opname het vaakst delirium lijken te ontwikkelen, draagt alleen in de subgroep 'patiënten van 65 jaar of ouder zonder ernstige sepsis' het gebruik van medicijnen met een anticholinerge werking bij aan een hogere kans op delirium.

In hoofdstuk 4 wordt beschreven dat de bewijslast voor de relatie tussen delirium en het toedienen van benzodiazepines niet consistent is. Benzodiazepines zijn medicijnen (GABA-agonisten) die de gevoeligheid van receptoren voor de neurotransmitter gamma-aminoboterzuur (GABA) verhogen waardoor een demping van de activiteit van het centrale zenuwstelsel wordt veroorzaakt wat zich uit in slaperigheid, verslechterde coördinatie, afgenomen concentratie en vergeetachtigheid. Bij IC-patiënten wordt veel gebruik gemaakt van benzodiazepines als slaap- en kalmeringsmiddelen. In hoofdstuk 6 is de relatie tussen benzodiazepines en delirium verder onderzocht en wordt aangetoond dat het toedienen van benzodiazepines bij IC-patiënten die wakker zijn zonder aanwezigheid van een delirium, een hogere kans geeft op het hebben van een delirium de dag daarna. In deze studie hebben we in de statistische analyse rekening gehouden met concurrerende risico's voor het ontstaan van delirium (immers, als mensen in coma zijn, ontslagen worden, of komen te overlijden de dag erna, kunnen zij geen delirium meer hebben) en hebben we onderscheid gemaakt tussen eenmalige toediening of continue toediening via het infuus, waarbij de relatie alleen werd gevonden bij de laatste toedieningsvorm. Aangezien er alternatieven bestaan voor benzodiazepines, moet dit verhoogde risico op delirium in het vervolg worden meegenomen in de beslissing om wel of geen continue toediening van benzodiazepines te geven aan een patiënt.

Men veronderstelt dat het verplegen van patiënten in een IC-omgeving, met veel licht en geluid, gebrek aan oriëntatiepunten, het ontbreken van ramen en een gebrek aan privacy, delirium kan uitlokken. Op de IC in het UMC Utrecht deed zich een unieke situatie voor om dit nader te bekijken omdat er een nieuw Intensive Care centrum werd gebouwd op het dak van het ziekenhuis. Met de bouw van dit IC-centrum is getracht een zo patiënt- en bezoekersvriendelijke omgeving te creëren met zo min mogelijk negatieve

prikkels voor de patiënt en meer blootstelling aan natuurlijk daglicht middels grote ramen. In hoofdstuk 7 is er in de periode voor en na de verhuizing van de IC gekeken hoe vaak delirium voorkwam en hoe lang het eventuele delirium aanwezig was. In de nieuwe IC-omgeving kwam delirium niet minder vaak voor, maar duurde het wel korter. Deze bevindingen laten zien dat de verpleegomgeving bij ernstige zieke IC-patiënten misschien niet delirium uitlokt, maar dat dit wel degelijk kan bijdragen aan de duur van een delirium.

Zoals eerder genoemd wordt delirium vaak geassocieerd met negatieve uitkomsten voor de IC-patiënt. In deel 3 (hoofdstuk 8) van dit proefschrift is de relatie tussen delirium en overlijden op de IC nader onderzocht. In de literatuur wordt soms wel een 2-3 keer verhoogd sterfterisico beschreven indien tijdens de IC-opname een delirium optreedt. In deze onderzoeken werd er echter in de statistische analyse geen rekening gehouden met de concurrerende risico's voor delirium, of met beloop van de ziekte-ernst gedurende de IC-opname. In onze analyses hebben we met deze factoren wel rekening kunnen houden. Onze resultaten laten zien dat het delirium zelf geen directe relatie heeft met overlijden tijdens de IC-opname, maar dat patiënten met een delirium minder snel ontslagen worden van de IC. Hierdoor liggen zij langer op IC en lopen zij langer het risico op het krijgen van een IC-complicatie of om te overlijden tijdens IC-opname. Opvallend was dat een delirium van twee dagen of langer wel een direct effect had op het IC sterfterisico. Aangezien in 57% van de delirante patiënten het delirium langer dan 1 dag duurt of vaker voorkomt is dit een belangrijke bevinding.

Tot slot worden in hoofdstuk 9 de onderzoeken die in dit proefschrift zijn gepresenteerd in een breder perspectief geplaatst. Allereerst worden de haken en ogen rondom de definitie en diagnosestelling van delirium bij IC-patiënten besproken. Zo impliceert een definitie dat het wel of niet hebben van delirium eenduidig is vast te stellen, terwijl dit bij IC-patiënten helemaal niet zo makkelijk is. Zo kunnen we bij een patiënt in coma de aanwezigheid van delirium niet bevestigen en kunnen patiënten die ontslagen worden van de IC of komen te overlijden geen delirium meer ontwikkelen. Met deze concurrerende risico's voor delirium (coma, ontslag, overlijden) moet rekening gehouden worden in vervolgonderzoek naar delirium bij IC-patiënten.

Omdat we de achterliggende mechanismen die tot delirium leiden nog niet hebben doorgrond gaan we er van uit dat delirium bij elke patiënt hetzelfde is. In hoofdstuk 9 wordt dieper ingegaan op de zin en onzin van het onderverdelen van delirium in verschillende subtypen, waarbij de onderverdeling in hypo-actief, hyperactief en mixed

(zowel hypo- als hyperactief) op de IC slecht toepasbaar lijkt door het veelvuldig gebruik van slaap- en kalmeringsmiddelen. Door onder andere de bevindingen uit hoofdstuk 3 en 8, lijkt het er op dat delirium van 1 dag anders is dan delirium dat langer duurt. Een suggestie is dat vervolgonderzoek zich meer concentreert om de risicofactoren en de achterliggende mechanismen van het langer durende IC-delirium te doorgronden.

CONCLUSIES

In dit proefschrift zijn meerdere risicofactoren voor delirium geïdentificeerd (anticholinerge medicatie, benzodiazepines en IC-omgeving). Daarnaast lijkt delirium zelf niet direct geassocieerd met een verhoogde kans op overlijden tijdens de IC-opname. Met dit proefschrift zijn belangrijke stappen gemaakt in ons begrip van delirium op de IC, echter de zoektocht naar uitlokkende factoren moet worden gecontinueerd. Of bij het vermijden van deze risicofactoren delirium daadwerkelijk minder vaak optreedt en of dit de uitkomst voor patiënten verbetert zal verder vervolgonderzoek moeten uitwijzen.

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About the author

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*both authors contributed equally to the manuscript

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CURRICULUM VITAE

I.J. (Irene) Zaal was born on June 6th 1985 in Veghel and grew up in Made, the Netherlands. After graduating from secondary school (Sint Oelbert gymnasium, Oosterhout, Noord-Brabant), she started Medical School at the University of Groningen. During her studies, she worked (unsalaried) at Disha Special School and Autism Centre in Vadodara (India). She was a board member (secretary, 1 year period) of the Foundation Groninger Studenten Cabaret and co-founded the Foundation Annual Benefit Dinner at the Isala Klinieken, Zwolle, of which she was a board member (treasurer, 1 year period). During one of her interships she worked at Magunga Hospital, Korogwe (Tanzania).

In 2010, she started her research on delirium in critically ill patients as part of a research internship under supervision of dr. A.J.C. Slooter, prof. dr. J. Kesecioglu and prof. dr. D. van Dijk, at the Department of Intensive Care Medicine, University Medical Center (UMC), Utrecht. After her graduation from Medical School in 2011 she started her residency at the Department of Intensive Care Medicine at Hospital Gelderse Vallei, Ede. In November 2011 she returned to the UMC, Utrecht, for continuing her research project on delirium. During her PhD project, she worked for several months as a resident in the department of Intensive Care Medicine, UMC, Utrecht and completed the master of Clinical Epidemiology at the University of Utrecht.

In September 2014, Irene started her residency training in Anesthesiology under supervision of dr. R.G. Hoff at the UMC, Utrecht. As a resident, she is a member of the medical ethics committee, UMC, Utrecht.