BRAIN DYSFUNCTION
IN CRITICAL CARE PATIENTS

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For reasons of consistency within this thesis, some terms have been standardized throughout the text. As a consequence the text may differ in this respect from the articles that have been published.

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BRAIN DYSFUNCTION
IN CRITICAL CARE PATIENTS

Hersendysfunctie in kritiek zieke patiënten

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof.dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op

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door

Annemiek Elise Wolters

geboren op 22 september 1987 te Enschede.

Promotor:	Prof. dr. D. van Dijk
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	Dr. D.S. Veldhuijzen

TABLE OF CONTENTS

1

GENERAL INTRODUCTION

BACKGROUND

Each year, approximately 80,000 critically ill patients are admitted to an intensive care unit (ICU) in the Netherlands.[1] On average, 15–20% of these critical care patients will die during their ICU admission.[1] Although this number is high, mortality rates are decreased considerably as compared to a decade ago (the standardized mortality ratio was 0.70 in 2013, compared to data from 2005).[1] The increase in survival probability of critical care patients testifies of the progress made in intensive care medicine.[1,2] Notwithstanding the fact that this decrease in mortality is positive, the growing number of ICU survivors poses a new challenging problem; the presence of long-term morbidity after ICU stay.[3,4] Many former ICU patients appear to experience a substantial amount of morbidity, characterized by physical problems and brain dysfunction (e.g., cognitive impairment and mental health problems). These morbidities are currently summarized as the postintensive care syndrome (PICS) by the Society of Critical Care Medicine, to increase clinical awareness for these morbidities.[5,6] To sufficiently address the problem of PICS, more insight is needed into risk factors for this heterogeneous syndrome. For research purposes, it is therefore important to describe and address the multifaceted dimensions of PICS as individual entities again; physical problems, cognitive impairment and mental health problems after critical illness.

One of the factors that seems to be associated with worse long-term outcome in critical care patients is the occurrence of a delirium during ICU stay, as it is associated with longer hospital stay, higher mortality, and long-term cognitive impairment.[7] ICU delirium is a form of brain dysfunction during critical illness. It is not a disease, but rather a syndrome consisting of a set of clinical features, characterized by a disturbance in consciousness and cognition that develops over a short period of time and, by definition, is a direct physiological consequence of a medical condition.[8] Affecting approximately 50% of all patients who stay in the ICU for more than 24 hours, it is the most often observed organ dysfunction in critical care patients.[7] The mechanisms by which delirium might lead to cognitive impairment have not been elucidated yet. Also, whether ICU delirium is associated with other long-term symptoms of brain dysfunction such as mental health problems is unclear. These remaining issues emphasize the need for further research on the association between ICU delirium and long-term brain dysfunction outcomes.

Despite its high occurrence and apparent associated morbidity, much about the etiology of delirium has not been clarified yet.[9] Risk factors for delirium can be either prognostic (i.e., associated but not causing delirium) or etiological (i.e., causing delirium). For unraveling the pathophysiology of delirium, identifying the etiological risk factors for

delirium is of major importance. Recognized key components of the etiology of delirium are direct brain insults, and aberrant reactions in response to certain stressors (further described below).[10] As delirium is undoubtedly multifactorial, these components are not mutually exclusive, and factors are likely to coexist and interact with each other.

Direct brain insults leading to delirium can be deprivation of energy supply to the brain, metabolic abnormalities, and the direct effect of medications.[10] As an example of the latter, anticholinergic medication might increase delirium risk as these medication can cause significant alteration in the cholinergic system and one of the key factors for delirium is proposed to be cholinergic deficiency.[10,11] Secondly, in response to physical or psychological stressors, several pathways are activated. Two of these pathways have been suggested to be involved in the development of delirium – activation of inflammatory processes (with the associated sickness behavior response) and stimulation of the hypothalamic-pituitary-adrenal axis (HPA axis).[10] In healthy conditions, these responses are adaptive, but in certain situations these responses can react abnormal. A maladaptive sickness behavior response might result from abnormally high levels of inflammatory signaling (e.g., during critical illness), or an exaggerated response of the target tissue to normal levels of inflammation (e.g., as a consequence of ageing, microglia in the brain can become hypersensitive to stimulation).[10,11] The maladaptive sickness behavior response might clinically manifest itself as a delirium.[10,11] Alongside the inflammatory aberrant response, delirium might also result from dysfunction of the HPA axis due to imbalanced feedback mechanisms.[10,11] This imbalanced activity of the HPA axis is for example seen in patients receiving corticosteroids, and in certain patients with a history of psychopathology, which may therefore both be risk factors for delirium.[10] An interplay between these components, and presumably other factors as well, could possibly underlie the etiology of delirium. Additional insight is needed into these components and its interplay, to further understand the etiological mechanisms causing delirium.

OBJECTIVE OF THIS THESIS

The main objective of this thesis is to assess the association between delirium during critical illness and long-term brain dysfunction outcomes after critical illness (in this thesis; cognitive impairment and mental health problems). To achieve this objective, three aims are set (Box 1.1). First, potential risk factors for delirium are assessed, as the key to understanding the association between delirium and long-term brain dysfunction starts with a better understanding of the etiology of delirium during critical illness. Secondly, a general overview of the occurrence of long-term brain dysfunction after critical illness is given, to comprehend the magnitude of the problem of long-

term brain dysfunction outcomes after critical illness. Subsequently, the association between ICU delirium and long-term brain dysfunction is assessed.

Box 1.1 Aims of this thesis

- Evaluate potential risk factors for delirium during critical illness.
- Describe the occurrence of brain dysfunction after critical illness.
- Assess the association between delirium during critical illness and brain dysfunction after critical illness.

OUTLINE OF THIS THESIS

Part I of this thesis focuses on the search for etiological risk factors of delirium during critical illness. First, two iatrogenic factors that potentially increase the risk of delirium are studied – exposure to anticholinergic medication (chapter 2) and corticosteroids (chapter 3) during ICU stay. In chapter 2, the effect of systemic inflammation and ageing on the occurrence of delirium is also examined. Subsequently, psychopathology prior to ICU admission is explored as a potential predisposing risk factor for ICU delirium (chapter 4).

Part II of this thesis starts with a general overview of long-term brain dysfunction after critical illness, with an emphasis on cognitive impairment (chapter 5) and a focus on mental health problems (i.e., symptoms of anxiety, depression and posttraumatic stress disorder) experienced by former ICU patients and family members in chapter 6. In the following three chapters, an evaluation of the effect of ICU delirium on different long-term outcomes is given. The association between ICU delirium and long-term symptoms of anxiety, depression and posttraumatic stress disorder is assessed in chapter 7. In chapter 8, the relationship between ICU delirium and long-term mortality, health-related quality of life, and cognitive problems after ICU discharge is evaluated. In-depth assessment of the presumed association between ICU delirium and long-term cognitive problems is conducted in chapter 9, where the potential mediating effect of systemic inflammation is explored.

The final part of this thesis provides a summary of the main findings, which is followed by a general discussion on challenges and future perspectives of research that focuses on brain dysfunction in critical care patients (chapter 10).

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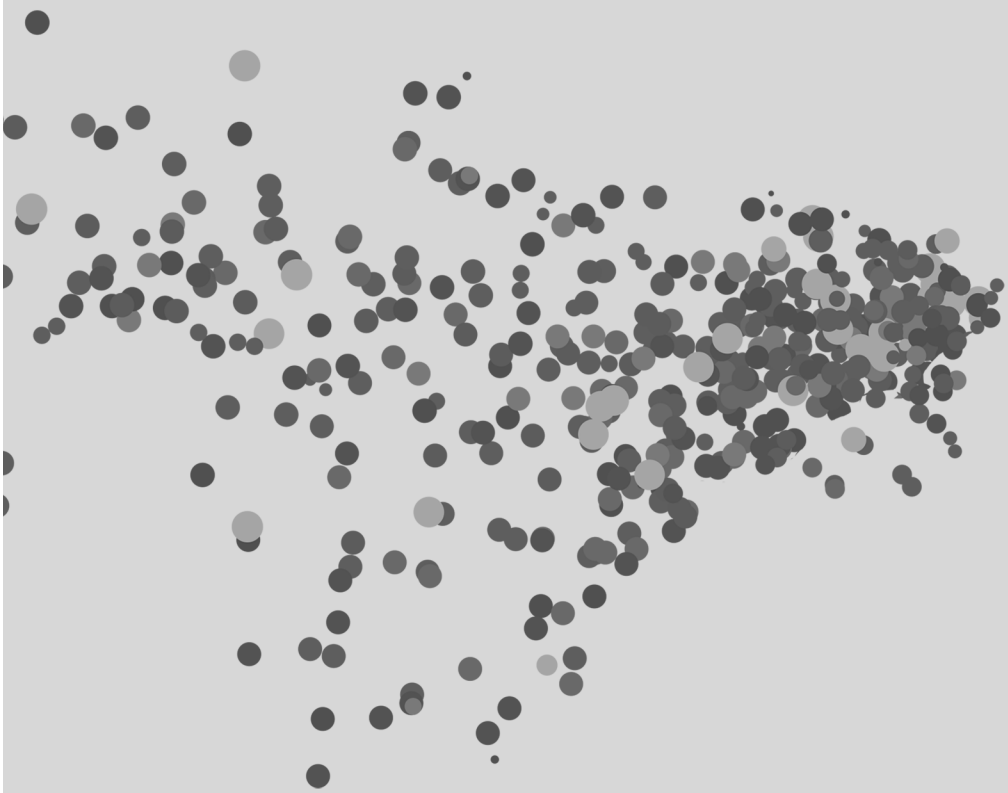

BRAIN DYSFUNCTION DURING CRITICAL ILLNESS

2

ANTICHOLINERGIC MEDICATION USE AND TRANSITION TO DELIRIUM IN CRITICALLY ILL PATIENTS

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Critical Care Medicine 2015;43(9):1846-1852

ABSTRACT

Objective

While cholinergic deficiency is presumed to increase delirium risk and use of medication with anticholinergic properties in the intensive care unit (ICU) is frequent, the relationship between anticholinergic medication use and delirium in this setting remains unclear. We investigated whether exposure to medication with anticholinergic properties increases the probability of transitioning to delirium in critically ill adults, and whether this relationship is affected by age or the presence of acute systemic inflammation.

Design

Prospective cohort study.

Setting

A 32-bed medical-surgical ICU at an academic medical center.

Patients

Critically ill adults admitted to the ICU for more than 24 hours without an acute neurological disorder or another condition that would hamper delirium assessment.

Interventions

None.

Measurements and Main Results

Daily anticholinergic burden was calculated for each patient based on the sum of the Anticholinergic Drug Scale (ADS) score for each medication administered. Daily mental status was classified as 'coma', 'delirium', or an 'awake without delirium' state. The primary outcome, the daily transition from an 'awake without delirium' state to 'delirium', was analyzed using a first order Markov model that adjusted for eight covariables. A total of 1,112 patients were evaluated over 9,867 ICU days. The daily median summed ADS score was 2 (interquartile range 1–3). The transition from being in an 'awake without delirium' state to 'delirium' occurred on 562 (6%) of ICU days. After correcting for confounding, a one unit increase in the ADS score resulted in a non-significant increase in the probability of delirium occurring the next day (odds ratio 1.05, 95% CI 0.99–1.10). Neither age nor the presence of acute systemic inflammation modified this relationship.

Conclusions

Exposure to medication with anticholinergic properties, as defined by the ADS, does not increase the probability of delirium onset in patients who are awake and not delirious in the ICU.

INTRODUCTION

Delirium is frequent among the critically ill and is associated with poor outcome.[1-3] Avoidance of risk factors for delirium remains the most important strategy to reduce the burden of delirium in intensive care unit (ICU) patients.[4,5] Disturbances in attention, a key clinical finding among any patient diagnosed with delirium, is regulated, in part, by the cholinergic neurotransmitter system.[6-8] A number of reports have therefore proposed cholinergic deficiency as being an important mechanistic cause for delirium occurrence.[7,9-12] Given the premise that use of a medication with anticholinergic properties will result in some degree of cholinergic deficiency and that the administration of medications with anticholinergic properties in the ICU is common, anticholinergic medication use may represent an important modifiable risk factor for delirium in the critically ill.[13-15]

Prior ICU studies attempting to evaluate the association between anticholinergic medication exposure and delirium occurrence have suffered from important methodological limitations and have yielded inconclusive results.[13-15] The likelihood of residual confounding is high due to the evaluation of small patient samples and the crude analysis methods that have been used.[13-15] Because of the time-varying nature of severity of illness, exposure to medication with anticholinergic properties, and delirium occurrence in the critically ill, it is essential to use time-dependent regression analyses when characterizing this relationship.[16] Furthermore, in previous studies neither the influence of age nor acute systemic inflammation were evaluated. This is important, as increased age and an acute inflammatory state each may lead to greater cholinergic neurotransmitter system dysfunction thus exaggerating the effect that anticholinergic medication exposure may have on delirium occurrence.[10] The aim of this study was to investigate whether exposure to medications with anticholinergic properties increases the daily risk of delirium occurrence in critically ill adults and whether this relationship is affected by age or the presence of acute systemic inflammation.

METHODS

Study design

This study was conducted as part of a prospective cohort study of consecutively admitted adult patients who stayed for at least 24 hours in the 32-bed medical-surgical ICU of the University Medical Center Utrecht (UMCU) between January 2011 and June 2013. Patients who had been transferred from an ICU at another hospital or with an acute neurological illness or condition with the potential to hamper delirium

assessment were excluded. The Medical Research Ethics Committee of the UMCU approved this study and waived the need for informed consent given the anonymity of data collection and the non-interventional nature of the study (protocol 12/421 and 10/056).

Mental status assessment

Level of sedation was evaluated by the bedside nurse every three hours using the richmond agitation sedation scale (RASS[17]). The presence of delirium during the preceding 24 hours was determined daily using a previously validated five-step algorithm (inter-observer agreement 0.94–0.97, sensitivity 0.75 and specificity 0.85).[18] This multi-step algorithm incorporates a review by a research nurse of all confusion assessment method for the ICU (CAM-ICU[19]) assessments conducted by the bedside nurses, whether delirium treatment was initiated and a meticulous chart review for the presence of documented terms clinically associated with delirium.[18] When delirium could not be ruled in or out using this procedure, the research nurse conducted an additional CAM-ICU assessment. The daily mental status for each patient was then classified as 'coma', 'delirium' or an 'awake without delirium' state.[18]

Evaluation of the anticholinergic burden of medication use

The daily anticholinergic burden was calculated using the sum of the Anticholinergic Drug Scale (ADS) levels for each medication administered on a particular ICU day.[20] The ADS of the previous day was linked to the outcome (i.e., 'awake without delirium', 'coma', 'delirium' or 'discharge or death') on the next day, so the calculated ADS preceded the assessment of the outcome entirely. The ADS characterizes the anticholinergic activity for 340 different medications, many of which are frequently used in the ICU. The level of anticholinergic activity for each medication is rated across four levels, with a score of 0 indicating no known anticholinergic activity, a score of 1 indicating a potential anticholinergic effect based on the result of receptor binding studies, a score of 2 indicating that anticholinergic adverse events have been observed with the use of medication, and a score of 3 indicating that anticholinergic clinical effects nearly always occur.[20] To account for the fact that a patient who received multiple intermittent doses of a medication with potential anticholinergic properties over a 24 hour period could end up with an ADS score higher than a patient who received the same medication, but as a continuous infusion, an ADS score was assigned only once per day for each medication, regardless of the number of doses administered. If a patient was receiving a medication not included in the ADS nomenclature, a score of zero was assigned.

To explore whether any relationship between anticholinergic medication use and delirium occurrence is dose-related, the dose adjustment strategy as proposed by Carnahan et al. was incorporated in a sensitivity analysis.[20] In this analysis, the administered daily dose was determined for all ADS level 2 and 3 medications. This daily dose was compared to the maximal daily dose of the medication as advised by the Royal Dutch Pharmacists Association. If the daily dose was less than or equal to one-third of the defined maximum daily dose, the dosing weight was defined as 1. If the daily dose was between one-third and two-thirds of the defined maximum daily dose, the dosing weight was defined as 2. If the daily dose was greater than two-thirds of the maximum dose, but did not exceed the maximum daily dose, the dosing weight was defined to be 3. If the daily dose exceeded the maximum daily dose, the dosing weight was deemed to be 4. The ADS-defined level for the medication was then multiplied by the dosing weight and summed for each patient each day to determine a dose-adjusted ADS score. For example, a level 2 medication with an administered dose between one-third and two-third of the maximum daily dose would have a dose-adjusted ADS score of 4. The application of a dose-adjustment strategy requires that the maximal daily dose should be defined. However, for the most frequently used level 1 medications (e.g., morphine and midazolam) this has never been defined and thus a dose-adjustment strategy was deemed unfeasible for level 1 medications.

Benzodiazepines are a potential risk factor for delirium in the ICU through both anticholinergic and non-anticholinergic mechanisms.[14,15,21] While the relationship between benzodiazepine's weakly anticholinergic properties and delirium was accounted for in our analysis given that the ADS categorizes benzodiazepines as a level 1 medication, we conducted two sensitivity analyses to explore the importance of potential non-anticholinergic deliriogenic mechanism(s): 1) Benzodiazepines were excluded from the daily ADS and 2) Benzodiazepine use (in milligrams of midazolam equivalents) was incorporated as a separate covariable in the model. Additional sensitivity analysis was conducted using only the level 2 and 3, and using only the level 3 medications, to explore whether consideration of these medications alone would affect the association between the ADS score and transitioning from an 'awake without delirium' state to 'delirium'. Although the ADS is currently the recommended scale when characterizing the anticholinergic effects of medication, we repeated all steps of our parent analysis in a post hoc fashion using the Anticholinergic Risk Scale (ARS).[22-24]

Covariables and stratification

Based on a prior literature review, variables with the potential to confound the occurrence of delirium were chosen for inclusion in the multivariable analyses.[21] Those

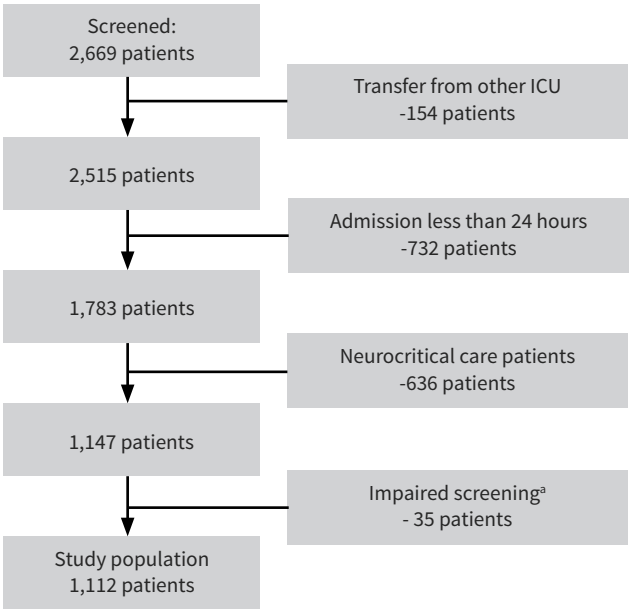
present at the time of ICU admission, and deemed to remain unchanged over the course of the ICU stay, included age, gender, charlson comorbidity index (CCI[25]), type of ICU admission (i.e., medical, elective surgical or acute surgical), and acute physiology and chronic health evaluation IV (APACHE IV[26]) score (as a measure of severity of illness during the first 24 hours of ICU admission). Other covariables, measured daily over the course of ICU stay, were use of mechanical ventilation, the duration of the ICU stay in days until the particular transition occurred, and the daily cumulative sequential organ failure assessment (SOFA) score.[27] The SOFA was calculated without the neurological component to prevent adjusting for a component of the outcome. Trend imputation was used for any missing value of a covariable, given the availability of longitudinal data both preceding and following each observation day.[28] Data were stratified by age (i.e., younger than 65 years versus 65 years or older) and the daily presence of acute systemic inflammation defined as the presence of the systemic inflammatory response syndrome (SIRS).[29]

Statistical analysis

To explore the isolated effect of the ADS score, age and the presence of an acute systemic inflammation on the probability of transitioning from an 'awake without delirium' state to 'delirium', first order Markov multinomial logistic regression models were used. These models included the patient's mental status in the prior 24 hours as a covariable. Additional adjustments were made for the covariables described above. In this study, the first order Markov models included 12 transitions (3 by 4) to account for competing events, as follows: from 'coma', 'delirium' or an 'awake without delirium' state on a particular ICU day, to the next day either 'coma', 'delirium', an 'awake without delirium' state, or 'discharged from the ICU or deceased'. The primary outcome was the transition from an 'awake without delirium' state to 'delirium' the next day. The transition from an 'awake without delirium' to an 'awake without delirium' state the next day was used as the reference transition. The transition from 'coma' to 'delirium' was also explored, with the transition from 'coma' to 'awake without delirium' as reference.

Subsequently, data was stratified and the same first order Markov regression model as described above was used to assess the daily temporal association between the ADS score in patients with an 'awake without delirium' state, and the transition to a 'delirium'. Odds ratios (OR) were presented with 95% confidence intervals (CI). Subset analysis excluding the 1% of patients with the longest length of ICU stay was conducted to see whether these patients disproportionally influenced the association between the ADS and delirium.

Figure 2.1 STUDY FLOWCHART



[a] Inability of screening due to e.g., mental retardation or language barrier.
Abbreviations: ICU = intensive care unit.

All data analyses were performed using IBM SPSS Statistics 20.0 for Windows and R version 3.0.2 for Windows (R Foundation for Statistical Computing, Vienna, Austria). The null hypotheses were tested against two-sided alternatives and a significance level of 0.05 was used for all statistical inferences.

RESULTS

During the study period, among 2,669 patients screened, 1,112 patients (42%) were included in the analyses. Reasons for patient exclusion are described in Figure 2.1. Characteristics of the study population are outlined in Table 2.1. The 1,112 patients stayed in the ICU for a median of 5 (interquartile range [IQR] 2–10) days and the data represented 9,867 ICU observation days. Acute systemic inflammation was present on 6,233 (63%) of the observation days. Among the 535 (48%) patients where delirium occurred, it was present for 3 (IQR 1–6) days. A transition from an 'awake without delirium' state to 'delirium' occurred on 562 (6%) of the ICU days at a median of 9 (IQR 4–20) days after ICU admission. The frequency of occurrence of all daily transitions is described in Table S2.1 (supplementary data).

TABLE 2.1 CHARACTERISTICS OF THE STUDY POPULATION (N=1,112)

Characteristic	Value	
Age in years, mean (SD)	60	(16)
Male, n (%)	672	(60)
Charlson comorbidity index, median (IQR)	6	(0–10)
Type of admission, n (%)		
Medical	519	(47)
Elective surgical	307	(28)
Acute surgical	286	(26)
APACHE IV, mean (SD)	74	(28)
SOFA per day, median (IQR)[a]	5	(2–9)
Delirium, n (%)	535	(48)
Number of delirium days during ICU stay, median (IQR)	3	(1–6)
Length of ICU stay in days, median (IQR)	5	(2–10)
Ever use of mechanical ventilation, n (%)	1,034	(93)

[a] SOFA score without the neurological component.
Abbreviations: APACHE IV = acute physiology and chronic health evaluation IV score, ICU = intensive care unit, IQR = interquartile range, n = number, SD = standard deviation, SOFA = sequential organ failure assessment.

Table S2.2 (supplementary data) provides an overview of the medication administered in the study cohort for ADS level 1, 2, and 3 and the frequency of administration across all ICU days. The daily exposure to anticholinergic medication, as characterized by the summed ADS score, ranged between 0 and 10 and averaged 2 (IQR 1–3). Among the cumulative daily ADS scores across all patients and ICU days, level 1 medications contributed for 90% of the total score, level 2 medications for 1%, and level 3 for 9%. Morphine, furosemide, midazolam, and prednisone were the most frequently used ADS-scored medications with an ADS score greater than 0.

TABLE 2.2 ODDS RATIOS FOR DAILY TRANSITIONING TO DELIRIUM (N= 9,867)

Determinant	Adjusted Odds Ratio (95% confidence interval)[a]	
Anticholinergic Drug Scale, per unit increase	1.05	(0.99–1.10)
Age, per year increase	1.02	(1.01–1.02)*
Presence of acute systemic inflammation[b]	1.37	(1.13–1.65)*

The primary outcome was the transition from an 'awake without delirium' state to 'delirium'. The transition from an 'awake without delirium' to an 'awake without delirium' state the next day was used as the reference transition.

* p-value < 0.05.

[a] Adjusted for: age, gender, charlson comorbidity index, type of admission, acute physiology and chronic health evaluation IV score, use of mechanical ventilation, length of intensive care unit stay until transition, and sequential organ failure assessment score without the neurological component.

[b] Odds ratio for days with acute systemic inflammation compared to days without acute systemic inflammation.

No significant increase in the odds for the daily transition from an 'awake without delirium' state to 'delirium' was found with every one unit ADS increase in the anticholinergic burden (adjusted OR=1.05, 95% CI 0.99–1.10) (Table 2.2). For every increase in age of one year, the probability of having 'delirium' the day after being in an 'awake without delirium' state increased significantly (adjusted OR=1.02, 95% CI 1.01–1.02). The probability of transitioning from an 'awake without delirium' state to 'delirium' also increased significantly on days that patients had acute systemic inflammation, compared to days where acute systemic inflammation was not present (adjusted OR=1.37, 95% CI 1.13–1.65). The stratified analyses revealed that neither age nor acute systemic inflammation affected the reported relationship between daily ADS score and the daily odds of transitioning to 'delirium' (Table 2.3). The crude results of the primary outcome from an 'awake without delirium' state to 'delirium', as well as the additional results for the transitions from 'coma' to 'delirium' can be found in Table S2.3 (supplementary data). In a subset analysis that excluded the 1% of patients with the longest length of ICU stay (i.e., more than 60 days, n=10, accounting for 758 (8%) of the ICU days), we also did not find an association between the ADS and the probability of transitioning to delirium.

In the sensitivity analysis that accounted for the dose of each level 2 and 3 medication administered, the odds for the daily transition from an 'awake without delirium' state to 'delirium' did not increase significantly (adjusted OR=1.03; 95% CI 0.98–1.08 per one unit increase in the dose-adjusted ADS).

In our cohort, the administered benzodiazepines defined in the ADS were alprazolam, clonazepam, clorazepate, diazepam, midazolam, lorazepam, oxazepam and temazepam; all of which were registered as level 1 anticholinergic medications. The OR for the daily transition from an 'awake without delirium' state to 'delirium' did not significantly change when either benzodiazepines were excluded from the ADS (adjusted OR=1.06; 95% CI 0.99–1.13, per one unit increase in ADS) or the daily amount of benzodiazepine administered in midazolam equivalents was incorporated as a separate covariable (adjusted OR=1.04; 95% CI 0.99–1.09).

When using only level 2 and 3, and only level 3 medications to describe the association between the ADS score and the daily transition from an 'awake without delirium' state to 'delirium', the results did not differ significantly (adjusted OR=0.82 (95% CI 0.65–1.03) per two unit increase for level 2 and 3 medications; adjusted OR=0.89 (95% CI 0.79–1.00) per three unit increase for level 3 medications).

TABLE 2.3 STRATIFIED EFFECT FOR EVERY ONE UNIT INCREASE IN THE ANTICHOLINERGIC DRUG SCALE AND THE ODDS OF TRANSITIONING TO DELIRIUM

Number of observation days	Number of transitions from 'awake without delirium' to 'delirium'	Age group	Acute systemic inflammation present	Adjusted Odds Ratio (95% confidence interval)[a]	
1,832	70	< 65 years	No	1.04	(0.90–1.20)
1,802	127	≥ 65 years	No	0.98	(0.85–1.11)
3,644	178	< 65 years	Yes	1.09	(0.99–1.19)
2,589	187	≥ 65 years	Yes	1.10	(0.99–1.23)

The primary outcome was the transition from an 'awake without delirium' state to 'delirium'. The transition from an 'awake without delirium' to an 'awake without delirium' state the next day was used as the reference transition.

[a] Adjusted for: age, gender, charlson comorbidity index, type of admission, acute physiology and chronic health evaluation IV score, use of mechanical ventilation, length of intensive care unit stay until transition, and sequential organ failure assessment score without the neurological component.

Use of the ARS, rather than the ADS, to calculate anticholinergic burden resulted in a significant increase in the probability to transition from an 'awake without delirium' state to a 'delirium' (adjusted OR=1.12, 95% CI 1.03–1.22). However, this association was present in only those patients who were older and on the days they were acutely inflamed (Table S2.4, supplementary data).

DISCUSSION

This investigation is the first to describe the association between exposure to medication with anticholinergic properties and the daily risk of delirium in a large cohort of critically ill adults. Exposure to medication with anticholinergic properties, as defined by the ADS, was not associated with an increased probability for transitioning from an 'awake without delirium' state to 'delirium' the following day.

Microglia are the macrophages of the brain and when activated will result in neuronal dysfunction, an important precursor for delirium.[10,12] While microglia are inhibited by the cholinergic system, they are also sensitive to activating factors like the acute neuroinflammation commonly seen during critical illness.[10,11,30] During the aging process, the cholinergic system will start to atrophy and thus microglial priming will increase. The critically ill, especially those that are older, have therefore been hypothesized to be particularly sensitive to the anticholinergic properties of medications, specifically in the setting of acute systemic inflammation.[10] Our results confirm the importance of acute systemic inflammation and increasing age as individual risk factors for delirium. However, they do not support the hypothesis that use of a medication that increases cholinergic inhibition (i.e., anticholinergic medication) in the critically ill are a clinically important factor for the development

of delirium.[5,7,10] Alternative anticholinergic burden scales to the ADS, such as the ARS[24], the list by Summers et al.[31], and the Anticholinergic Cognitive Burden Scale (ACB) exist.[32] However, unlike the ADS, none are validated against serum anticholinergic burden, each are based solely on clinical outcomes and/or expert opinion and each has poor agreement.[22,23,33] Hence, while the results of the ARS post-hoc analysis suggests that a relationship between anticholinergic medication use and delirium occurrence may exist in the older inflamed patients, the ARS is not as well accepted a method as the ADS to characterize anticholinergic burden.

Compared to other investigations that have explored the relationship between anticholinergic drug use and delirium in both ICU and non-ICU populations, our analysis has many strengths.[13-15] Multinomial logistic regression models were used to account for both competing events such as coma, discharge or death, and the presence of other factors associated with delirium occurrence.[16] Key sensitivity analyses showed that the effect measure as calculated was robust, also when adjusting for dosage, when excluding benzodiazepines from the analysis or adding benzodiazepine use as additional covariable and when limiting analysis to level 2 and level 3. The risk for misclassification bias when defining the daily mental status of each patient was minimized because a validated multi-step research algorithm was used.[18] Using the entire previous 24 hours to assess the presence of delirium instead of one moment a day, reduced misclassification, given that the symptoms of delirium may fluctuate.[18]

While one small sampled study of 25 ICU patients reported a significant relationship between anticholinergic medication use and delirium occurrence, the conclusions of this investigation are tempered by the fact that the serum anticholinergic activity rather than a validated anticholinergic drug scale was used to define anticholinergic exposure and that factors with the potential to confound delirium occurrence were not accounted for.[13] While two other published studies in ICU populations reached the same conclusion as our analysis, neither were designed to answer this question in a robust fashion given the number of patients evaluated were small, a validated method to characterize anticholinergic drug exposure was not used, and important baseline and time-dependent risk factors for delirium were analyzed in an independent way.[14,15]

Our analysis has several potential limitations. Measures of anticholinergic burden, including the ADS, may lack the sensitivity to detect small differences in anticholinergic burden between days hence, potentially resulting in a type II error. Although the ADS score was corrected for the medication dose administered, factors other than dose may influence the anticholinergic burden estimated by the ADS. While

ADS level 1 medications accounted for the majority of medications with anticholinergic effects that were administered in the cohort, we were not able to consider the effect of dose on the delirium transition rate for these medications. Although level 2 and 3 medications together accounted for only 10% of the total ADS score, sensitivity analyses using only the level 2 and 3, and only the level 3 medications did not differ from results of analyses that considered all anticholinergic medications. Exposure to medication with anticholinergic effects in our cohort is likely similar to that of other institutions. However, we cannot exclude that confounding by (contra)indication might have occurred (i.e., a clinician might have avoided prescribing a medication with anticholinergic effects for a patient they deemed to be at higher risk for delirium). This was addressed by covariable adjustment and the use of multiple different measures for the same construct (e.g. severity of illness). However, residual confounding may still have occurred. While potential risk factors for delirium, other than anticholinergic drug exposure, were based on a recent systematic review and incorporated in the analysis whenever possible, the number of patients with a history of delirium preceding ICU admission was unknown. This may also have led to residual confounding. This is unfortunately a common issue in all observational studies. Under the first order Markov assumption, all day-to-day transitions are considered independent. Yet, this is not true, as patients are represented in the dataset multiple times. The assumption may in particular be violated in patients with a long ICU length of stay. However, our findings did not change when we excluded the 1% of study participants with the longest ICU length of stay. This indicates that these patients did not influence the calculated associations disproportionately. Lastly, although anticholinergic medication use prior to ICU admission was not considered, the fact that a transition from an 'awake without delirium' state to 'delirium' occurred a median of 9 (IQR 4–20) days after ICU admission makes pre-admission ICU medication use likely to be of little importance.

CONCLUSION

This study did not find that exposure to higher ADS scores, as a measure of anticholinergic burden, increases the probability of transitioning to delirium in ICU patients. However, given the complexity of characterizing anticholinergic burden, further research in this area is required.

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SUPPLEMENTARY DATA

TABLE S2.1 FREQUENCY DISTRIBUTION OF OBSERVED DAILY TRANSITIONS

Day X (transition from)	Day X + 1 (transition to)			
	Awake without delirium	Delirium	Coma	Discharge or death
Awake without delirium	3,712	562	204	814
Delirium	741	1,628	205	98
Coma	194	255	1,254	193

TABLE S2.2 NUMBER OF DAYS ON WHICH MEDICATIONS WITH AN ANTICHOLINERGIC DRUG SCALE LEVEL OF 1, 2, OR 3 WERE ADMINISTERED AMONG THE 1,112 PATIENTS, ADMITTED TO THE ICU OF THE UMCU BETWEEN JANUARY 2011 AND JUNE 2013.

Anticholinergic Drug Scale level 1 medication			
Medication	Number of days	Medication	Number of days
Morphine	4,232	Loperamide	72
Furosemide	3,543	Lorazepam	69
Midazolam	2,522	Azathioprine	63
Prednisone	2,116	Paroxetine	61
Oxazepam	1,343	Oxycodone	57
Hydrocortisone	1,184	Triamterene	56
Vancomycin	1,156	Isosorbide mononitrate	46
Fentanyl	1,046	Gentamicin	32
Temazepam	674	Olanzapine	27
Captopril	388	Codeine	18
Clindamycin	293	Clonazepam	14
Digoxin	292	Nifedipine	14
Piperacillin	175	Fluvoxamine	9
Dexamethasone	160	Alprazolam	7
Methylprednisone	137	Fluoxetine	7
Valproic acid	131	Diazepam	7
Dipyridamole	122	Clorazepate	4
Tramadol	103	Chlorthalidone	1
Theophylline	86		

Anticholinergic Drug Scale level 2 medication	
Medication	Number of days
Carbamazepine	89
Ranitidine	38
Oxcarbazepine	7

Anticholinergic Drug Scale level 3 medication			
Medication	Number of days	Medication	Number of days
Amitriptyline	376	Nortriptyline	15
Oxybutynin	93	Clozapine	11
Clemastine	66	Scopolamine	6
Promethazine	40	Tolterodine	3
Clomipramine	32	Imipramine	2
Atropine	31	Chlorpromazine	1

TABLE S2.3 ASSOCIATION BETWEEN ANTICHOLINERGIC EXPOSURE DEFINED BY THE ANTICHOLINERGIC DRUG SCALE AND THE DAILY TRANSITION TO 'DELIRIUM'.

TABLE S2.3.1 TRANSITION FROM AN 'AWAKE WITHOUT DELIRIUM' STATE TO 'DELIRIUM'

Table S2.3.1a ODDS RATIOS FOR DAILY TRANSITIONING TO DELIRIUM

Determinant	Crude Odds Ratio (95% confidence interval)[a]		Adjusted Odds Ratio (95% confidence interval)[a]	
Anticholinergic Drug Scale, per unit increase	1.03	(0.98–1.09)	1.05	(0.99–1.10)

Table S2.3.1b STRATIFIED EFFECT FOR EVERY ONE UNIT INCREASE IN THE ANTICHOLINERGIC DRUG SCALE AND THE ODDS OF TRANSITIONING TO DELIRIUM

Age group	Acute systemic inflammation present	Crude Odds Ratio (95% confidence interval)[a]		Adjusted Odds Ratio (95% confidence interval)[a]	
< 65 years	No	1.07	(0.93–1.22)	1.04	(0.90–1.20)
≥ 65 years	No	0.98	(0.86–1.11)	0.97	(0.85–1.11)
< 65 years	Yes	1.10	(1.00–1.21)*	1.09	(0.99–1.19)
≥ 65 years	Yes	1.08	(0.97–1.21)	1.10	(0.99–1.23)

The transition from an 'awake without delirium' to an 'awake without delirium' state the next day was used as the reference transition.

TABLE S2.3.2 TRANSITION FROM 'COMA' TO 'DELIRIUM'

Table S2.3.2a ODDS RATIOS FOR DAILY TRANSITIONING TO DELIRIUM

Determinant	Crude Odds Ratio (95% confidence interval)[a]		Adjusted Odds Ratio (95% confidence interval)[a]	
Anticholinergic Drug Scale, per unit increase	0.99	(0.86–1.10)	0.99	(0.99–1.08)

Table S2.3.2b STRATIFIED EFFECT FOR EVERY ONE UNIT INCREASE IN THE ANTICHOLINERGIC DRUG SCALE AND THE ODDS OF TRANSITIONING TO DELIRIUM

Age group	Acute systemic inflammation present	Crude Odds Ratio (95% confidence interval)[a]		Adjusted Odds Ratio (95% confidence interval)[a]	
< 65 years	No	0.96	(0.71–1.29)	0.93	(0.69–1.26)
≥ 65 years	No	1.10	(0.76–1.59)	1.15	(0.80–1.66)
< 65 years	Yes	0.96	(0.80–1.17)	0.96	(0.84–1.10)
≥ 65 years	Yes	1.08	(0.82–1.40)	1.07	(0.88–1.29)

The transition from 'coma' to an 'awake without delirium' state the next day was used as the reference transition.

* p-value < 0.05.

[a] Adjusted for: age, gender, charlson comorbidity index, type of admission, acute physiology and chronic health evaluation IV score, use of mechanical ventilation, length of intensive care unit stay until transition, and sequential organ failure assessment score without the neurological component.

TABLE S2.4 ASSOCIATION BETWEEN ANTICHOLINERGIC EXPOSURE, DEFINED BY THE ANTICHOLINERGIC RISK SCALE, AND THE DAILY TRANSITION TO 'DELIRIUM'

TABLE S2.4.1 TRANSITION FROM AN 'AWAKE WITHOUT DELIRIUM' STATE TO 'DELIRIUM'

Table S2.4.1a ODDS RATIOS FOR DAILY TRANSITIONING TO DELIRIUM

Determinant	Crude Odds Ratio (95% confidence interval)[a]		Adjusted Odds Ratio (95% confidence interval)[a]	
Anticholinergic Risk Scale, per unit increase	1.09	(1.01–1.18)*	1.12	(1.03–1.22)*

Table S2.4.1b STRATIFIED EFFECT FOR EVERY ONE UNIT INCREASE IN THE ANTICHOLINERGIC RISK SCALE AND THE ODDS OF TRANSITIONING TO DELIRIUM

Age group	Acute systemic inflammation present	Crude Odds Ratio (95% confidence interval)[a]		Adjusted Odds Ratio (95% confidence interval)[a]	
< 65 years	No	0.87	(0.68–1.11)	0.89	(0.69–1.16)
≥ 65 years	No	1.17	(0.93–1.47)	1.12	(0.88–1.43)
< 65 years	Yes	1.07	(0.94–1.23)	1.12	(0.97–1.29)
≥ 65 years	Yes	1.26	(1.09–1.46)*	1.37	(1.17–1.60)*

The transition from an 'awake without delirium' to an 'awake without delirium' state the next day was used as the reference transition.

* p-value < 0.05

[a] Adjusted for: age, gender, charlson comorbidity index, type of admission, acute physiology and chronic health evaluation IV score, use of mechanical ventilation, length of intensive care unit stay until transition, and sequential organ failure assessment score without the neurological component.

TABLE S2.4.2 MEDICATION DEFINED IN THE ANTICHOLINERGIC RISK SCALE AND USED IN OUR COHORT

Level 1	Level 2	Level 3
carbidopa,levodopa	baclofen	amitriptyline
haloperidol	cetirizine	atropine
metoclopramide	clozapine	imipramine
mirtazapine	loperamide	oxybutynin
paroxetine	nortriptyline	promethazine
quetiapine	olanzapine	tizanidine
ranitidine	tolterodine	
risperidon		
trazodon		

3

SYSTEMIC CORTICOSTEROIDS AND TRANSITION TO DELIRIUM IN CRITICALLY ILL PATIENTS

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ABSTRACT

Objective

Corticosteroids are frequently used in critically ill patients. We investigated whether systemic corticosteroid use increases the probability of transitioning to delirium in a large population of mixed medical-surgical intensive care unit (ICU) patients.

Design

Prospective cohort study.

Setting

A 32-bed medical-surgical ICU at an academic medical center.

Patients

Critically ill adults (n=1,112), admitted to the ICU for more than 24 hours without a condition that could hamper delirium assessment.

Interventions

None.

Measurements and Main Results

Systemic corticosteroid exposure was measured daily and converted to prednisone equivalents (milligrams). Daily mental status was classified as 'coma', 'delirium', or an 'awake without delirium' state. Transitions between states were analyzed using a first-order Markov multinomial logistic regression model with 11 different covariables, with the transition from an 'awake without delirium' state to 'delirium' as primary interest. Among the 1,112 patients, corticosteroids were administered on 35% (3,483/9,867) of the ICU days at a median dose of 50 (interquartile range 25–75) mg prednisone equivalent. Administration of a corticosteroid, and any increase in the dose of the corticosteroid given on exposure days, were not significantly associated with the transition to 'delirium' (adjusted odds ratios respectively 1.08, 95% confidence interval [CI] 0.89–1.32 and 1.00, 95% CI 0.99–1.01, per 10 milligrams increase in prednisone equivalent).

Conclusions

In a large population of mixed medical-surgical ICU patients, systemic corticosteroid use was not associated with an increased probability of transitioning to delirium.

INTRODUCTION

Systemic corticosteroids may have beneficial effects in certain critically ill populations.[1,2] However, corticosteroids have long been associated with delirium, albeit up to the year 2000 steroid-associated delirium was generally called steroid-associated psychosis.[3-5] It is possible that corticosteroids will lead to hypothalamic-pituitary-adrenal axis dysfunction, dopaminergic system inhibition, or have a direct toxic effect on different brain regions, particularly the hippocampus, which may hamper selective attention and memory function and thus increase the odds of transitioning to delirium.[6,7]

A recent cohort study in intensive care unit (ICU) patients found that systemic corticosteroid administration was associated with an increased probability of transitioning to delirium.[8] However, the patient cohort in this study was relatively small and limited to only patients with acute lung injury (ALI).[8] We evaluated the association between systemic corticosteroid use and the daily transition from an 'awake without delirium' state to 'delirium' in a larger population of mixed medical-surgical ICU patients.

METHODS

Data were gathered as part of a prospective cohort study of consecutively admitted adult patients who stayed in the 32-bed medical-surgical ICU of the University Medical Center Utrecht (UMCU) for at least 24 hours, between January 2011 and June 2013.[9] Patients were excluded when they had been transferred from an ICU of another hospital, or if they had any neurological disorder or another condition that could hamper delirium assessment. The Medical Research Ethics Committee of the UMCU approved this study and waived the need for informed consent (protocol 12/421 and 10/056).

Patients' mental status was assessed daily in a research setting using a validated multi-step algorithm encompassing the full previous 24 hours. The algorithm was based on CAM-ICU assessments by the bedside nurse, a chart review for symptoms of delirium, whether antipsychotic therapy was initiated and the results of an additional CAM-ICU assessment by a research nurse.[10] Patients were classified each day as being in 'coma', 'delirium', or an 'awake without delirium' state.[10]

Systemic corticosteroid exposure was derived from medication administration records. After accounting for the lower bioavailability of oral administration, the daily dose of each corticosteroid administered was converted to the prednisone milligrams (mg) equivalent and a total daily prednisone equivalent dose was calculated. The conversion factors for bioavailability adjustment, as well as the conversion factor for calculating the prednisone equivalents, are outlined in Table S3.1 (supplementary data).

Based on prior literature, the following potential confounders were included in the multivariable analyses.[11] Covariables measured at ICU admission were age, corticosteroid use prior to ICU admission (yes/no), the charlson comorbidity index (CCI), the type of ICU admission (i.e., medical, elective surgical or acute surgical), and the acute physiology and chronic health evaluation (APACHE) IV score. Covariables measured daily were the length of ICU stay until the defined transition occurred, the daily sequential organ failure assessment (SOFA) score without the neurological component, use of mechanical ventilation (yes/no), presence of inflammation (defined by systemic inflammatory response syndrome (SIRS) criteria; yes/no), use of opioids (yes/no) and use of benzodiazepines (yes/no).

Categorical variables were reported as frequencies. Continuous data, where appropriate, were presented as mean with standard deviation (SD) or median with interquartile ranges (IQR). First-order Markov multinomial logistic regression models were used to describe the relationship between corticosteroid exposure and the odds of transitioning from an 'awake without delirium' state to 'delirium' in terms of odds ratios (ORs). As previously described, these models included 12 possible transitions to account for competing events, with the transition from an 'awake without delirium' state to an 'awake without delirium' state defined as the reference.[9] First, the association was established between any corticosteroid exposure and the transition to 'delirium'. In addition, on those days that corticosteroids were administered, the association between the dose of corticosteroid administered and the transition to delirium was analyzed.

Considering that the potential deliriogenic mechanism of corticosteroids might be based on their direct toxic effect on the hippocampus, and that dexamethasone penetrates the blood-brain barrier poorly, we completed a secondary analysis that excluded dexamethasone exposure.[7,12] To explore whether the administration of a high corticosteroid dose on any ICU day affected the transition to delirium disproportionately, two other sensitivity analyses were completed. In the first analysis, the high-dose days (>100 mg of prednisone equivalent) were excluded from the analysis. Secondly, low dose corticosteroid exposure (≤100 mg of prednisone equivalent) were excluded, and the analysis was performed with high dose corticosteroid days versus days with no corticosteroid exposure. Furthermore, in an attempt to replicate the analysis of Schreiber et al., we conducted a post-hoc sensitivity analysis in patients who experienced one or more days with severe hypoxemia (i.e., PaO2:FiO2 ratio of ≤200 mmHg).

All data analyses were performed with IBM SPSS Statistics 21.0 for Windows and R version 3.1.1 for Windows (R Foundation for Statistical Computing Vienna, Austria). Null hypotheses were tested against two-sided alternatives and statistical inference was done using a significance level of 0.05.

RESULTS

The study population consisted of 1,112 medical-surgical patients, accounting for 9,867 ICU observation days. Patient characteristics are described in Table 3.1. The flowchart of the applied exclusion criteria has recently been published.[6]

Corticosteroids were administered on 35% (3,483/9,867) of the observation days to 513 (46%) patients. The patients exposed to corticosteroids had more comorbidities, stayed longer in the ICU, were more severely ill, had more often received corticosteroids before ICU admission, and were more often delirious (Table 3.1).

TABLE 3.1 CHARACTERISTICS OF THE STUDY POPULATION

Characteristic	All patients		Patients receiving no corticosteroid		Patients receiving corticosteroid		p-value[a]
	n=1,112 (100%)		n=599 (54%)		n=513 (46%)		
Age in years, mean (SD)	60	(16)	61	(16)	60	(17)	0.43
Male, n (%)	672	(60)	379	(63)	293	(57)	0.04
CCI, median (IQR)	6	(0–10)	6	(0–10)	7	(3–11)	<0.001
Type of admission, n (%)							
Medical	519	(47)	258	(43)	261	(51)	<0.001
Elective surgical	307	(28)	195	(33)	112	(22)	
Acute surgical	286	(26)	146	(24)	140	(27)	
APACHE IV, mean (SD)	74	(28)	68	(26)	81	(29)	<0.001
Length of ICU stay in days, median (IQR)	5	(2–10)	4	(2–7)	7	(3–14)	<0.001
Home medication use of corticosteroid, n (%)	181	(16)	20	(3)	161	(31)	<0.001
Delirium, n (%)	535	(48)	251	(42)	284	(55)	<0.001
Number of delirium days during ICU stay, median (IQR)[b]	3	(1–6)	2	(1–5)	3	(2–7)	0.003

[a] Comparison between patients with and without systemic corticosteroids administered during ICU stay were made using a t-test for normally distributed continuous data, the Mann-Whitney U for non-normally distributed continuous data and the Chi^2 test for categorical data.

[b] Number of delirium days during ICU stay, when delirium was present.

Abbreviations: APACHE IV = acute physiology and chronic health evaluation IV score, CCI = charlson comorbidity index, ICU = intensive care unit, IQR = interquartile range, n = number, SD = standard deviation

TABLE 3.2 ODDS RATIOS FOR DAILY TRANSITIONING FROM 'AWAKE WITHOUT DELIRIUM' TO 'DELIRIUM'

Determinant	Crude Odds Ratio (95% confidence interval)[a]		Adjusted Odds Ratio (95% confidence interval)[a]	
Corticosteroid administration (versus no administration)	1.12	(0.93–1.35)	1.08	(0.89–1.32)
Corticosteroid dose (per 10 mg prednisone equivalent increase)	0.99	(0.98 - 1.00)	1.00	(0.99 - 1.01)

The transition from an 'awake without delirium' to an 'awake without delirium' state the next day was used as the reference transition.

[a] Adjusted for: age, home use of corticosteroids, charlson comorbidity index, type of intensive care unit admission, acute physiology and chronic health evaluation IV score, length of intensive care unit stay until transition, sequential organ failure assessment score without the neurological component, use of mechanical ventilation, presence of inflammation defined by systemic inflammatory response syndrome criteria, use of opioids and use of benzodiazepines.

A comparison of the covariables that changed daily between the days a corticosteroid was administered and the days it was not, are presented in Table S3.2 (Supplementary data). Patients were more severely ill on days that corticosteroids were administered (Table S3.2, supplementary data). The administered corticosteroids included dexamethasone, fludrocortisone, hydrocortisone, methylprednisolone and prednisone, and were administered either intravenously or orally. The median daily prednisone equivalent dose was 50 (IQR 25–75) mg. The transition from an 'awake without delirium' state to 'delirium' was observed 562 (6%) times. On 205 (37%) of these transition days corticosteroids were administered, at a median dose of 38 (IQR 20–66) mg prednisone equivalent.

The administration of corticosteroids was not associated with a higher probability of transitioning to 'delirium' from an 'awake without delirium' state (adjusted OR=1.08, 95% confidence interval [CI] 0.89–1.32) (Table 3.2). In patients who received corticosteroids, the dose of corticosteroids was not associated with a transition to delirium (adjusted OR=1.00, 95% CI 0.99–1.01, per 10 mg prednisone equivalent increase). Exclusion of dexamethasone did not alter the odds of transitioning to delirium significantly (adjusted OR=1.05, 95% CI 0.86–1.28). High dose corticosteroid therapy (>100 mg prednisone equivalent) was administered on 13% of corticosteroid days. The odds of transitioning to delirium were not significantly different on days patients received low dose corticosteroids (adjusted OR=1.10, 95% CI 0.89–1.34) and on those days patient received high dose of corticosteroids (adjusted OR=0.87, 95% CI 0.51–1.48) when compared to days with no corticosteroid exposure. Limiting the analysis to the 495 (45%) patients who experienced severe hypoxemia during their ICU stay did not alter the association significantly either (adjusted OR=1.00, 95% CI 0.79–1.25).

DISCUSSION

Using time-varying multivariable statistical analysis that incorporated both known risk factors for delirium and considered competing events, we found that the administration of corticosteroids in a large population of mixed critically ill adults is not a risk factor for the transition to delirium. While it appears that neither the dose of corticosteroid administered, nor the administration of high daily corticosteroid doses affects this transition, ICU clinicians should still down-titrate corticosteroid therapy to the lowest-effective dose whenever clinically appropriate and focus on identifying and removing other modifiable delirium risk factors, where possible, which are more strongly associated with delirium.

A recent study suggested that administration of corticosteroids to ALI patients increases the risk for a transition to delirium.[8] It could be that the choice of this study population accounted for the discordance with our results. However, when we attempted to replicate these findings by investigating patients in our cohort who experienced at least one day of severe hypoxemia, we found that corticosteroid administration did not influence the odds of transitioning to delirium. The results of this secondary analysis must be interpreted with caution given that we used a non-specific clinical marker to define ALI and had fewer patients with ALI compared to the Schreiber et al. cohort.

There are several other potential reasons for the discordance between our analysis and that of Schreiber et al. While we used a validated algorithm that encompassed the full previous 24 hours to classify the daily mental status[10], Schreiber et al. used a single daily assessment. Given the fluctuating nature of delirium, a single daily bedside assessment could have missed some delirious patients, which may have resulted in an overrepresentation of more persistent delirium. With the patients most severely ill more likely to develop delirium, but also at the same time more likely to receive corticosteroids, it is possible that the association observed by Schreiber et al. is only applicable to the sickest patients in the ICU. Differences in the method by which covariables were selected may also have led to the observed discordance between our results and those of Schreiber et al. Currently, no consensus exists on the preferred method for covariable selection.[13] While we used published literature to identify confounders that should be included in the multivariable analysis, Schreiber et al. relied on statistical testing. This approach may lead to the exclusion of important confounders (e.g., home corticosteroid use) resulting in residual confounding, or to the inclusion of redundant confounders that may result in model overfitting and the reporting of an apparent effect when one does not truly exist.[13]

Our study also has limitations. Although a rigorous and validated multi-step

delirium assessment algorithm was used daily in all patients, it remains possible that delirium may have been misclassified on some ICU days. While the first-order Markov assumption states that multiple records on a single individual are considered to be independent, in the case of day-to-day transitions, as was evaluated in our analysis, this does not necessarily hold true.[9] Furthermore, the occurrence of confounding by indication cannot be ruled out. The number of occurrences included in some of the secondary analyses (e.g., days of high-dose corticosteroid therapy, and patients with potential ALI) may have been too low to establish differences between the groups. Conclusions from our study on whether corticosteroid use effects either delirium severity or duration cannot be made. In addition, the results of our analysis may be different at centers where corticosteroid prescribing practices are different. Also, as with all observational studies, residual confounding might have occurred. To assess causality, a randomized controlled trial (RCT) would be needed. Therefore, we agree with Schreiber et al. that future RCTs of corticosteroids in the ICU need to carefully evaluate the incidence of delirium with their use.[8]

CONCLUSION

In a large population of mixed medical-surgical ICU patients, corticosteroid use was not associated with an increased probability of transitioning to delirium.

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SUPPLEMENTARY DATA

TABLE S3.1 CORTICOSTEROID BIOAVAILABILITY FACTOR AND CONVERSION FACTOR TO PREDNISONE EQUIVALENTS

Determinant	Bioavailability factor to convert from oral to IV administration route	Conversion factor for prednisone equivalent
Prednisone	1.00	Reference
Dexamethasone	0.80	6.67
Fludrocortisone	1.00	100
Hydrocortisone	0.96	0.25
Methylprednisolone	NA	1.25

NA = Not applicable. Methylprednisolone was not administered orally.

TABLE S3.2 COMPARISON OF DAILY ICU VARIABLES BETWEEN DAYS WHERE CORTICOSTEROIDS WERE ADMINISTERED AND DAYS WHERE THEY WERE NOT.

Characteristic	Days without corticosteroid administration n=6,384 (65%)		Days with corticosteroid administration n=3,483 (35%)		p-value[a]
SOFA per day, median (IQR)[b]	4	(2–6)	6	(3–9)	<0.001
Use of mechanical ventilation, n (%)	4,714	(74)	2,992	(86)	<0.001
Presence of inflammation, n (%)	3,824	(60)	2,409	(69)	<0.001
Use of a benzodiazepine(s), n (%)	2,699	(42)	2,045	(59)	<0.001
Use of opioid(s), n (%)	2,761	(43)	1,932	(55)	<0.001

[a] Comparison between days with and without systemic corticosteroids administration, using the Mann-Whitney U for non-normally distributed continuous data and the Chi^2 test for categorical data.

[b] Daily Sequential Organ Failure Assessment score (SOFA) without the neurological component.

4

PSYCHOPATHOLOGY PRIOR TO CRITICAL ILLNESS AND THE RISK OF DELIRIUM ONSET DURING INTENSIVE CARE UNIT STAY

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ABSTRACT

Objective

The aim of our study was to investigate whether psychopathology prior to hospital admission predisposes critically ill patients to delirium during intensive care unit (ICU) stay.

Design

Prospective cohort study.

Setting

32-bed mixed medical-surgical ICU of the University Medical Center Utrecht.

Patients

Adult critically ill patients who were admitted to the ICU for more than 24 hours without delirium at ICU admission and without a neurological disorder or any other condition that would hamper delirium assessment.

Interventions

None.

Measurements and Main Results

A history of psychopathology prior to hospital admission was extracted from the hospital information system using a standardized approach. The presence of delirium was measured daily using a validated algorithm. As ICU discharge and death both hinder the occurrence of delirium during ICU stay, both can be regarded as competing events of delirium. Hence, a multivariable competing-risk Cox proportional hazard analysis was used to describe the association between psychopathology prior to hospital admission and the occurrence of delirium. Analyses were adjusted for six patient demographic and ICU specific covariables. Our study population consisted of 1,090 patients. There were 334 patients with psychopathology prior to hospital admission, of whom 172 (51%) developed delirium. In the 756 patients without pre-existing psychopathology, 341 (45%) developed delirium. The adjusted cause-specific hazard ratio for developing delirium in patients who had psychopathology prior to hospital admission was 1.30 (95% confidence interval [CI] 1.08–1.57). The subdistribution hazard ratio (SHR) for developing delirium was 1.35 (95% CI 1.12–1.63), indicating that pre-existing psychopathology was significantly associated with an increased instantaneous risk of developing delirium during ICU stay.

Conclusions

Our study suggests that psychopathology prior to hospital admission increases the risk of delirium during ICU stay.

INTRODUCTION

During intensive care unit (ICU) stay, delirium is a common and serious medical problem, as it is associated with short-term as well as long-term morbidity.[1-4] Delirium in critically ill patients has a multifactorial pathogenesis, but the pathophysiology is still largely unknown.[5] Identifying predisposing and precipitating factors related to the occurrence of delirium will contribute to our understanding of the etiology of delirium.[5,6] One of the proposed predisposing factors for delirium is a history of psychopathology prior to hospital admission.[7,8] In patients who underwent non-cardiac major elective surgery, depression and psychotropic drug use prior to surgery were important predictors for the occurrence of post-operative delirium.[7] Also, in elective and emergency cardiac care, with study populations partially consisting of ICU patients, pre-existing depression was associated with delirium incidence.[8-12] However, not all studies could demonstrate that pre-existing psychopathology was associated with post-operative delirium.[13] Previous studies on a history of psychopathology and delirium were thus inconsistent and limited to post-operative and/or cardiac care patients.[7-13] Whether a history of psychopathology prior to critical illness is a predisposing factor for developing delirium in patients requiring ICU admission has never been investigated. Therefore, the aim of our study was to investigate whether psychopathology prior to hospital admission predisposes critically ill patients to delirium during ICU stay.

METHODS

Setting and study population

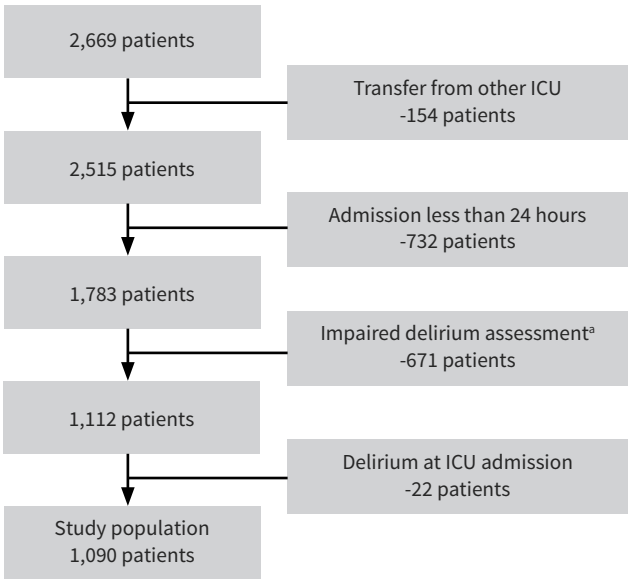
This cohort study was conducted in consecutively admitted adult patients, who stayed in the 32-bed mixed ICU of the University Medical Center Utrecht (UMCU) for at least 24 hours between January 2011 and June 2013. Patients who were transferred from an ICU of another hospital, as well as patients with a neurological illness or any other condition which may impede delirium assessment, were excluded. Also, patients who had delirium at the time of ICU admission were excluded. The Medical Research Ethics Committee of the UMCU waived the need for informed consent (protocol 12/421 and 10/056).

History of psychopathology

Whether patients had a history of psychopathology prior to hospital admission was determined using medical records of the hospital information system. Based on the degree of evidence from the medical record, patients were categorized in 'definite -', 'probable -', 'possible -', or 'no pre-existing psychopathology'. Patients were categorized

as having 'definite psychopathology' when a psychopathology diagnosis designated by a psychiatrist or psychologist was described in the medical records, based on the Diagnostic and Statistical Manual of Mental Disorders.[14] Patients were categorized as having 'probable psychopathology' when there was evidence of psychopathology in the medical records, but it was not explicitly stated whether the diagnosis was made by an expert in psychopathology (i.e., a psychiatrist or psychologist) or another healthcare professional (e.g., a general practitioner). Patients were categorized as having 'possible psychopathology' when patients used psychoactive medication before hospital admission but no further psychopathology was described in the medical records. All other patients were categorized as having 'no psychopathology'. The list of disorders defined as 'definite -' or 'probable psychopathology' is described in Table S4.1 (supplementary data), frequencies of occurrence for the different disorders are described below. Within the group of 'possible psychopathology', grouping based on different disorders could not be made, because the indication for prescribing the psychoactive medication was missing in the medical records. The psychoactive medication used by the patients in our study is listed in Table S4.2 (supplementary data). If there was any doubt with regard to categorization of the subjects, categorization was made by consensus of two researchers (AEW and MCW). The inter-observer agreement, calculated with a weighted Cohen's kappa in a random sample of 47 patients was 0.86, indicating excellent agreement.[15]

FIGURE 4.1 STUDY FLOWCHART



[a]Neurological patients and/or other reasons for impaired delirium assessment e.g., mental retardation or language barrier.
Abbreviations: ICU = intensive care unit.

Delirium classification

Delirium status was classified for each admission day in the ICU, using a validated algorithm encompassing the preceding 24 hours, as described in detail elsewhere.[16] For this assessment, the richmond agitation sedation scale (RASS[17]) and confusion assessment method for the ICU (CAM-ICU[18]) scores from the bedside nurses were used, in addition to initiation of delirium treatment, chart review, and an additional CAM-ICU by the research nurses, where applicable.[16] Based on this assessment procedure, patients were classified each ICU day as either being awake without delirium, delirious, or comatose.[16]

Statistical analysis

Categorical variables were reported as frequencies. Continuous variables were presented as mean with standard deviation (SD), or median with interquartile ranges (IQR), for normally and non-normally distributed variables respectively. Differences between the characteristics of patients with 'definite - ', 'probable –', 'possible -', and 'no pre-existing psychopathology' were assessed using a Chi Square test, an ANOVA, or a Kruskall-Wallis, where appropriate.

ICU discharge and death both prevent the occurrence of delirium during ICU stay (i.e., the event of interest), and can therefore both be regarded as competing events of delirium.[19,20] Therefore, to study the association between psychopathology prior to hospital admission and the occurrence of ICU delirium, multivariable competing-risk Cox proportional hazard analyses were used.[2,19,21] With the competing event analyses two measures of association were computed. First, we calculated the cause-specific hazard ratios (CSHR) as an estimate of the direct effect of psychopathology on delirium, ICU discharge, or death respectively. The CSHR can be interpreted as 'the risk of delirium, ICU discharge, or death among those patients who did not experience any of these outcomes yet'.[19,21] Second, the subdistribution hazard ratio (SHR) was calculated, which estimates the instantaneous risk of developing delirium dependent on the presence of psychopathology prior to hospital admission.[22] The subdistribution hazard ratio is a summary measure of the separate cause specific hazards and can be used to calculate the cumulative incidence of the outcome of interest. Interpretation is for those patients who did not experience an ICU delirium yet, and with patients who have experienced one of the competing events (i.e., ICU discharge or death) considered among those still event-free with respect to the event of interest (i.e., ICU delirium).[23] Both measures were calculated for any psychopathology (i.e., 'definite', 'probable', and 'possible' combined) and for the psychopathology categories separately, using 'no psychopathology' as the reference group.

Possible confounders included in the multivariable models were selected, based on expert opinion and a recent systematic review on risk factors for ICU delirium.[5] Covariables measured at ICU admission were age, gender, the charlson comorbidity index (CCI[24]) as a measure of chronic disease burden, type of admission (i.e., medical, acute surgical, or elective surgical) and the acute physiology and chronic health evaluation IV score (APACHE IV[25]) to assess for the severity of illness in the first 24 hours of ICU admission. Further, the daily sequential organ failure assessment (SOFA[26]) was used as a measure of severity of illness, leaving out the neurological component, as this is highly correlated with delirium and inclusion may result in overcorrection. Daily SOFA scores were cumulated until the event of interest (i.e., delirium) or competing events (i.e., ICU discharge or death), whichever occurred first, resulting in a cumulative SOFA score per patient. Trend imputation was used for missing values of daily measured SOFA scores, based on the availability of longitudinal data.[27]

All data analyses were performed with IBM SPSS Statistics 21.0 for Windows and R version 3.1.1 for Windows (R Foundation for Statistical Computing Vienna, Austria). Statistical inference was performed against two-sided alternatives, using a significance level of 0.05.

RESULTS

Of the 2,669 patients who were admitted between January 2011 and June 2013, 1,579 patients were excluded because they were transferred from another ICU, stayed in the ICU for less than 24 hours, had conditions which would potentially hamper delirium assessment (e.g., neurological illnesses), or had a delirium at admission. This resulted in a study population of 1,090 patients (Figure 4.1). The characteristics of the study population are outlined in Table 4.1. In the study population, 334 (31%) patients had a history of psychopathology prior to hospital admission (i.e., 'definite', 'probable', or 'possible'). Patients with pre-existing psychopathology were more often female, and were more often admitted to the ICU by a medical discipline compared to patients with no psychopathology prior to hospital admission.

There were 188 patients who were categorized as 'definite -' or 'probable psychopathology'. Of these 188 patients, 38 patients (20%) had anxiety disorders, 98 (52%) had mood disorders, 71 patients (38%) had any form of substance abuse, 20 patients (11%) were diagnosed with a personality disorder, and 13 (7%) with a psychotic disorder. There were 19 patients (10%) who had other psychopathologies, which are further categorized in Table S4.1 (supplementary data). In 71 (38%) patients, different psychopathological disorders prior to hospital admission were present simultaneously (e.g., an anxiety as well as a mood disorder).

TABLE 4.1 CHARACTERISTICS OF THE STUDY POPULATION

	Psychopathology								
	No		Possible		Probable		Definite		p-value[a]
	n=756 (69%)		n=146 (13%)		n=109 (10%)		n=79 (7%)		
Age in years, mean (SD)	61	(16)	62	(14)	58	(14)	56	(15)	<0.01
Male, n (%)	476	(63)	79	(54)	64	(59)	37	(47)	<0.05
CCI, median (IQR)	6	(0–10)	6	(3–11)	6	(0–10)	6	(0–11)	0.12
APACHE IV score, mean (SD)	74	(28)	77	(26)	69	(28)	73	(26)	0.19
Cumulative SOFA, median (IQR)[b]	14	(7–40)	10	(6–30)	12	(7–36)	12	(6–35)	0.07
ICU LOS in days, median (IQR)	5	(2–10)	4	(2–11)	5	(3–11)	6	(2–10)	0.58
Type of admission, n (%)									
Medical	322	(43)	77	(53)	58	(53)	50	(63)	<0.005
Elective surgical	216	(29)	43	(30)	27	(25)	16	(20)	
Acute surgical	218	(29)	26	(18)	24	(22)	13	(17)	
Delirium, n (%)	341	(45)	77	(53)	61	(56)	34	(43)	0.07
Delirium days, median (IQR)	0	(0–2)	1	(0–3)	1	(0–3)	0	(0–2)	<0.05

[a] Comparison between patients with 'no', 'possible', 'probable' and 'definite' psychopathology were assessed using ANOVA for normally distributed data, Kruskall-Wallis for non-normally distributed data, and Chi2 test for categorical data.

[b] Cumulative SOFA score without neurological component, until event of interest or competing event.

Abbreviations: APACHE IV = acute physiology and chronic health evaluation IV score, CCI = charlson comorbidity index, ICU = intensive care unit, IQR = interquartile range, LOS = length of stay, n = number, SD = standard deviation, SOFA = sequential organ failure assessment.

In the 334 patients with 'any psychopathology', 172 (51%) developed delirium. Of the 756 patients without psychopathology, 341 (45%) developed delirium. The occurrence of delirium or the competing events (i.e., ICU discharge or death) within the different categories of psychopathology prior to hospital admission are outlined in Table 4.2. Table 4.2 also shows the CSHRs for 'any psychopathology' versus 'no psychopathology', for each of the events. The adjusted CSHR for developing delirium in patients with 'any psychopathology' was 1.30 (95% confidence interval [CI] 1.08–1.57). Furthermore, patients with 'probable -' or 'possible psychopathology' prior to hospital admission were at increased risk of developing delirium, with adjusted CSHRs of 1.40 (95% CI 1.06–1.84) and 1.33 (95% CI 1.04–1.71), respectively. For patients with 'definite psychopathology' no statistically significant association with delirium was found (adjusted CSHR=1.09, 95% CI 0.76–1.57).

Compared to 'no psychopathology', and after adjusting for competing events and covariables, pre-existing psychopathology was associated with an increased instantaneous risk of developing delirium (adjusted SHR=1.35, 95% CI 1.12–1.63). For the different categories of psychopathology, 'probable -' and 'possible psychopathology' prior to hospital admission was associated with an increased delirium risk (adjusted SHR=1.55, 95% CI 1.17–2.04 and 1.30, 95% CI 1.01–1.66, respectively) (Table 4.3). 'Definite psychopathology' prior to hospital admission was not associated with an increased instantaneous risk of delirium incidence (adjusted SHR=1.18, 95% CI 0.82–1.68).

TABLE 4.2 CAUSE-SPECIFIC HAZARD RATIOS WITH ACCOMPANYING 95% CONFIDENCE INTERVAL FOR THE ASSOCIATION BETWEEN MEDICAL HISTORY OF PSYCHOPATHOLOGY AND DELIRIUM ONSET, ICU DISCHARGE OR DEATH

	Event of interest					Competing events									
Psycho-pathology	Delirium n=513 (47%)					ICU discharge n=515 (47%)					Death n=62 (6%)				
	n	Crude		Adjusted[a]		n	Crude		Adjusted[a]		n	Crude		Adjusted[a]	
No	341	1.00	(reference)	1.00	(reference)	374	1.00	(reference)	1.00	(reference)	41	1.00	(reference)	1.00	(reference)
Any	172	1.19	(0.99-1.43)	1.30	(1.08-1.57)*	141	0.86	(0.71-1.05)	0.91	(0.74-1.11)	21	1.07	(0.63-1.82)	1.17	(0.67-2.04)
	n	Crude		Adjusted[a]		n	Crude		Adjusted[a]		n	Crude		Adjusted[a]	
No	341	1.00	(reference)	1.00	(reference)	374	1.00	(reference)	1.00	(reference)	41	1.00	(reference)	1.00	(reference)
Possible	77	1.31	(1.02-1.67)*	1.33	(1.04-1.71)*	60	1.17	(0.56-2.41)	1.33	(0.63-2.80)	9	0.91	(0.69-1.21)	0.89	(0.67-1.17)
Probable	61	1.28	(0.97-1.68)	1.40	(1.06-1.84)*	39	1.46	(0.71-3.01)	1.90	(0.91-3.98)	9	0.73	(0.52-1.01)	0.79	(0.56-1.12)
Definite	34	0.90	(0.63-1.28)	1.09	(0.76-1.57)	42	0.50	(0.15-1.65)	0.37	(0.10-1.39)	3	0.97	(0.71-1.35)	1.10	(0.79-1.53)

*p-value < 0.05.

*Adjusted for: age, gender, charlson comorbidity index, type of admission, acute phsysiology and chronic health evaluation IV score, comulative sequential organ failure assessment until event of interest or competing event, without the neurological component.

TABLE 4.3 SUBDISTRIBUTION HAZARD RATIOS FOR THE ASSOCIATION BETWEEN A HISTORY OF PSYCHOPATHOLOGY AND THE DEVELOPMENT OF DELIRIUM

Psychopathology	Subdistribution Hazard Ratio (95% confidence interval)			
	Crude		Adjusted[a]	
No	1.00	(reference)	1.00	(reference)
Any	1.24	(1.03-1.48)*	1.35	(1.12-1.63)*
	Crude		Adjusted[a]	
No	1.00	(reference)	1.00	(reference)
Possible	1.28	(1.00-1.64)*	1.30	(1.01-1.66)*
Probable	1.38	(1.05-1.82)*	1.55	(1.17-2.04)*
Definite	0.97	(0.68-1.38)	1.18	(0.82-1.68)

* p-value < 0.05.

[a] Adjusted for: age, gender, charlson comorbidity index, type of admission, acute physiology and chronic health evaluation IV score, cumulative sequential organ failure assessment until event of interest or competing event, without the neurological component.

DISCUSSION

To the best of our knowledge this is the first study conducted in a heterogeneous population of ICU patients describing the association between psychopathology prior to hospital admission and the occurrence of ICU delirium. We found that psychopathology prior to hospital admission was associated with an increased delirium risk. Although preceding evidence was limited, the findings are consistent with the majority of previous investigations in other patient populations.[7-12] Except for one study, which could not demonstrate that pre-existing anxiety and depression was associated with post-operative delirium.[13] However, this study was relatively small and restricted to cardiac surgery patients only.[13]

The association between psychopathology and delirium found in our study was driven by the group of patients with 'probable -' and 'possible psychopathology' prior to hospital admission. We could not demonstrate an association between 'definite psychopathology' prior to hospital admission and delirium. A number of reasons exist for this apparent contradiction. Firstly, patients who were categorized as 'definite' had a diagnosis made by a psychiatrist or psychologist, and were likely to have had more severe psychopathology than the patients with 'probable -' and 'possible psychopathology'. It is known that in patients with severe psychiatric diseases delirium is often underdiagnosed, as it can be difficult to distinguish behavior belonging to the

pre-existing psychiatric disease from a delirium.[28] Hence, the incidence of delirium may be underestimated in this group of patients. Secondly, it might be that the incidence of delirium is truly lower in these patients, due to preventive measures in patients with a medical history of severe psychiatric disorders. Possibly, more attention is paid to orientation and comfort for patients with psychiatric problems. Increasing evidence suggests that applying such prevention strategies can be effective in reducing delirium occurrence.[29] Lastly, the group of patients with 'definite psychopathology' was relatively small, in comparison with other groups. Hence, it could be that the sample size was not sufficient to demonstrate a true association.

The mechanism by which psychopathology prior to hospital admission is predisposing patients to delirium during ICU stay has not been elucidated yet. However, psychopathology (e.g., a major depressive disorder) is associated with increased cytokine levels, which may result in priming of microglia, which are the macrophages of the brain. Primed microglia are hypersensitive to stimuli such as peripheral inflammation.[10] Delirium has been proposed to be instigated by an exaggerated responsiveness of microglia to peripheral inflammation, leading to neuroinflammation.[30] Patients with pre-existing psychopathology may thus already be more susceptible for delirium due to the presence of primed microglia, prior to precipitating factors for delirium (e.g., factors associated with critical illness and treatment in the ICU). The presence of psychopathology is also associated with disturbances in cortisol levels.[10,31,32] It may be that abnormal cortisol levels induce dysfunction of the hypothalamic-pituitary-adrenal axis, which may also result in patients being more prone to the development of delirium.[31,33] Other factors that are associated with psychopathology are disturbances in neurotransmitters (e.g., dopamine and serotonin), and neuronal network changes, which could also make these patients more prone to delirium.[34,35] To evaluate these hypotheses, additional research is required, combining serum analyses of cytokines and cortisol levels, neuronal network analyses, and post-mortem brain studies.

Our investigation has several strengths. First of all, we analyzed data of a large population of heterogeneous ICU patients, which contributes to the generalizability of the results. Secondly, this study is the first to use competing events analysis to describe the association between psychopathology prior to hospital admission and the risk of in-hospital delirium. It is important to include competing events in the statistical analysis when attempting to answer an etiological question, as occurrence of any of these events prevents the development of delirium. Not taking these competing events into account may lead to biased results.[2,20] In addition, adjustments for important confounders were made, largely based on a recent systematic review on

risk factors for ICU delirium.[5] Furthermore, we used a validated algorithm to determine whether delirium was present, which reduced the risk of misclassification.[16] Some limitations of our investigation should also be acknowledged. The presence or absence of psychopathology was determined in retrospect, using medical records. Preferably this information should be assessed prospectively by a psychiatrist or psychologist, as this will reduce misclassification of patients. However, in an ICU population where admission often is unplanned, it is difficult to assess the presence of psychopathology prior to hospital admission prospectively. Further, although this is one of the largest studies on the association between pre-existing psychopathology and delirium, our study population size was not large enough for various subgroup analyses. Future research should investigate whether the risk of delirium differs between patients with different pre-existing psychiatric illnesses (e.g., anxiety, mood and psychotic disorders). Furthermore, stratification based on age and inflammation are interesting, as well as the study of cortisol levels, to further elucidate on the mechanism by which pre-existing psychopathology increases the risk of delirium.

CONCLUSION

Psychopathology prior to hospital admission is associated with an increased delirium risk in the ICU. Further research is needed to investigate the pathophysiologic mechanisms, and to establish which disorders are particularly associated with this increased delirium risk.

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SUPPLEMENTARY DATA

TABLE S4.1 LIST OF PSYCHOPATHOLOGY (CATEGORIZED ACCORDING TO THE DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS 4TH EDITION)

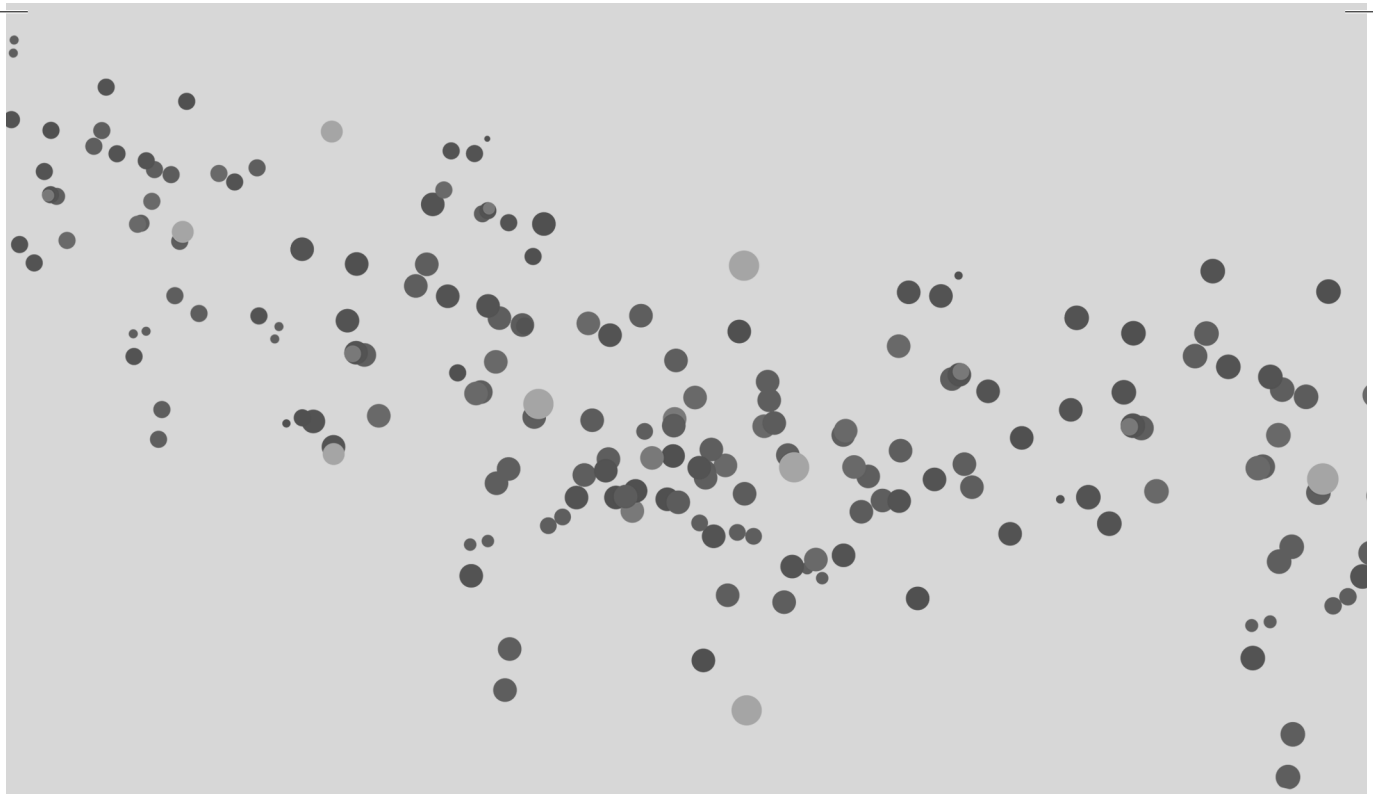
Category	Disorder
Anxiety disorders	
	Panic disorder
	Panic disorder with/without agoraphobia
	Agoraphobia without history of panic disorder
	Specific phobia
	Social phobia
	Obsessive-compulsive disorder
	Posttraumatic stress disorder
	Acute stress disorder
	Generalized anxiety disorder
	Anxiety disorder due to a general medical condition
	Substance-induced anxiety disorder
	Anxiety disorder not otherwise specified
Mood disorders	
	Major depressive disorder
	Dysthymic disorder
	Depressive disorder not otherwise specified
	Bipolar I disorder
	Bipolar II disorder
	Cyclothymic disorder
	Bipolar disorder not otherwise specified
	Mood disorder due to a general medical condition
	Substance-induced mood disorder
	Mood disorder not otherwise specified
Psychotic disorders	
	Schizophrenia
	Schizophreniform disorder
	Schizoaffective disorder
	Delusional disorder
	Brief psychotic disorder
	Shared psychotic disorder
	Psychotic disorder due to a general medical condition
	Substance-induced psychotic disorder
	Psychotic disorder not otherwise specified

Personality disorders	
	Cluster A (paranoid, schizoid, schizotypical)
	Cluster B (antisocial, borderline, histrionic, narcissistic)
	Cluster C (avoidant, dependent, obsessive-compulsive)
Substance abuse	
	Alcohol
	Drugs
	Other substances
Other	
	Eating disorders
	Somatoform disorders
	Factitious disorders
	Dissociative disorders
	Adjustment disorder
	Autism spectrum disorders
	Attention deficit hyperactivity disorder
	Impulse control disorders
	Sexual disorder

TABLE S4.2 LIST OF USED PSYCHOACTIVE HOME MEDICATIONS (CATEGORIZED ACCORDING TO THE DUTCH ROYAL PHARMACISTS ASSOCIATION)

Category		Drug name
Anticonvulsants		
		carbamazepine
		lamotrigine
		valproic acid
Antidepressants		
	Tricyclic antidepressants	amitriptyline
		clomipramine
		dosulepin
		imipramine
		nortriptyline
	Selective serotonin reuptake inhibitors	citalopram
		escitalopram
		fluoxetine
		fluvoxamine
		paroxetine
		sertraline
		venlafaxine

Other	duloxetine
	agomelatine
	bupropion
	mirtazapine
	mianserin
	trazodone
	tranylcypromine
Antipsychotics	
First generation	flupentixol
	haloperidol
	periciazine
	pipamperon
Second generation	clozapine
	olanzapine
	quetiapine
	risperidone
Anxiolytics	
	hydroxyzine
	pregabalin
Benzodiazepines	
	alprazolam
	chlordiazepoxide
	clobazam
	clorazepate
	diazepam
	lorazepam
	oxazepam
	temazepam
Drugs for treatment of addiction	
	disulfiram
	methadon
	naltrexone
Other	
	lithium
	methylphenidate



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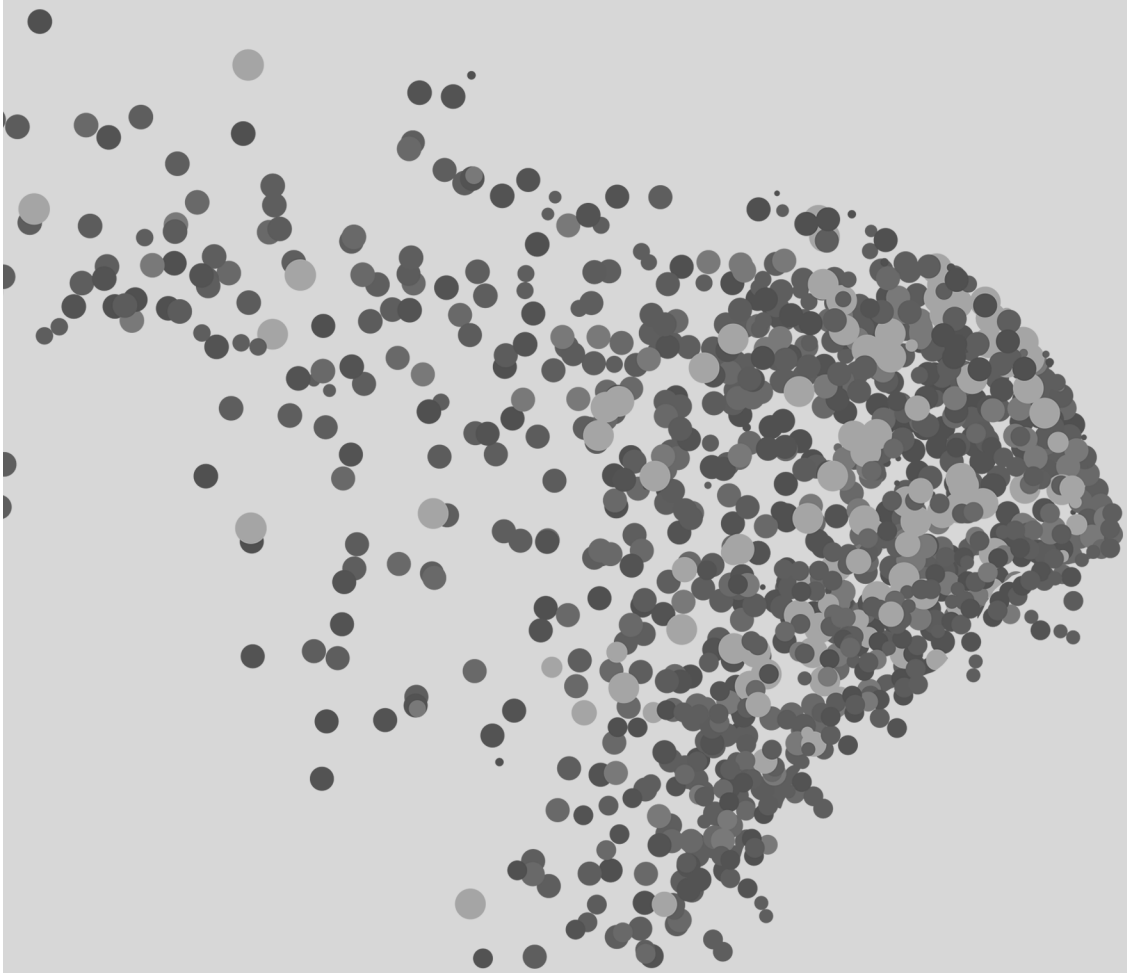

BRAIN DYSFUNCTION AFTER CRITICAL ILLNESS

5

COGNITIVE IMPAIRMENT AFTER INTENSIVE CARE UNIT ADMISSION: A SYSTEMATIC REVIEW

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ABSTRACT

Objective

There is increasing evidence that critical illness and treatment in an intensive care unit (ICU) may result in significant long-term morbidity. The purpose of this systematic review was to summarize the current literature on long-term cognitive impairment in ICU survivors.

Methods

PubMed/MEDLINE, CINAHL, Cochrane Library, PsycINFO and Embase were searched from January 1980 until July 2012 for relevant articles evaluating cognitive functioning after ICU admission. Publications with an adult population and a follow-up duration of at least two months were eligible for inclusion in the review. Studies in cardiac surgery patients or subjects with brain injury or cardiac arrest prior to ICU admission were excluded. The main outcome measure was cognitive functioning.

Results

The search strategy identified 1,128 unique studies, of which 19 met the selection criteria and were included. Only one article compared neuropsychological test performance before and after ICU admission. The 19 studies that were selected reported a wide range of cognitive impairment in 4–62% of the patients, after a follow-up of 2–156 months.

Conclusions

The results of most studies of the studies reviewed suggest that critical illness and ICU treatment are associated with long-term cognitive impairment. Due to the complexity of defining cognitive impairment, it is difficult to standardize definitions and to reach consensus on how to categorize neurocognitive dysfunction. Therefore, the magnitude of the problem is uncertain.

INTRODUCTION

The utilization of intensive care units (ICUs) has expanded rapidly over the past decades, with a concomitant increase in the proportion of patients surviving an episode of critical illness. This has resulted in a growing number of ICU survivors.[1] Results from previous studies suggest that ICU survivors may suffer from significant long-term morbidity.[2] An important long-term complication of critical illness and ICU treatment is cognitive impairment. Cognitive impairment is associated with a reduced quality of life, and it is a major determinant of societal health care costs and caregiving needs.[3-5] A large proportion of ICU patients consist of elderly people and especially this population is prone to develop cognitive impairment.[6] However, it appears that younger, relatively healthy patients are also at risk for cognitive impairment following critical illness Cognitive impairment often becomes apparent after ICU discharge, and intensivists may therefore not be aware of the occurrence of this complication. In the last two years, some high-quality studies on this topic have been published.[1,5] The aim of this systematic review was to summarize the current evidence for long-term cognitive impairment in ICU survivors.

METHODS

This systematic review was performed in accordance with the recent standards for systematic reviews published by the Institute of Medicine in March 2011.[7]

Search strategy

We conducted a search of PubMed/MEDLINE, CINAHL, Cochrane Library, PsycINFO and Embase from January 1980 through July 2012 using relevant search terms relating to cognition and ICU admission. The exact search strategy is described in Table 5.1. The reference lists from the selected articles were screened to identify additional articles. To assess the comprehensiveness of the search strategy, we tested the search string with eight studies that we already had on file and which we considered relevant for this systematic review.

Study selection

Studies with cognitive functioning after ICU admission in adults as the primary or secondary endpoint were included in our review.

The following studies/articles were excluded:

- Reviews, case-studies and animal studies, as well as articles published in languages other than English, Dutch, German or French;
- Investigations with a follow-up duration on cognitive functioning shorter than two months;
- Studies on patients undergoing heart surgery and on those with cardiac arrest or brain injury prior to ICU admission;
- Articles describing the same, or an overlapping, patient sample as described in an article already included in the review; in this case, we only used the most recent article, which described both new data and the data reported earlier.

TABLE 5.1 SEARCH STRATEGY

Database All: 1980 to 07/2012	Search filter	Retrieved
PubMed/Medline	((("Intensive Care"[Mesh] OR "Critical Illness"[Mesh] OR "Intensive Care Units"[Mesh] OR "Critical care"[Mesh]) OR "Respiratory Distress Syndrome, Adult"[Mesh]) OR ("sepsis"[Mesh]) OR ("Intensive care"[title/abstract]) OR ("Critical illness"[title/abstract]) OR ("ICU"[title/abstract]) OR ("Critical care"[title/abstract]) OR ("Acute Respiratory Distress Syndrome"[title/abstract]) OR ("sepsis"[title/abstract]))) AND (("cognition"[MeSH Terms] OR "cognition"[title/abstract]) OR cognitive[title/abstract] OR "neurocognitive"[title/abstract])	603
EMBASE	'intensive care':ab,ti OR 'intensive care unit':ab,ti OR 'critical illness':ab,ti OR 'critical care':ab,ti OR 'acute respiratory distress syndrome':ab,ti OR 'sepsis':ab,ti AND ('cognition':ab,ti OR 'cognitive':ab,ti OR 'neurocognitive':ab,ti)	368
CINAHL	(TI ("Intensive Care" OR "Critical illness" OR "Intensive Care Unit" OR "Critical care" OR "ICU" OR "respiratory distress syndrome, adult" OR "sepsis") OR AB ("Intensive Care" OR "Critical illness" OR "Intensive Care Unit" OR "Critical care" OR "ICU" OR "respiratory distress syndrome, adult" OR "sepsis")) AND (TI ("Cognition" OR "Cognitive" OR "Neurocognitive") OR AB ("Cognition" OR "Cognitive" OR "Neurocognitive"))	393
PsycINFO	(("Intensive Care" or "Critical care" or "Critical illness" or "Intensive Care Unit" or "Acute respiratory distress syndrome" or "Sepsis").ti. or "Intensive Care".ab. or "Critical care".ab. or "Critical illness".ab. or "Intensive Care Unit".ab. or "Acute respiratory distress syndrome". ab. or "Sepsis".ab.) AND ((Cognition or Cognitive or Neurocognitive). ti. or Cognition.ab. or Cognitive.ab. or Neurocognitive.ab.)	284
Cochrane Libary	("Intensive Care" in Title, Abstract or Keywords or "Intensive Care Unit" in Title, Abstract or Keywords or "Critical care" in Title, Abstract or Keywords or "Critical illness" in Title, Abstract or Keywords or "Acute respiratory distress syndrome" in Title, Abstract or Keywords or "Sepsis" in Title, Abstract or Keywords") AND ("Cognition" in Title, Abstract or Keywords and "Cognitive" in Title, Abstract or Keywords and "Neurocognitive" in Title, Abstract or Keywords)	116 non-reviews and non-groups
Total number of uniue titels		1,128

The eligibility of each article that was found was independently evaluated on title, abstract and, if necessary, full text, by two reviewers using the abovementioned selection criteria (AEW and AWvdK). If the two reviewers disagreed about the eligibility of an article, a third reviewer (AJCS) was consulted.

Data extraction

Both reviewers independently assessed the articles that were selected, using a standardized data collection form to record the required data (Table S5.1, supplementary data). The following characteristics were recorded: first author, year of publication, study design, study population with in- and exclusion criteria, number of enrolled participants and age at baseline, number of deceased subjects and loss-to-follow-up, measurement of baseline cognition and the neuropsychological tests used and the test results.

Study quality was assessed based on four criteria: (1) availability of data on cognitive functioning at baseline; (2) use of neuropsychological tests to assess cognition; (3) description of inclusion and exclusion criteria; (4) adjustment for predictors which could interfere with the cognitive outcome, such as age and gender. These quality criteria were chosen because these are universally applicable (item 3 and 4) and specific for studies evaluating neurocognitive outcome (criteria 1 and 2).

Statistical analysis

The data of the included studies were not pooled because we expected considerable methodological differences between studies, especially with respect to the selection of neuropsychological tests, timing of assessment and definitions of cognitive impairment.

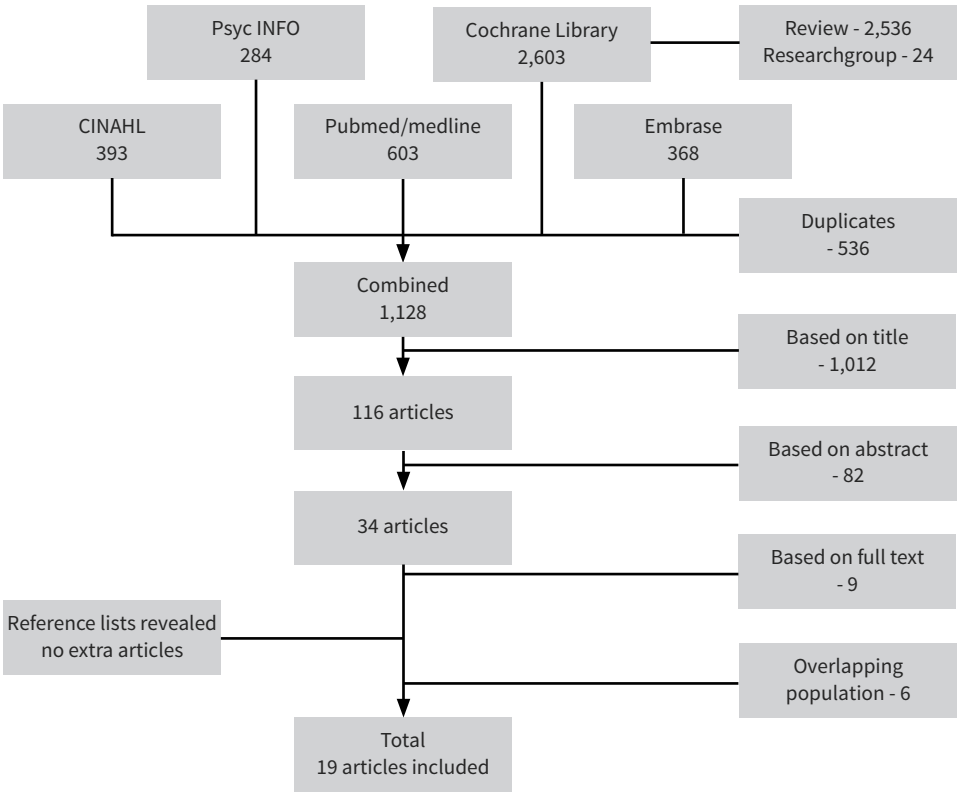
Some authors hypothesize that the risk of neurocognitive impairment is higher in patients with acute respiratory distress syndrome (ARDS) than in the general ICU population.[4,8] Elderly ICU patients may also have an increased risk of cognitive impairment.[6] In the presentation of the selected studies, we therefore, distinguished studies with focus on ARDS and studies with focus on elderly patients. The other three ICU population categories were: surgical, medical and general.

RESULTS

The search string (Table 5.1) yielded a total of 1,664 publications, of which 1,128 were unique. The defined search strategy did identify all eight studies that we already had on file and which we considered relevant for this systematic review. We excluded 1,094 articles based on title or abstract and evaluated 34 full-text articles (Figure 5.1). There was disagreement on the eligibility of one article between the first two reviewers.[5] The study was of a high quality, especially because of the presence of baseline

neuropsychological data, but the patient cohort did not exclusively comprise an ICU population. In consultation with the third reviewer, consensus was reached to exclude this study from the systematic review, but mention its results in the Discussion. Eventually, 19 articles met the selection criteria and were included. No extra titles were identified after screening the reference lists.

FIGURE 5.1 FLOWCHART SEARCH AND SELECTION OF LITERATURE



The included studies are shown in Tables 5.2 and 5.3. Table 5.2 summarizes the data of the 14 studies which extensively used neuropsychological testing to measure cognitive functioning, and Table 5.3 outlines five additional studies which used questionnaires or screening test data to assess cognitive performance. The number of subjects per study varied between 30 and 1,822. Most studies consisted of young, relatively healthy ICU survivors. Eleven studies had a study population with a mean age

of 54 years or less. Four studies focused on the elderly or very elderly (>65, >75 and >80 years, respectively).[1,9-11] The patient populations of seven comprised ARDS patients. The studies had a follow-up duration varying from 2 months up to 13 years after ICU discharge.

Only one of the 19 articles met all four quality criteria, with the inclusion of a neuropsychological assessment prior to ICU admission.[1] Seven other investigations took an estimated premorbid cognitive functioning into account.[8,10-15] Fourteen studies met the second quality criterion, which was the use of neuropsychological testing to assess cognitive functioning (Table 5.2).[1,8,12-23] All 19 articles reported in- and exclusion criteria. The fourth quality criterion (i.e., adjustment for covariables which could interfere with the cognitive outcome) was met by 16 studies which compared the post-ICU test performance to normative age- and gender-matched population data.[1,8,11-24] One study used age- and gender-matched data from a population with longstanding illness for comparison.[3] In some studies a correction was made for educational level,[8,11-15,17-19] 11 studies made an adjustment for severity of illness during ICU admission [8,9,12-17,21,23,24] and nine studies took the length of ICU admission into account.[3,9,12,15,16,19,21,23,24]

Of the 19 articles reviewed, four reported a relatively good cognitive status amongst ICU survivors, which was defined as ≤10% of patients with cognitive impairment [10,16,22] or a p value of >0.05.[11] Absence of cognitive impairment was reported more often in studies with screening tests (2/5 (40%), Table 5.3) than in investigations based on neuropsychological tests (2/13 (15%), Table 5.2). In addition, in one of the studies which used neuropsychological tests, half of the patients (n=27) were excluded because they could not complete the cognitive testing;[16] if all these 27 patients had cognitive impairments, the rate of impairment would be close to 100%. The other 15 studies reported at least "mild" cognitive impairment in a larger proportion of ICU survivors. The studies with the screening test data reported impairment in 11–56% of the population.[3,9,24] The investigations with neuropsychological testing showed impairment in 11–62% of the examined population.[1,8,12-15,17-21] Although the range of cognitive impairment was comparable, in general the studies with extensive neuropsychological testing reported a higher incidence of cognitive impairment than those with screening test data.

The incidence of cognitive impairment of ARDS survivors ranged from 4–56%.[8,12,15,19,22-24] Within the general, medical and surgical ICU survivors the incidence of cognitive impairment ranged from 4–62%.[3,13,14,16-18,21] Four studies assessed cognitive impairment in the elderly,[1,9-11] two of which, both based on screening test data, did not find significant cognitive impairment among their elderly subjects.[10,11] The other two studies in elderly patients reported cognitive impairment varying from 17–56%.[1,9]

The tested cognitive domains per article are shown in Table 5.4. Of the included studies, 14 tested for 'memory', which was therefore the most tested domain. The domains of memory, attention, verbal fluency, and executive functioning were most frequently impaired.[12,18-21,24] Two studies reported an association between a higher estimated premorbid IQ and less cognitive impairment.[8,13]

Seven studies measured cognitive functioning at multiple points in time after ICU admission.[8,12,17,21,23,24] However, one study only reported the proportion of patients with cognitive impairment at the final assessment.[23] Two studies found no improvement of cognitive function from one to two years of follow-up.[8,12] One article reported no improvement, even after five years of follow-up.[24] However, another study reported a return towards normal cognitive functioning by nine months,[21] and one study reported a decrease in severe impairment after one year.[17]

TABLE 5.2 SUMMARY OF INCLUDED STUDIES WHICH USED NEUROPSYCHOLOGICAL TESTS

First author	Year of study	Design	Population	Co.	n	Age at baseline (years)	Follow-up duration (months)	Deceased n (%)	Follow-up loss n (%)	Definition of cognitive impairment	Proportion cognitive impairment
Mikkelsen [23]	2012	Prosp. cohort	ARDS	No	213	49 (40-58)	12	22	53 (28)	≥2 SD below the population norm	41/75 (55%)
Torgersen [16]	2011	Prosp. cohort	Surgical ICU	No	55	51 (16)	3	0 (0)	20 (36)	≥ 3 tests ≥ 1.5 SD or ≥ 2 test ≥ 2 SD below the mean	4/35 (11%)
							12	0 (0)	5 (14)		3/30 (10%)
Girard [17]	2010	Prosp. cohort	Medical ICU	No	126	61 (47-71)	3	27 (21)	9 (9)	2 tests ≥ 1.5 SD or 1 test ≥ 2 SD below the mean (mild) ≥ 3 tests ≥ 1.5 SD or ≥ 2 tests ≥ 2 SD below the mean (severe)	13/76 (17%) 47/76 (62%)
							12	12 (15)	13 (17)		18/52 (35%) 19/52 (36%)
Ehlenbach[1]	2010	Prosp. cohort	Elderly	Yes	41	75 (7)	96 (49-119)	NR	NR	< 86 on the CASI and diagnostic criteria for dementia at standardized clinical examination	5/41 (12%)

TABLE 5.2 SUMMARY OF INCLUDED STUDIES WHICH USED NEUROPSYCHOLOGICAL TESTS (CONTINUED)

First author	Year of study	Design	Population	Co.	n	Age at baseline (years)	Follow-up duration (months)	Deceased n (%)	Follow-up loss n (%)	Definition of cognitive impairment	Proportion cognitive impairment
Duning [18]	2010	Retrosp. Case-Control	Surgical ICU	No	74	66 (1)	≥12	4 (7)	8 (11)	"Close below average" with matched healthy control subjects, "Far below average" with matched healthy control subjects, mean over 74 subjects	10/17 tests 3/17 tests
Mikkelsen [19]	2008	Cross-sectional	ARDS	No	79	43 (13)	28 (35)	NR	NR	≥ 2 tests ≥ 1 SD or ≥ 1 test ≥ 1.5 SD below the population norm	44/79 (56%)
Jackson[14]	2007	Retrosp. cohort	Surgical ICU[b]	No[a]	97	45 (14)	12 to 24	10 (10)	29 (3)	≥ 2 tests > 1.5 SD or 1 test ≥ 2 SD below the mean	16/37 (43%)
Larson[8]	2007	Prosp. cohort	ARDS	No[a]	74	45 (16)	12	3 (4)	5 (7)	≥ 2 tests > 1.5 SD or 1 test > 2 SD below the population norm	29/63 (46%)
							24	2 (3)	2 (3)		26/59 (44%)
Jones[20]	2006	Prosp. cohort	General ICU	No	30	54 (18-78)	2	2 (7)	NR	≤ 25 percentile of matched control for memory and problem solving	5/16 (31%) 8/16 (50%)

TABLE 5.2 SUMMARY OF INCLUDED STUDIES WHICH USED NEUROPSYCHOLOGICAL TESTS (CONTINUED)

First author	Year of study	Design	Population	Co.	n	Age at baseline (years)	Follow-up duration (months)	Deceased n (%)	Follow-up loss n (%)	Definition of cognitive impairment	Proportion cognitive impairment
Sukantarat [21]	2005	Prosp. cohort	General ICU	No	51	60 (26-82)	3	NR	6 (12)	1 test ≤ 5th percentile of normative data	28/51 (55%)
											18/51 (35%)
							9			≥ 2 test ≤ 5th percentile of normative data	12/45 (27%)
											2/45 (4%)
Hopkins [21]	2005	Prosp. cohort	ARDS	No[a]	74	46 (16)	12	3 (4)	5 (7)	≥ 2 tests ≥ 1.5 SD or 1 test ≥ 2 SD below the population norm	30/66 (45%)
							24	2 (3)	2 (3)		29/62 (47%)
Kapfhammer[22]	2004	Retrosp. cohort	ARDS	No	80	37 (18-50)	96 (36-156)	2 (3)	17 (21)	Norm value ≥5 are clinically relevant.	4/46 (9%)
Jackson[13]	2003	Prosp. cohort	Medical ICU	No[a]	275	53 (15)	6	119 (43)	116 (74)	≥ 2 tests > 2 SD or ≥ 3 test > 1.5 SD below the population norm	11/34 (32%)
Rothenhäusler[15]	2001	Retrosp. cohort	ARDS	No[a]	119	42 (15)	76.8 (38.4)	17 (14)	43 (42)	Norm value ≥ 5 are clinically relevant.	11/46 (24%)

[a] Analyses with use of estimated premorbid cognitive function. [b] With regard to trauma patients, we only used data from the subpopulation without traumatic brain injury. Abbreviations: ARDS = acute respiratory distress syndrome, CASI = cognitive abilities screening instrument, Co. = baseline cognition, ICU = intensive care unit, NR = not reported, Prosp. = propective, Resp. = retrospective, SD = standard deviation

TABLE 5.3 SUMMARY OF INCLUDED STUDIES WHICH USED QUESTIONNAIRES OR SCREENING TEST DATA

First author	Year of study	Design	Population	Co.	n	Age at baseline (years)	Follow-up duration (months)	Deceased n (%)	Follow-up loss n (%)	Definition of cognitive impairment	Proportion cognitive impairment
Daubin [11]	2011	Prosp. cohort	Elderly	No[a]	100	79.3 (3.4)	3	61 (61)	1 (3)	IADL Score 0 till 4 (0 = no)	2.9 ± 1.4 (p = 0.62)
Adhikari [24]	2011	Prosp. cohort	ARDS	No	109	42 (35-56)	22 (6-48)	13 (12)	18 (19)	MAC-S (ability and frequency of occurrence) > 2 SD; > 1.5 SD; > 1 SD below population norms	5/64 (8%) 5/61 (8%) 10/64 (16%) 11/61 (18%) 13/64 (20%) 11/61 (18%)
							41 (33-52)[b]	8 (12)	6 (7)		2/46 (4%) 0/38 (0%) 4/46 (9%) 4/38 (11%) 7/46 (15%) 4/38 (11%)
Sacanella[10]	2011	Prosp. cohort	Elderly	No[a]	230	73.4 (5.5)	12	118 (51)	0 (0)	MMSE < 24	11/112 (10%)
Timmers[3]	2010	Prosp. cohort	Surgical ICU	No	1,822	61 (16)	96 (72-132)	936 (51)	288 (33)	EQ6D 2 (moderate) or 3 (severe)	247/575 (43%) Reference group 8% impairment
De Rooij[9]	2008	Retrosp. cohort	Elderly	No	578	85.4 (3.0)	44 (12-71)	347 (60)	71 (31)	IQCODE-SF > 3.9 (severe) > 3.1 ≤ 3.8 (mild)	27/164 (17%) 92/164 (56%)

[a] Analyses with use of estimated premorbid cognitive function. [b] Follow-up duration after first measurement. Abbreviations: ARDS = acute respiratory distress syndrome, Co.= baseline cognition, EQ-6D = euroqoL-6d, IADL = lawton index of daily living, ICU = intensive care unit, IQCODE-SF = informant questionnaire on cognitive decline in the elderly-short form, MAC-S = memory assessment clinic self-rating scale, MMSE = mini-mental state examination, NR = not reported, Prosp.= prospective, Retrosp.= retrospective, SD = standard deviation

TABLE 5.4 TESTED COGNITIVE DOMAINS

Cognitive domain	First Author																		
	Mikkelsen[23]	Daubin[11]	Torgersen[16]	Adhikari[24]	Sacanella[10]	Timmers[3]	Girard[17]	Ehlenbach[1]	Duning[18]	De Rooij[9]	Mikkelsen[19]	Jackson[14]	Jones[20]	Larson[8]	Sukantarat[21]	Hopkins[12]	Kapfhammer[22]	Jackson[13]	Rothenhäusler[15]
Global functioning[a]		■			■	■	■	■	■	■	■		■	■	■	■			
Verbal fluency	■						■	■			■	■		■				■	
(Visuo) Spatial skills							■		■			■		■		■			
Attention and concentration							■	■	■		■	■		■		■	■		■
Memory	■		■	■			■	■	■		■	■	■	■		■	■	■	■
Executive functioning	■		■				■		■		■	■		■	■	■		■	
Psychomotor speed			■				■					■		■		■			
Abstraction/visual construction								■										■	

[a] Global cognitive and intellectual functioning.

DISCUSSION

In this review, we systematically assessed publications on cognitive impairment after admission to an ICU. The 19 studies that met the selection criteria reported a wide range of cognitive impairment in 4–62% of the patients, after a follow-up of 2–156 months. Compared to studies which used neuropsychological testing, lower percentages of patients with cognitive impairment were reported in studies which only used screening test data. We found no difference in the risk of cognitive impairment between studies involving only ARDS patients and those which also included other ICU patients. In addition, we did not find a higher risk of cognitive impairment in studies in elderly patients, although three of the studies assessed only used screening test data.

The pathophysiology of cognitive impairment after ICU admission is believed to be multifactorial.[13,21] The most frequently reported explanation for an abrupt decrease in cognitive functioning after ICU admission is that patients with multi-organ failure may also develop brain damage.[13,25] Severe sepsis can lead to a neuroinflammatory response resulting in increased levels of cytokines in the brain.[25,26] Elevated cytokine levels are associated with impaired memory in healthy volunteers [27] and neuroinflammation is associated with the development of Alzheimer's disease.[28] Long-term cognitive impairment in patients may therefore represent a maladaptive version of cytokine induced disease.[26] Other possible causes are hypoxemia and hypotension, which have been related to cognitive impairment in numerous investigations.[12,13] Sedatives and analgesics are used extensively in the ICU and some studies suggest that this may also play a causal role in the development of long-term cognitive impairment.[13] Both hyperglycemia and hypoglycaemia as well as fluctuations in blood glucose are also associated with poor cognitive outcomes.[18,29] An association between delirium and long-term cognitive impairment has been reported, but the underlying cause remains to be elucidated.[17,30]

The focus of this review was on long-term cognitive impairment. We excluded those studies with a follow-up duration of less than two months. An early cognitive assessment may reflect residual pain, the effects of analgesic and sedative drugs and/or residual delirium.[12,16] The results of studies that measured cognition immediately after ICU admission and also at various time points during a long-term follow-up indicate that the incidence of cognitive impairment is high after ICU discharge but improves during the first few months after discharge.[12]

Even with the use of strict selection criteria, it was difficult to compare the reviewed studies and therefore, it was impossible to present pooled data. Among the reviewed studies which reported the results of neuropsychological testing,

there was a substantial variation in the definition of impairment, sample size and timing of assessment. In addition, medical practices in the ICU have substantially changed during the past decade, and these practical changes may also affect cognitive outcomes. However, we were unable to observe such an effect over time because all studies included in this review were published in the last 10 years.

A major limitation of most of the studies reviewed is that a baseline assessment of cognitive status before ICU admission is lacking. Ideally, cognition should be measured before and after ICU admission because the real interest is not the absolute level of cognitive performance but rather the change in cognitive functioning. ICU admissions, however, are often not elective and, consequently, a baseline assessment is usually not available. Some studies estimated the baseline cognitive performance after ICU admission rather than testing it in advance. Adjustments were made for patients who showed signs of pre-existing cognitive impairment.[8,12-15] Remarkably, there are two recent population based studies with premorbid cognitive data.[1,5] The first is a population based longitudinal study of aging and dementia, designed to establish the incidence of both cognitive impairment and risk factors for cognitive decline.[1] Of the 2,929 subjects who underwent repeated neuropsychological testing, 41 were admitted to an ICU. The authors of this study concluded that those who were hospitalized for a critical illness had a greater likelihood of cognitive impairment, even after adjusting for premorbid cognitive screening scores and comorbidity. The rate of cognitive decline did not change after admission to the ICU compared with the normal rate of decline. Therefore, the authors suggested that critical illness may cause an abrupt loss of cognitive function rather than accelerate the decline in cognitive functioning.[1] The second study with premorbid cognitive data was conducted among patients who survived severe sepsis.[5] Baseline cognitive assessments were performed in 9,223 respondents, of whom 516 survived severe sepsis. This study was not included in the Results of this review because the study did not require that patients were treated in an ICU. Consultation with the authors of this study revealed that 43% of the sepsis survivors were admitted to the ICU but that no subanalysis data on the ICU patients were available. The authors measured an increase from moderate to severe cognitive impairment among sepsis survivors. Before sepsis, 6.1% of the eventual survivors showed moderate to severe cognitive impairment;[5] after severe sepsis, the prevalence increased to 16.7%. These results led the authors to conclude that severe sepsis was independently associated with new cognitive impairment, which appeared to be substantial and persistent.[5] In the subgroup of the ICU patients, the risk of cognitive impairment was comparable to that of the whole study population [TJ Iwashyna, personal communication].

The effects of severity of illness on the risk for developing long-term cognitive impairment remain uncertain. Due to the small size of the patient groups, the availability of analyses in patients subgroups is limited. It is even more relevant to evaluate the effect of interventions that may reduce the risk of cognitive impairment. A possible intervention that could be evaluated in a randomized study is early mobilization.[31] Early mobilization has a positive effect on length of stay in the ICU and physical independence after discharge;[31,32] it also reduces depression in survivors of critical illness.[32]

It remains uncertain whether a low performance on neuropsychological tests reflects an impairment in cognitive functioning related to critical illness and ICU admission, or whether it is perhaps merely a marker of patients with poor health and an increased risk of ICU admission. However, the two studies with premorbid cognitive data show that at least part of the measured cognitive impairment is related to the ICU admission and critical illness.[1,5] There are similarities between recent studies on cognitive impairment after critical illness and ICU treatment, and the slightly older studies on cognitive impairment after cardiac surgery.[33-35] It has become apparent in the field of cardiac surgery that it is extremely difficult to distinguish normal variation in test performance from true cognitive impairment.[36,37] Consequently, in cardiac surgery, it is now accepted that the incidence of cognitive injury has long been overestimated because normal variations in test performance were formerly not always recognized.[35,38,39] However, cardiac surgical patients clearly differ from general ICU patients, and a comparison with the post-cardiac surgery literature might therefore be misleading. Additional research is still required to establish a reliable incidence of cognitive decline following ICU admission.

CONCLUSION

In conclusion, most of the studies reviewed here suggest that critical illness and ICU treatment are associated with long-term cognitive impairment. Due to the complexity of defining cognitive impairment, the magnitude and severity of the problem are uncertain. It is therefore crucial that the definition of neurocognitive dysfunction is standardized. The pathophysiology of cognitive impairment after ICU admission is believed to be multifactorial, and more research is needed to identify key risk factors. Previously identified risk factors for neurocognitive dysfunction are severity of illness, hypoxemia, hypotension, the use of sedatives and analgesics, hyper- and hypoglycaemia and the presence of a delirium. The aim of future studies should be to adjust for cognitive functioning before ICU admission, psychological co-morbidities, and other possible confounders. Eventually, these investigations may lead to improved long-term outcome after ICU admission.

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SUPPLEMENTARY DATA

TABLE S5.1 DATA COLLECTION FORM

Article nr: .....

First authors name .....

Title .....

Year of publication .....

Study Quality

1 Group size

2 Study method

3a Loss to follow-up

3b Deceased

4 Population

5

Inclusion criteria	Exclusion criteria

6 Used test for cognition: ……..

Data

7 Age

8 Baseline-data "cognition" Yes No No[a]

9 Main outcomes of this study

a. Definition of cognitive impairment:

b.

Outcome	Population:	Time to follow-up (mo)
Cognitive impairment		

10 Main conclusion(s)

.....

11 Remarks

.....

[a] Analyses with use of estimated premorbid cognitive function

6

THE POSTINTENSIVE CARE SYNDROME OF SURVIVORS OF CRITICAL ILLNESS AND THEIR FAMILIES

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SUMMARY

- This study gives insight into the aspects of life after critical illness, with regard to hampered physical or psychological problems for former critical care patients and their families.
- Results emphasize the importance of multidisciplinary structured follow-up and support for former critical care patients and their families.

INTRODUCTION

A recent Editorial emphasized the need for insight into the impact of a critical illness on both intensive care unit (ICU) survivors and their families.[1] Increasing number of ICU survivors are seen in outpatient clinics for post-ICU follow-up.[2] Current evidence indicates that former ICU patients might have substantial physiological problems, cognitive impairment and mental health problems after ICU stay, summarized as the postintensive care syndrome.[3] It also seems that an ICU stay has considerable impact on social aspects of life after critical illness, such as impaired ability to re-engage with previous social life play and work. However, evidence is limited.[1] Family members have an important role in support for the general health care system and the individual patient.[4,5] A term recently introduced is the postintensive care syndrome of families. The treatment of patients in the ICU most likely incurs a large impact on mental health wellbeing of families, also after discharge.[3-5] Families are understood here as a self-defined unit and therefore also includes close friends.

We aimed to describe the impact of an acute illness with ICU admission on mental health (e.g., symptoms of anxiety, depression and posttraumatic stress disorder [PTSD]) and social wellbeing of former ICU patients and their families.

METHODS

We performed a descriptive cohort analysis of a follow-up program of ICU survivors and a study on resumption of work among ICU survivors, in our level three ICU hospital in the Netherlands. Both follow-up investigations were part of usual clinical care, and because of the use of deidentified databases for the analyses, no informed consent was needed.

Follow-up program; the outpatient clinic

The follow-up program was intended for all patients admitted to the ICU for more than 48 hours, and for their families, three months after ICU discharge. All patients and family members who visited the outpatient clinic between January and December 2012, and who completed the questionnaires were included in this cohort.

Symptoms of anxiety and depression in former ICU patients were measured with the hospital anxiety and depression scale (HADS). A subscore of ≥8 suggested the subject had symptoms of anxiety or depression, respectively. To screen for symptoms of PTSD the trauma screening questionnaire (TSQ) was used. A positive screen (≥6) indicated the probable presence of symptoms of PTSD. To assess the health status of patients, the short form 36 (SF36) was used.

Family was asked to fill in the TSQ, to screen for symptoms of PTSD. To assess whether there were signs of caregiver overload, the caregiver strain index (CSI) and caregivers task questionnaire (CTQ) were also included in the questionnaire.

The survey on resumption of work

All patients younger than 69 years who had been admitted to the ICU for at least 72 hours between 2007 and 2010 were sent a postal survey. The survey comprised questions on age, hospital and ICU length of stay, education, paid work, and amount and time to resume work.

RESULTS

Follow-up program; the outpatient clinic

Between January and December 2012, 152 patients were eligible for the outpatient clinic. Of this group, 22 (14%) patients died before they could visit the clinic and 31 (24%) did not visit. Thus, 99 patients were seen in the outpatient clinic, with 88 family members. Results are shown in Table 6.1.

A high rate of symptoms of anxiety and depression was found; acutely admitted surgical ICU patients presented significantly more symptoms of anxiety than other patients (Chi^2 6.3; p=0.04). No significant differences were seen between admission types with respect to symptoms of depression (Chi^2 4.8; p=0.6) or PTSD (Chi^2 3.4; p=0.2). Former ICU patients scored a mean of 39 (standard deviation [SD] 11) on physical functioning and 47 (SD 12) on mental health status, when measured with the SF36. These scores are low compared to the average Dutch population: 49 (SD 10) and 51 (SD 10).

Family members completed the TSQ in 59 cases, of whom 9 (15%) were likely to suffer from symptoms of PTSD. The CSI was completed by 66 family members, 15 (23%) family members scored positive for possible overburden. When measured with the CTQ 5 (6%) of the family members were likely to have overburden. When asked whether or not they missed help after discharge, 16 (18%) of the family members admitted that they had.

The survey on resumption of work

Of the 87 eligible subjects for the survey on work resumption, 57 (66%) responded. Of the 57 responders, 34 (59%) were male, and 26 (45%) were older than 60 years. 29 subjects (51%) had a paid job, and most worked for more than 32 hours before ICU admission (68%). Workload after ICU discharge was most frequently build up within 6 months (62%). Of the 6 patients (21%) who did not resume work, two retired and

four were physically and psychologically unable to return to work. Lack of energy and strength was the main causative factor for not resuming work. Strikingly, we found that critical illness in patients with own companies poses a high risk for bankruptcy, selling or transfer of the patients' company to family members induced by the long duration of rehabilitation and risk of suboptimal recovery.

TABLE 6.1 SUMMARY OF CHARACTERISTICS AND RESULTS OF FOLLOW-UP PROGRAM

Characteristics and results	Population	
	Patients, n=99	
Male, n (%)	66	(67)
Age in years, median (IQR)	66	(55-74)
Admission type, n (%)		
Medical	52	(53)
Acute surgical	17	(17)
Elective surgical	30	(30)
Mechanical ventilation, n (%)	79	(80)
ICU length of stay in days, median (IQR)	7	(4-15)
Hospital length of stay in days, including ICU, median (IQR)	22	(13-36)
SF36: physical functioning, mean (SD)	39	(11)
SF36: mental functioning, mean (SD)	47	(12)
HADS: Positive for symptoms of anxiety, n (%)	58	(59)
HADS: Positive for symptoms of depression, n (%)	73	(74)
TSQ: Positive for symptoms of PTSD, n (%)	16	(15)
	Family, n = 88	
Male, n (%)	21	(24)
Age in years, median (IQR)	64	(50-73)
Relationship with patient, n (%)[a]		
Maried or common-law	70	(80)
Family	12	(14)
Other	5	(6)
TSQ: Positive for symptoms of PTSD, n (%)	9	(15)
CTQ: Overcharge	5	(6)
CSI: Overcharge	15	(13)
Proportion of family members that missed help after discharge	16	(18)

[a] 1 missing in relationship with patient.

Abbreviations: CSI = caregiver strain index, CTQ = caregiver task questionnaire, HADS = hospital anxiety and depression scale, IQR = interquartile range, ICU = intensive care unit, SD = standard deviation, n = number, SF36 = short form 36, PTSD = posttraumatic stress disorder, TSQ= trauma screening questionnaire.

CONCLUSION

Three months after discharge, former ICU patients markedly suffer from symptoms of anxiety, depression and PTSD. Health status is substantially lower compared to the general Dutch population. Family members of former ICU patients may suffer from symptoms of PTSD and overburden. Resumption of paid work was possible in 80% of the case, although in most cases this took at least six months.

These findings support the presence of a postintensive care syndrome in former patients as well as their family members. Multidisciplinary follow-up of both former ICU patients and their family members is warranted. Although information provision is of paramount importance, we call for more efforts concerning structured follow-up and early successful interventions for patients and their family members.

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7

LONG-TERM MENTAL HEALTH PROBLEMS AFTER DELIRIUM IN THE INTENSIVE CARE UNIT

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ABSTRACT

Objective

To determine whether delirium during intensive care unit (ICU) stay was associated with long-term symptoms of anxiety, depression, and posttraumatic stress disorder (PTSD).

Design

Prospective cohort study.

Setting

Survey study, one year after discharge from a medical-surgical ICU in the Netherlands.

Patients

One year ICU survivors, who were admitted to the ICU for more than 48 hours, without a neurological disorder or any other condition that would impede delirium assessment.

Interventions

None.

Measurements and Main Results

ICU survivors received a survey containing the hospital anxiety and depression scale (HADS), and the impact of event scale 15 item (IES-15) one year after discharge. The HADS has two subscales, measuring symptoms of anxiety and depression, with both a threshold of greater than or equal to 8 for the presence of these symptoms. The IES-15 measures symptoms of PTSD, with a score ranging from 0 to 75, and a score of 35 or higher indicating the presence of symptoms of PTSD. Subjects were divided into having experienced no, a single day, or multiple days of delirium during ICU stay. Log-binomial regression was used to assess the association between delirium and symptoms of anxiety, depression and PTSD. For missing outcome values multiple imputation was used. The study population consisted of 567 subjects: 244 (43%) subjects reported symptoms of anxiety, and 256 (45%) symptoms of depression. In 220 (39%) subjects the IES-15 was ≥35, indicating a high probability of PTSD. There was substantial overlap between these symptoms – 63% of the subjects who scored positive for the presence of any three of the symptoms, scored positive on all three, and 77% on at least two. No association could be established between either a single day or multiple days of delirium and symptoms of anxiety, depression, or PTSD.

Conclusions

Although symptoms of anxiety, depression, and PTSD are common mental health problems after critical illness, no association with the occurrence of ICU delirium was found.

INTRODUCTION

Delirium is a common problem in hospitalized patients, especially in the critically ill.[1] It is also an important problem, as it has negative effects on cognitive functioning after ICU stay, and prolongs the duration of mechanical ventilation and hospital length of stay.[2,3] Furthermore, it has been shown that a substantial number of ICU survivors develop long-term mental health problems, such as symptoms of anxiety, depression, and posttraumatic stress disorder (PTSD).[4-10] Previous research associated delirium with an increased risk of long-term mental health problems in non-ICU patients.[11] One may hypothesize that a similar association can be found in former ICU patients. Only a few relatively small studies have investigated this association between ICU delirium and subsequent psychiatric morbidity in ICU survivors, and interestingly, the majority of these studies could not establish any relationship.[4,12-14] One study found an association between a long duration of ICU delirium, and symptoms of depression one year after ICU discharge.[14] None of the current studies have evaluated the presence of symptoms of anxiety, depression, and PTSD simultaneously yet.[4,12-14] Evaluating these symptoms concurrently is important as a substantial overlap between symptoms of mental health problems is inherent.[11]

Patients with a short duration of delirium were recently found to have a better prognosis than patients with a persistent delirium, regarding mortality.[15] It is conceivable that patients with a single day of ICU delirium also have a different association with other long-term outcomes, as compared to patients with multiple days of delirium. The aim of the present large prospective cohort study was to determine whether a single or multiple delirium days during ICU stay was associated with long-term symptoms of anxiety, depression, and PTSD, in a large sample of medical-surgical ICU patients, one year after ICU discharge.

METHODS

Study design and population

A prospective cohort study was conducted in adult subjects, who stayed for at least 48 hours in the 32-bed mixed medical-surgical ICU of the University Medical Center Utrecht (UMCU) between January 2011 and June 2013, and who were alive one year after discharge according to the Dutch municipal database. Patients who had been transferred from another ICU, as well as subjects presenting with a condition that may have hampered delirium assessment (e.g., a neurological disorder or mental retardation) were excluded. The Medical Research Ethics Committee of the UMCU approved this study and waived the need to obtain informed consent (protocols 12/421, 10/056 and 10/006).

Data collection

Mental status during ICU stay was classified for all patients on a daily basis as 'coma', 'delirium', or an 'awake without delirium' state, using a validated multistep algorithm.[16] In summary, this algorithm was based upon the confusion assessment method for the ICU (CAM-ICU[17]) scores from the clinical nurses, the start of delirium treatment, review of medical and nursing charts for delirium symptoms during the preceding 24 hours, and an additional CAM-ICU by a research nurse.[16] Prior to data analysis, the occurrence of delirium during ICU stay was categorized in three categories: i.e., no delirium, a single day of delirium, or multiple days of delirium.

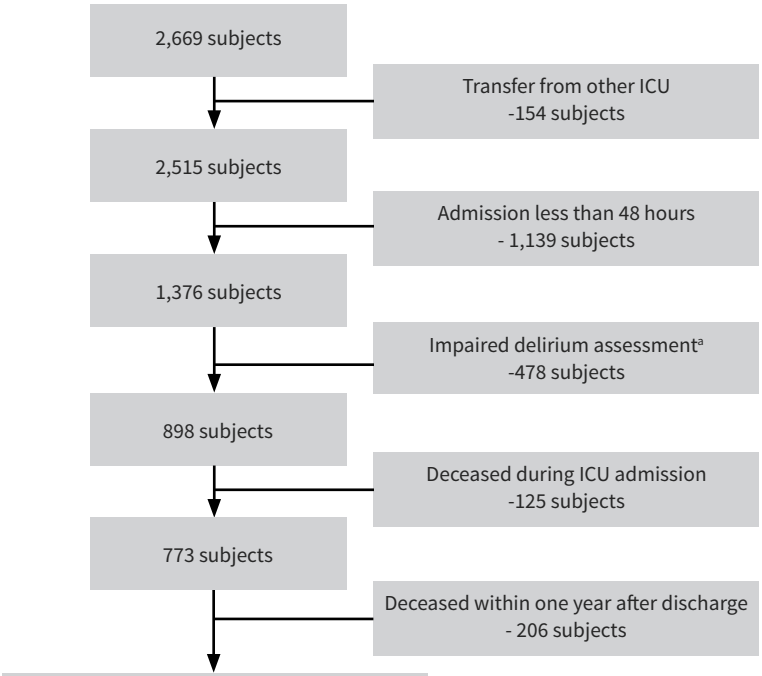
All subjects received a postal survey one year after ICU discharge, which consisted of multiple questionnaires, including the validated Dutch versions of the hospital anxiety and depression scale (HADS[18,19]) and the impact of event scale 15 item (IES-15[20,21]). When patients did not respond to the first postal survey, a follow-up questionnaire was sent and phone calls were made to increase the response rate. The HADS is a 14-item questionnaire, with a 7-question subscale for symptoms of anxiety and a 7-question subscale for symptoms of depression. Questions are ranked on a 4-point Likert scale ranging from 0 to 3, with cumulative scores summing up to a maximum of 21 for either one of the subscales. A score of 8 or higher on either one of the subscales indicates that a subject experiences symptoms of anxiety or depression.[18] The IES-15 consists of 15 questions. The answers are scored as: 0=not at all; 1=rarely; 3=sometimes; and 5=often, with the total score ranging from 0 to 75.[20,21] Patients with 35 points or higher are considered to have a high probability of PTSD presence.[10]

From the hospital information system data was obtained for age, gender, a history of psychopathology, the charlson comorbidity index (CCI[22]), type of ICU admission, the severity of illness according to the acute physiology and chronic health evaluation IV score (APACHE IV[23]), and the daily severity of illness according to the sequential organ failure assessment (SOFA[24]) scores. Daily medication administration was also collected from the medical record.

Statistical analysis

Continuous data were presented as median (interquartile range [IQR]) or mean (standard deviation [SD]), where appropriate, and categorical variables as number (%). Group comparisons were made using the Kruskal-Wallis test for non-normally distributed continuous variables, one-way ANOVA for normally distributed continuous variables, and the Chi Square Test for categorical variables.

FIGURE 7.1 STUDY FLOWCHART



[a] Impaired delirium assessment due to e.g., neurological diseases, mental retardation or language barrier. Abbreviations: ICU = intensive care unit.

To assess whether a single day or multiple days of delirium during ICU stay were independent risk factors for the presence of symptoms of anxiety, depression, and PTSD, we used multivariable log-binomial regression to calculate risk ratios (RRs) with their accompanying 95% confidence intervals (95% CI). An additional multivariable linear regression with the continuous IES-15 total score (0 to 75) was conducted, to assess whether delirium was associated with higher IES-15 scores, regardless of the threshold value. Unstandardized regression coefficients B with 95% CI were reported. Analyses were adjusted for potential confounders that were a priori selected based on previous literature and expert opinion.[10,25,26] These included

age, gender, a history of psychopathology, other comorbidities according to the CCI, type of ICU admission (i.e., medical, surgical elective and surgical emergency), and the APACHE IV. Daily SOFA scores, without the neurological component to prevent adjusting for a component of delirium, were cumulated as a measure of severity of illness during ICU stay, and as an indirect measure for ICU length of stay. Additional adjustment was made for the continuous infusion of benzodiazepines during critical illness (yes/no) as it is both a risk factor for the development of delirium, as for the development of long-term mental health problems.[10,26]

Multiple imputation was used to assign values to missing outcome values in our study domain of one year ICU survivors who fulfilled our inclusion criteria, as a complete case analysis (i.e., excluding the cases with missing outcomes) might introduce selection bias. For multiple imputation we included variables specific for the subject (e.g., gender, age, and comorbidity score) and ICU specific variables (e.g., severity of illness measures, the use of mechanical ventilation and length of ICU stay) as predictors, as well as responses to other questionnaires that were included in the postal survey. Throughout the analyses we used 10 imputation sets. A complete case analysis was also conducted and presented in the supplementary data.

One previous study found an association between five days of delirium and depression.[14] Therefore, a secondary analysis was conducted, repeating the log-binomial regression analyses in the subset of patients experiencing delirium for five days or more, with the patients without an ICU delirium as the reference group.

All analyses were performed with IBM SPSS Statistics 21.0 for Windows. For statistical inferences we used a significance level of 0.05, and the null hypotheses were tested against two-sided alternatives.

RESULTS

The study domain of one year ICU survivors who fulfilled our inclusion criteria consisted of 567 persons. Reasons for exclusion are outlined in Figure 7.1. Characteristics of the study population are described in Table 7.1. The median duration of delirium was 3 days (IQR 1–6). Patients who experienced an ICU delirium were older, had more comorbidities, more psychopathology prior to ICU admission, stayed longer in the ICU, and were more severely ill. Of the 567 subjects, 21 did not receive a questionnaire as a consequence of logistical reasons (i.e., subjects died one year after discharge but before the questionnaire was sent, or they moved abroad) or because they refrained from participation before the questionnaire was sent. There were 426 subjects who responded to the questionnaire (response rate 78%). The median time between ICU discharge and response to the survey was 419 days (IQR 399–437).

TABLE 7.1 CHARACTERISTICS OF THE STUDY POPULATION

Characteristic	Delirium during ICU stay						
	No		Single day		Multiple days		p-value[a]
	n=270 (48%)		n=86 (15%)		n=211 (37%)		
Age in years, mean (SD)	55	(17)	58	(16)	61	(15)	0.001
Male, n (%)	148	(55)	53	(62)	133	(63)	0.16
CCI, median (IQR)	3	(0-10)	6	(0-11)	6	(0-11)	0.07
APACHE IV score, mean (SD)	62	(24)	72	(27)	75	(23)	<0.001
CumSOFA score, median (IQR)[b]	14	(7-24)	24	(13-43)	46	(26-96)	<0.001
ICU LOS in days, median (IQR)	4	(3-6)	6	(4-9)	9	(6-20)	<0.001
Type of admission, n (%)							
Medical	118	(44)	38	(44)	85	(40)	0.86
Acute surgical	79	(29)	25	(29)	60	(28)	
Elective surgical	73	(27)	23	(27)	66	(31)	
History of psychopathology, n (%)	79	(29)	33	(38)	86	(41)	0.02

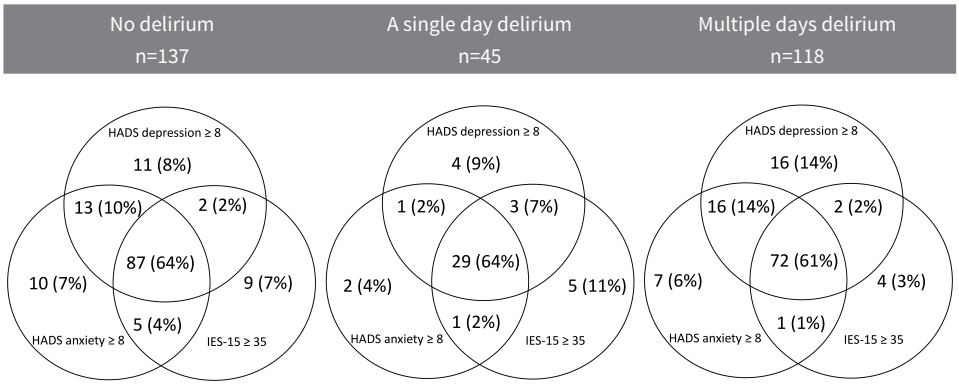
[a] Group comparisons were made using the Kruskal-Wallis test for non-normally distributed continuous variables, one-way ANOVA for normally distributed continuous variables, or Chi² Test for categorical variables. [b] Cumulative SOFA score without the neurological component.

Abbreviations: APACHE IV score = acute physiology and chronic health evaluation IV score, CCI = charlson comorbidity index, CumSOFA = cumulative sequential organ failure assessment, ICU = intensive care unit, IQR = interquartile range, LOS = length of stay, n =number, SD = standard deviation.

Of the 426 responders, 365 subjects completed the full HADS and IES-15 (i.e., the complete cases). Characteristics and differences between the complete cases, subjects who partially completed the HADS and/or IES-15 (i.e., partial responders), subjects who did not respond at all (i.e., nonresponders), and subjects who did not receive a questionnaire (i.e., nonreceivers) are outlined in Table S7.1 (supplementary data). Nonresponders and partial responders more often had a prior history of psychopathology than the complete cases. There were also differences in age, gender, and comorbidity, but no statistically significant difference in delirium occurrence could be demonstrated.

In the study population of 567 persons, symptoms of anxiety were reported 244 (43%) times, symptoms of depression 256 (45%) times, and symptoms of PTSD in 220 (39%) subjects. In total, 300 subjects (53%) showed either symptoms of anxiety, depression, or PTSD. Overlapping symptoms were frequent – of the 300 subjects with a positive score for any one of the symptoms, there were 188 (63%) subjects who reported all three symptoms, 44 (15%) had two out of three, whereas only 68 subjects (23%) scored positive on just one of the three symptoms. The overlap between the presence of the three outcomes, divided in the different delirium categories, is presented in Figure 7.2.

FIGURE 7.2 OVERLAPPING SYMPTOMS IN SUBJECTS WITH LONG-TERM MENTAL HEALTH PROBLEMS (N=300)



Abbreviations: HADS anxiety = hospital anxiety and depression scale subscale for anxiety, HADS depression= hospital anxiety and depression scale subscale for depression, IES-15 = impact of event scale 15 items

When multivariable log-binomial regression was used, a single day or multiple days of ICU delirium did not increase the risk of having symptoms of anxiety, depression, or PTSD, as compared to no ICU delirium (Table 7.2). The median IES-15 scores for no, a single day, and multiple days of delirium were respectively 20 (IQR 3–40), 25 (IQR 5–40), and 23 (IQR 6–39). In multivariable linear regression, a single day and multiple days of ICU delirium were not associated with higher scores on the IES-15, compared to no delirium during ICU stay (Table 7.3).

Multivariable regression analyses of the complete case analyses are described in Table S7.2 (supplementary data) and showed similar results as compared to the imputed data analyses – no association was found between a single day and multiple days of ICU delirium and the risk of symptoms of anxiety, depression or PTSD, as compared to no ICU delirium.

There were 83 subjects who experienced an ICU delirium for five days or more. These patients did not have a higher risk of experiencing symptoms of anxiety, depression or PTSD, as compared to patients with no delirium during ICU stay. Risk ratios and their accompanying 95% CI are described in Table S7.3 (supplementary data).

TABLE 7.2 ASSOCIATION BETWEEN DELIRIUM AND LONG-TERM MENTAL HEALTH SYMPTOMS

Outcome	ICU delirium	Risk Ratio (95% confidence interval)			
		Crude		Adjusted[a]	
HADS anxiety (≥8)	No	Reference		Reference	
	Single day	0.96	(0.72-1.28)	1.01	(0.76-1.33)
	Multiple days	1.07	(0.87-1.31)	1.08	(0.87-1.35)
HADS depression (≥8)	No	Reference		Reference	
	Single day	0.97	(0.73-1.30)	0.99	(0.74-1.31)
	Multiple days	1.20	(0.99-1.46)	1.21	(0.98-1.50)
IES-15 (≥35)	No	Reference		Reference	
	Single day	1.16	(0.87-1.54)	1.23	(0.93-1.63)
	Multiple days	0.98	(0.78-1.24)	1.04	(0.82-1.34)

[a] Adjusted for: age, gender, a history of psychopathology prior to intensive care unit admission, type of admission (i.e., medical, acute surgical or elective surgical), charlson comorbidity index, acute physiology and chronic health evaluation IV score, cumulative sequential organ failure assessment without the central nervous system score, and the use of continuous infusion of benzodiazepines during ICU stay.

Abbreviations: HADS anxiety = hospital anxiety and depression scale subscale for anxiety, HADS depression= hospital anxiety and depression scale subscale for depression, ICU = intensive care unit, IES = impact of event scale 15 item.

TABLE 7.3 ASSOCIATION BETWEEN DELIRIUM AND THE TOTAL SCORE OF THE IMPACT OF EVENT SCALE

ICU delirium	Unstandardized coefficient B (95% confidence interval)			
	Crude		Adjusted[a]	
No	Reference		Reference	
Single day	2.06	(-2.22-6.34)	2.63	(-1.66-6.92)
Multiple days	0.90	(-2.28-4.08)	2.18	(-1.47-5.82)

[a] Adjusted for: age, gender, a history of psychopathology prior to intensive care unit admission, type of admission (i.e., medical, acute surgical or elective surgical), charlson comorbidity index, acute physiology and chronic health evaluation IV score, cumulative sequential organ failure assessment without the central nervous system score, and the use of continuous infusion of benzodiazepines during ICU stay.

DISCUSSION

In our study we could not demonstrate an association between a single or multiple days of delirium and long-term symptoms of anxiety, depression or PTSD. Our study did show a high occurrence of symptoms of anxiety, depression and PTSD in former ICU patients[27], with frequencies concordant with previous literature.[10] This study, therefore, adds to the increasing evidence of psychiatric morbidity after critical illness.[5-9] More than 60% of the subjects who experienced symptoms of mental health problems experienced all three symptoms, and three quarter had at least two. We therefore emphasize that the complex nature and the substantial overlap of mental health outcomes demands attention to symptoms of anxiety, depression, and PTSD concurrently.

The absence of an association between ICU delirium and impaired mental health outcomes is consistent with the majority of previous literature.[4,12-14] Most previous studies in former ICU patients were relatively small and symptoms of anxiety have not been analyzed as a separate entity yet.[4,12-14] One recent relatively large cohort study (n=382) assessed the presence of depression and PTSD one year after ICU stay and could not demonstrate an association with the duration of delirium and PTSD, which is consistent with our findings.[14] Interestingly, the prevalence of PTSD, as measured with the posttraumatic stress disorder checklist in this cohort was relatively low (7%), compared to our results and other previous studies in former ICU[9,10], suggesting their results were mainly applicable to the subjects with severe symptoms of PTSD. In contrast to our study, these authors did find an association between five days of delirium and depression, measured with the beck depression inventory II.[14] In secondary analysis, we were not able to demonstrate an association between ICU delirium for five days or more and any of the symptoms of mental health problems. In non-ICU patients, delirium has previously been associated with depression[28-31], anxiety[31] and PTSD[32], but evidence is limited as these studies were small and the majority did not correct for confounding and thus did not relate delirium etiologically to these outcomes.[11] The discordance of these results can also be explained by case mix[28-32], a shorter follow up duration[28,30-32], or the measurement tool used to assess the presence of mental health problems.[14,28-32]

In our imputed data set we found higher scores of the HADS and IES-15 as compared to the complete cases, indicating more symptoms of anxiety, depression and PTSD in the domain of one year ICU survivors, as compared to the complete cases. This is highly plausible as the non- and partial responders had significantly more psychopathology in the history, which would have made these subjects more prone for these symptoms. Although speculative, it is conceivable that subjects having mental health problems were perhaps less willing to fill out a questionnaire, as it is confrontational with regard to the problems that they experienced. With these results we emphasize on the importance of using imputation strategies to complete missing values in the study domain, to adjusted for potential selection bias.

Strengths of our large cohort study were the use of a validated algorithm for delirium classification, which reduced the risk of misclassification.[16] Furthermore, adjustments were made for relevant and important covariables. Also, we had a high response rate. Despite the high response rate, we did use multiple imputation to supplement the missing values of the answers to the HADS and IES-15. Some limitations of our study should also be addressed. Firstly, we used questionnaires to describe symptoms of anxiety, depression or PTSD, which are no diagnostic tools.

Establishing diagnoses is not feasible in such a large cohort, and therefore, we chose to use validated questionnaires as a surrogate measure. Secondly, the domain of our study was one year ICU survivors. Hence, we cannot draw conclusions on the presence of symptoms of anxiety, depression and PTSD at other moments in time. Thirdly, as with all observational studies, there might be residual confounding (e.g., information on events between ICU discharge and follow up were not available) and causation cannot be established. Furthermore, as this was a single center study, the generalizability of our results may be limited, although our results are consistent with the majority of previous studies.

CONCLUSION

Symptoms of anxiety, depression, and PTSD were commonly reported one year after ICU stay, but no association between the occurrence of ICU delirium and mental health problems could be demonstrated.

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SUPPLEMENTARY DATA

TABLE S7.1 CHARACTERISTICS OF THE ONE YEAR ICU SURVIVORS; DIVIDED IN COMPLETE CASES, PARTIAL RESPONDERS, NONRESPONDERS AND NONRECEIVERS

Characteristic	Complete cases		Partial responders		Nonresponders		Nonreceivers[a]		p-value[b]
	n=365 (64%)		n=61 (11%)		n=120 (22%)		n=21(4%)		
Age in years, mean (SD)	51	(16)	64	(15)	53	(17)	50	(20)	<0.001
Male, n (%)	225	(62)	35	(57)	68	(57)	6	(29)	0.02
CCI, median (IQR)	6	(0–10)	3	(0–9)	3	(0–10)	1	(0–9)	0.02
APACHE IV score, mean (SD)	69	(25)	68	(26)	67	(28)	71	(23)	0.88
CumSOFA score, median (IQR)[c]	23	(12–45)	27	(14–53)	23	(10–48)	20	(8-39)	0.60
ICU LOS in days, median (IQR)	5	(3–10)	6	(4–11)	5	(3–11)	6	(4-11)	0.40
Type of admission, n (%)									
Medical	148	(41)	55	(46)	27	(44)	11	(52)	0.87
Acute surgical	112	(31)	31	(26)	16	(26)	5	(24)	
Elective surgical	105	(29)	34	(28)	18	(30)	5	(24)	
History of psychopathology, n (%)	109	(30)	25	(41)	56	(47)	8	(38)	<0.001
Delirium, n (%)	189	(52)	32	(61)	67	(56)	9	(43)	0.71

[a] We refrained from sending a questionnaire to these subjects because: they moved abroad (n=10), they died more than one year after discharge, but before questionnaire was sent (n=6) or they declined any follow-up, and announced this in advance (n=5).

[b] Group comparisons were made using the Kruskal-Wallis test for non-normally distributed continuous variables, one-way ANOVA for normally distributed continuous variables, or Chi^2 Test for categorical variables.
[c] Cumulative SOFA score without the neurological component.

Abbreviations: APACHE IV score = acute physiology and chronic health evaluation IV score, CCI = charlson comorbidity index, CumSOFA = cumulative total daily sequential organ failure assessment, ICU = intensive care unit, IQR = interquartile range, LOS = length of stay, n = number, SD=standard deviation.

TABLE S7.2 RESULTS OF THE COMPLETE CASE ANALYSIS (N=365)

TABLE S7.2.1 CHARACTERISTICS OF THE COMPLETE CASES

Characteristic	Delirium during ICU stay						
	No		Single day		Multiple days		p-value[a]
	n=176 (48%)		n=56 (15%)		n=133 (36%)		
Age in years, mean (SD)	56	(17)	59	(15)	61	(15)	0.02
Male, n (%)	104	(59)	33	(59)	88	(66)	0.41
CCI, median (IQR)	4	(0–10)	6	(0–13)	7	(0–11)	0.25
APACHE IV score, mean (SD)	62	(24)	72	(26)	76	(24)	<0.001
Cum SOFA score, median (IQR)[b]	14	(7–23)	22	(14–44)	46	(28–103)	<0.001
ICU LOS in days, median (IQR)	3	(3–6)	5	(4–9)	10	(6–20)	<0.001
Type of admission, n (%)							
Medical	71	(40)	25	(45)	52	(39)	0.81
Acute surgical	58	(33)	15	(27)	39	(29)	
Elective surgical	47	(27)	16	(29)	42	(32)	
History of psychopathology, n (%)	45	(26)	13	(23)	51	(38)	0.03
HADS anxiety ≥8, n (%)	31	(18)	8	(14)	27	(20)	0.60
HADS depression ≥8, n (%)	31	(18)	7	(13)	34	(26)	0.07
IES-15 total score, median (IQR)	9	(1–21)	13	(1–24)	10	(1–24)	0.93

[a] Group comparisons were made using the Kruskal-Wallis test for non-normally distributed continuous variables, one-way ANOVA for normally distributed continuous variables, or Chi² Test for categorical variables.

[b] Cumulative SOFA score without the neurological component.

Abbreviations: APACHE IV score = acute physiology and chronic health evaluation IV score, CCI = charlson comorbidity index, CumSOFA = cumulative total daily sequential organ failure assessment, HADS anxiety = hospital anxiety and depression scale subscale for anxiety, HADS depression= hospital anxiety and depression scale subscale for depression, ICU = intensive care unit, IES-15 = impact of event scale 15 items, IQR = interquartile range, LOS = length of stay, n = number, SD = standard deviation.

TABLE S7.2.2 ASSOCIATION BETWEEN DELIRIUM AND LONG-TERM MENTAL HEALTH SYMPTOMS

Outcome	ICU delirium	Risk Ratio (95% confidence interval)			
		Crude		Adjusted[a]	
HADS anxiety (≥8)	No	Reference		Reference	
	Single day	0.81	(0.40–1.66)	0.95	(0.47–1.94)
	Multiple days	1.15	(0.73–1.83)	1.54	(0.91–2.60)
HADS depression (≥8)	No	Reference		Reference	
	Single day	0.71	(0.33–1.52)	0.68	(0.32–1.46)
	Multiple days	1.45	(0.94–2.23)	1.45	(0.89–2.36)
IES-15 (≥35)	No	Reference		Reference	
	Single day	1.73	(0.88–3.38)	1.84	(0.93–3.64)
	Multiple days	0.93	(0.49–1.77)	1.28	(0.64–2.54)

[a] Adjusted for: age, gender, a history of psychopathology prior to intensive care unit admission, type of admission (i.e., medical, acute surgical or elective surgical), charlson comorbidity index, acute physiology and chronic health evaluation IV score, cumulative sequential organ failure assessment without the central nervous system score, and the use of continuous infusion of benzodiazepines during ICU stay.

Abbreviations: HADS anxiety = hospital anxiety and depression scale subscale for anxiety, HADS depression= hospital anxiety and depression scale subscale for depression, ICU = intensive care unit, IES = impact of event scale 15 item.

TABLE S7.2.3 ASSOCIATION BETWEEN DELIRIUM AND THE TOTAL SCORE OF THE IMPACT OF EVENT SCALE

ICU delirium	Unstandardized coefficient B (95% confidence interval)			
	Crude		Adjusted[a]	
No	Reference		Reference	
Single day	2.74	(-1.99– 7.46)	3.12	(-1.56– 7.81)
Multiple days	1.42	(-2.12– 4.96)	2.38	(-1.67– 6.44)

[a] Adjusted for: age, gender, a history of psychopathology prior to intensive care unit admission, type of admission (i.e., medical, acute surgical or elective surgical), charlson comorbidity index, acute physiology and chronic health evaluation IV score, cumulative sequential organ failure assessment without the central nervous system score, and the use of continuous infusion of benzodiazepines during ICU stay.

TABLE S7.3 ASSOCIATION BETWEEN ≥5 DAYS OF ICU DELIRIUM AND LONG-TERM MENTAL HEALTH PROBLEMS

Outcome	ICU delirium	Risk Ratio (95% confidence interval)	
		Crude	Adjusted[a]
HADS anxiety (≥8)	No	Reference	Reference
	≥5 days	0.97 (0.70 – 1.34)	1.08 (0.72 – 1.62)
HADS depression (≥8)	No	Reference	Reference
	≥5 days	1.12 (0.89 – 1.49)	1.20 (0.81 – 1.76)
IES-15 (≥35)	No	Reference	Reference
	≥5 days	0.88 (0.54 – 1.43)	1.15 (0.63 – 2.13)

[a] Adjusted for: age, gender, a history of psychopathology prior to intensive care unit admission, type of admission (i.e., medical, acute surgical or elective surgical), charlson comorbidity index, acute physiology and chronic health evaluation IV score, cumulative sequential organ failure assessment without the central nervous system score, and the use of continuous infusion of benzodiazepines during ICU stay.

Abbreviations: HADS anxiety = hospital anxiety and depression scale subscale for anxiety, HADS depression= hospital anxiety and depression scale subscale for depression, ICU = intensive care unit, IES = impact of event scale 15 item.

8

LONG-TERM OUTCOME OF DELIRIUM DURING INTENSIVE CARE UNIT STAY IN SURVIVORS OF CRITICAL ILLNESS

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ABSTRACT

Objective

Delirium is associated with impaired outcome, but it is unclear whether this relationship is limited to in-hospital outcomes and whether this relationship is independent of the severity of underlying conditions. The aim of this study was to investigate the association between delirium in the intensive care unit (ICU) and long-term mortality, self-reported health-related quality of life (HRQoL), and self-reported problems with cognitive functioning in survivors of critical illness, taken severity of illness at baseline and throughout ICU stay into account.

Methods

A prospective cohort study was conducted. We included patients who survived an ICU stay of at least a day; exclusions were neurocritical care patients and patients who sustained deep sedation during the entire ICU stay. Delirium was assessed twice daily with the confusion assessment method for the ICU (CAM-ICU) and additionally, patients who received haloperidol were considered delirious. Twelve months after ICU admission, data on mortality was obtained and HRQoL and cognitive functioning were measured with the European quality of life–6 dimensions self-classifier (EQ-6D). Regression analyses were used to assess the associations between delirium and the outcome measures adjusted for gender, type of ICU admission, the acute physiology and chronic health evaluation IV (APACHE IV) score, and the cumulative sequential organ failure assessment (SOFA) score throughout ICU stay.

Results

Of 1,101 survivors of critical illness, 412 persons (37%) had been delirious during ICU stay, and 198 (18%) died within twelve months. When correcting for confounders, no significant association between delirium and long-term mortality was found (hazard ratio: 1.26, 95% confidence interval [CI] 0.93–1.71). In multivariable analysis, ICU delirium was not associated with HRQoL either (regression coefficient: -0.04, 95% CI -0.10–0.01). Yet, delirium remained associated with mild and severe problems with cognitive functioning in multivariable analysis (odds ratios: 2.41, 95% CI 1.57–3.69 and 3.10, 95% CI 1.10–8.74, respectively).

Conclusions

In this group of survivors of critical illness, delirium during ICU stay was not associated with long-term mortality or HRQoL after adjusting for confounding, including severity of illness throughout ICU stay. In contrast, delirium appears to be an independent risk factor for long-term self-reported problems with cognitive functioning.

INTRODUCTION

Because of improved medical care, the number of intensive care unit (ICU) survivors has increased considerably, but recent studies demonstrate that ICU survivors can experience substantial long-term morbidity.[1-5] To further improve care for survivors of critical illness, it is important to elucidate which factors increase the risk of long-term morbidity and mortality.

Delirium, characterized by an acute change in attention and cognition, is a common disorder in ICU patients.[6-8] Previous studies have consistently found that delirium in the ICU is associated with long-term mortality and cognitive impairment.[9-14] It is however unclear whether delirium also affects long-term health related quality of life (HRQoL). HRQoL is defined as health, in the medical definition, but also as the importance of independent physical, social and emotional functioning.[15] Two studies suggest that delirium is a risk factor for lower long-term HRQoL,[12,14] while others state that there is no association.[11,16]

However, the relationship of delirium with long-term outcome is complex and affected by several confounding factors.[17] Previous studies adjusted for severity of illness at baseline, but only one investigation additionally adjusted for severity of illness during ICU stay,[10] which is another potentially important determinant of long-term outcome.[18] In that study, delirium was found to increase the risk of long-term cognitive impairment, independent of the burden of disease during the entire ICU stay.[10] It is currently unclear to what extent the associations between delirium and long-term mortality and HRQoL are confounded by severity of illness throughout the course of ICU stay.

We conducted a large prospective cohort study of a diverse population of ICU survivors to assess the association between delirium in the ICU and long-term mortality, self-reported HRQoL, and self-reported problems with cognitive functioning, while adjusting for important confounding factors such as severity of illness at baseline and throughout the course of ICU stay. We hypothesized that persons who were delirious during ICU stay had worse long-term outcomes compared to individuals who were not delirious.

METHODS

Study design

We performed a prospective cohort study within a larger follow-up investigation of all patients admitted to the ICU of the University Medical Center Utrecht (UMCU) in the Netherlands. The Medical Research Ethics Committee of the UMCU approved this study and waived the need to ask for informed consent (protocol 10/006), since the objective

of the follow-up investigation was continuous quality assessment and evaluation of regular patient care.

Study population

We included all patients who were admitted to the ICU of the UMCU for more than 24 hours, between July 2009 and August 2011. We excluded neurotrauma, neurosurgery, and neurology patients, because the sensitivity of the confusion assessment method for the ICU (CAM-ICU) is less reliable in patients with neurologic disorders.[7] In this investigation, we aimed to study mortality and morbidity in ICU survivors, therefore we excluded all patients who died during ICU stay. Additionally, we excluded patients who had a sustained RASS of -4 or -5, as delirium screening could not be conducted in these patients. Furthermore, we excluded all subjects who had no data on sequential organ failure assessment (SOFA) scores.

To determine which subjects were alive one year after ICU admission, the hospital information system and the Dutch municipal database were consulted. Individuals who could not be traced were excluded. Nonsurvivors were defined as all persons known to have died after discharge from the ICU during the one year follow-up period.

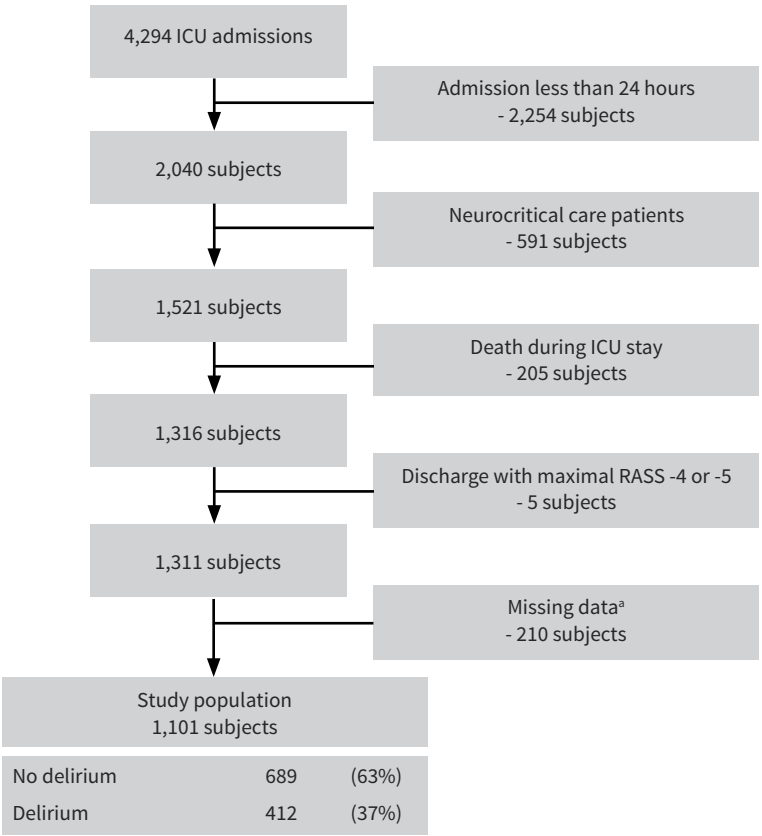
Measurements during ICU stay

The acute physiology and chronic health evaluation IV (APACHE IV) was registered for every patient in the ICU after the first 24 hours of admission as an estimate of baseline severity of illness. In addition, SOFA was scored three times daily for the entire ICU length of stay and the cumulative score was used to provide an estimate of severity of illness throughout the course of ICU stay. To calculate the cumulative SOFA score, we summed all daily SOFA scores without the central nervous system component, as this is altered in delirium and otherwise analyses would be subject to overcorrection. The cumulative SOFA score was considered a better measure than the mean or maximum SOFA score as it better represents the burden of illness over the entire ICU stay. We conducted a sensitivity analysis using the mean SOFA and maximal SOFA in the analysis of the primary outcome, mortality. The presence of delirium was assessed twice daily by bedside nurses using the CAM-ICU, in the morning and evening shift.[19] Further, the administration of haloperidol was considered. Delirium during ICU stay was defined as at least one positive CAM-ICU and/or administration of haloperidol during ICU stay. In our clinic, haloperidol was not prescribed prophylactically during this study and therefore could be used as an indicator of delirium.[20]

Outcomes

The primary outcome was mortality in survivors of critical illness, within the first year after ICU admission, while adjusting for important confounding factors such as severity of illness at baseline and throughout the course of ICU stay. Secondary outcomes were self-reported HRQoL and self-reported problems with cognitive functioning, one year after ICU admission, adjusted for the same confounders. To assess mortality, we used all available information, including the hospital information system and the Dutch municipal database. Persons who survived up to one year after admission to the ICU received a postal questionnaire to assess their physical and psychological well-being. Phonecalls were made to all persons who did not reply to the survey, to increase the response rate. Nonresponders were all subjects who received a survey but did not return or did not fill in the survey.

FIGURE 8.1 STUDY FLOWCHART



[a] Missing SOFA scores (n=178) and subjects who could not be traced in the Dutch manicipal database (n=32). Abbreviations: ICU = intensive care unit, RASS = richmond agitation sedation scale, SOFA = sequential organ failure assesment.

The questionnaire included the Dutch European quality of life–6 dimensions self-classifier (EQ-6D), which is an instrument that measures quality of life in six dimensions. Every dimension consists of one item, subdivided into three levels (no, mild and severe).[21] To assess HRQoL, we analyzed the first five questions of the Dutch EQ-6D which corresponds to the validated Dutch European quality of life–5 dimensions self-classifier (EQ-5D™).[21,22] We used a validated syntax to calculate the EQ-5D™ index.[22-24] For assessment of problems with cognitive functioning we used the sixth question of the EQ-6D questionnaire.[21]

Statistical analysis

For categorical data a Chi Square test was used. To assess whether or not continuous data were normally distributed, a Q-Q plot was made and a Kolmogorov-Smirnov test was conducted. For normally distributed, continuous data, a Student T-test was used, and values were presented as means and standard deviations (SD). Skewed, continuous data were studied with the Mann-Whitney U test, and presented as medians with interquartile ranges (IQR).

To study the association between delirium and mortality, Cox proportional hazard regression analyses were used, and a hazard ratio (HR) was computed. HRQoL was compared between persons who had been delirious and those who had not been delirious during ICU stay, using multivariable linear regression, which was presented as a regression coefficient. The HRQoL in these two groups was also compared with the HRQoL normative scores of the general Dutch population. Problems with cognitive functioning were subdivided into no problems, mild problems, and severe problems. Multinomial logistic regression was performed to quantify the association between delirium and problems with cognitive functioning, and data were presented as odds ratio (OR).

In the analyses on mortality, HRQoL, and problems with cognitive functioning, the following two models were applied: Model 1 did not contain additional covariates, and was used for unadjusted analyses. With model 2, adjustments were made for gender, type of ICU admission, the APACHE IV score and the cumulative SOFA score during the entire ICU stay. Age is part of the APACHE IV score and was therefore not additionally entered in the model. By using the cumulative SOFA score, indirect correction for length of stay was made. Statistical significance was defined at a p-value less than 0.05. The Statistical Package for Social Sciences 20.0 (SPSS 20.0) was used for all statistical analysis.

RESULTS

Between July 2009 and August 2011, 4,294 patients were admitted to the ICU, of whom 2,254 subjects stayed for less than one day. In addition, 519 neurocritical care patients were excluded. Of the remaining 1,521 subjects, 205 died during ICU stay and 5 persons remained comatose during ICU stay. Missing information about SOFA scores, or missings in Dutch municipal database registration, resulted in exclusion of another 210 subjects. Therefore, the final study population consisted of 1,101 persons, of whom 412 (37%) were delirious during ICU stay (Figure 8.1). No patients were classified as delirious based on the prescription of haloperidol alone. After hospital discharge, 650 (59%) of the subjects could return home.

TABLE 8.1 CHARACTERISTICS OF THE STUDY POPULATION

Characteristic	All subjects		No delirium		Delirium		p-value
	n=1,101 (100%)		n=689 (63%)		n=412 (37%)		
Age in years, mean (SD)	60	(17)	59	(17)	61	(17)	0.29
Male, n (%)	677	(62)	406	(59)	271	(66)	0.03
APACHE IV score, mean (SD)	62	(29)	54	(22)	74	(28)	<0.001
Cum SOFA score, median (IQR)[b]	40	(19–99)	27	(13–51)	99	(47–207)	<0.001
ICU length of stay in days, median (IQR)	4	(3–8)	3	(2–5)	8	(5–15)	<0.001
Type of admission, n (%)							
Medical	430	(40)	208	(30)	222	(54)	<0.001
Elective surgical	447	(41)	351	(51)	96	(23)	
Acute surgical	224	(20)	130	(19)	94	(23)	

Abbreviations: APACHE IV = acute physiology and chronic health evaluation IV score, CumSOFA = cumulative sequential organ failure assessment without the central nervous system component, ICU = intensive care unit, IQR = interquartile range, n = number, SD = standard deviation.

Characteristics of the study population are outlined in Table 8.1. Subjects who were excluded based on missing data did not differ from the study population with regard to delirium frequency, age, gender, APACHE IV, or type of admission. The length of ICU stay of the study population was longer than that of the subjects excluded due to missing data (median 4, IQR 3–7, p=0.01). Persons who were delirious during ICU stay differed from subjects who did not have delirium during ICU stay in gender, severity of illness scores, ICU length of stay and type of admission (Table 8.1). One year after ICU admission, 903 of the 1,101 subjects (82%) were known to have survived. Because of an administrative error, 16 individuals who appeared still alive did not receive a questionnaire, and therefore 887 surveys were send.

The response rate was 64% (571/887). After ICU admission, the median time until the surveys were send back was 420 days after discharge (IQR 402–444 days).

In total, 198 patients died during follow-up, with a median duration of 62 days after ICU admission (IQR 25–181). Univariable survival analysis showed that delirious patients had a significantly increased risk of death in the year following ICU admission. However, when adjustments were made for the confounders described above, delirium was no longer independently associated with mortality (Table 8.2).

In univariable analysis, patients with delirium during ICU had a significantly lower HRQoL score at follow-up than patients who did not have delirium. After adjustment for confounders, again the difference between the two groups was no longer statistically significant (Table 8.3). The assumption of homoscedasticity was verified by plotting the residuals against the fitted values. Compared to the general Dutch population, both patient groups scored lower on the EQ-5D™. Persons without delirium in the ICU scored 0.85 (IQR 0.72–1.00) and subjects with ICU delirium scored 0.75 (IQR 0.69–1.00). In comparison, the estimated average EQ-5D™ index for the general Dutch population is 0.87 (IQR 0.82–1.00).[24]

TABLE 8.2 RISK OF DEATH ASSOCIATED WITH DELIRIUM IN SURVIVORS OF CRITICAL ILLNESS, WITHIN ONE YEAR AFTER ICU ADMISSION

Determinant	Hazard Ratio (95% confidence interval)			
	Crude		Adjusted[a]	
No delirium	Reference		Reference	
Delirium	1.91	(1.44-2.52)*	1.26	(0.93-1.71)

* p-value < 0.05.

[a] Adjusted for: gender, acute physiology and chronic health evaluation IV, type of admission and cumulative sequential organ failure assessment without central nervous system component.

198 patients died within one year. Delirium: n = 102. No delirium: n = 96.

TABLE 8.3 DIFFERENCES IN HEALTH-RELATED QUALITY OF LIFE BETWEEN DELIRIOUS AND NON-DELIRIOUS ICU SURVIVORS, WITHIN ONE YEAR AFTER ICU ADMISSION

Determinant	Standardized coefficient β (95% confidence interval)			
	Crude		Adjusted[a]	
No delirium	Reference		Reference	
Delirium	-0.06	(-0.10- -0.01)*	-0.04	(-0.10-0.01)

* p-value < 0.05.

[a] Adjusted for: gender, acute physiology and chronic health evaluation IV, type of admission and cumulative sequential organ failure assessment without central nervous system component.

Data on health-related quality of life was available for 546 patients. Delirium: n = 182. No delirium: n = 364.

Persons who had been delirious during ICU stay experienced significantly more mild and more severe self-reported problems in cognitive

functioning compared to subjects who did not have delirium in the ICU. The strength of this association did not weaken and remained statistically significant when adjustments were made for confounding variables (Table 8.4).

To verify whether the effect measure for mortality was robust when using the cumulative SOFA, we conducted a sensitivity analysis where we made Cox proportional hazard models with the mean SOFA and the maximal SOFA scores. We furthermore evaluated the effect of adding length of ICU stay to these models. Other variables were left unchanged. The hazard ratios for death of these models remained similar, which shows that our effect measure is robust, and length of ICU stay is not a mediator in the causal pathway between delirium and mortality.

TABLE 8.4 ODDS OF PROBLEMS WITH COGNITIVE FUNCTIONING ASSOCIATED WITH DELIRIUM IN SURVIVORS OF CRITICAL ILLNESS, WITHIN ONE YEAR AFTER ICU ADMISSION

Determinant	Odds Ratio (95% confidence interval)			
	Crude		Adjusted[a]	
No problems	Reference		Reference	
Mild problems	2.02	(1.39-2.94)*	2.93	(1.16-7.42)*
Severe problems	2.41	(1.57-3.69)*	3.10	(1.10-8.74)*

* p-value < 0.05

[a] Adjusted for: gender, acute physiology and chronic health evaluation IV, type of admission and cumulative sequential organ failure assessment without central nervous system component.

Data on cognitive functioning was available for 561 patients. The delirium group (n = 188) was divided into: no problems (n = 99), mild problems (n = 79) and severe problems (n = 10). The group with no delirium served as the reference group (n = 373): no problems (n = 261), mild problems (n = 103) and severe problems (n = 9).

DISCUSSION

We studied the association between delirium in the ICU and long-term mortality, HRQoL, and problems with cognitive functioning in survivors of critical illness. We found that delirium was not associated with mortality and HRQoL when adjustments were made for confounding. By contrast, subjects who had delirium during their ICU stay experienced more problems with cognitive functioning at follow-up than persons who did not have delirium in the ICU. The latter finding remained statistically significant when we adjusted for confounders, including estimates of severity of illness throughout the course of ICU stay.

To the best of our knowledge, our study is the first to adjust for severity of illness throughout the course of the ICU stay, in analyzing the association between delirium with long-term mortality and HRQoL. Previous studies on these issues adjusted for severity of illness at baseline only.[11-14,16] Next to correction for severity of illness, differences with previous studies could be the result of differences in case-mix, as we included ICU survivors only. Nevertheless, our study findings emphasize that the

burden of illness during ICU stay should be taken into account. For example, a patient after elective surgery may have a low predicted mortality. However, when such a patient develops a septic shock during ICU stay, the risk of mortality may change but this is not incorporated in the APACHE IV score. Therefore, severity of illness at admission should not be considered the sole predictor of long-term outcome. To adjust for severity of illness throughout the course of ICU stay, we used the cumulative SOFA score, which is dependent on both the duration and the extend of multi-organ failure, and which is strongly associated with long-term mortality.[18] We conducted a sensitivity analysis with the mean SOFA and maximal SOFA, which showed that our effect measure was robust.

The association that we found between delirium in the ICU and long-term problems with cognitive functioning is consistent with a recent study, in which adjustments for severity of illness throughout the course of ICU stay were made in a similar manner.[10] Factors that precipitate delirium may thus provoke events that contribute to the development or acceleration of cognitive impairment, even when delirium is no longer present. It would be interesting to see whether this holds only for persistent delirium, or also for rapidly reversible, sedation-related delirium.[25] Unfortunately, we were not able to distinguish between these types of delirium.

The evidence of no association between delirium and long-term mortality and HRQoL should not be used as an excuse to neglect delirium in the ICU. With our study we show again that delirium is associated with prolonged cognitive problems.[9-11] Interventions aimed at reducing delirium incidence may eventually lead to long-term beneficial effects on cognitive outcome.

It is remarkable that the self-reported cognitive problems do not seem to have an impact on patients self-reported quality of life in this population. An association between more cognitive problems and a lower HRQoL would be expected. It might be due to a rather limited HRQoL survey. However, our findings are consistent with previous studies in which more extensive tools were used to assess HRQoL and cognitive functioning, namely the ShortForm 36 and the Cognitive Failure Questionnaire.[11] Perhaps the expectation to find a lower HRQoL in subjects with more cognitive problems is not always applicable.

No *a priori* sample size calculation was performed. However, this is one of the largest studies so far to address this problem. We believe that our study population was large enough to study this issue. Nevertheless, our study has several limitations. Due to missing data a relatively large group had to be excluded, which may have introduced bias. Excluded subjects had a shorter length of ICU stay than the study population, and

did not differ in other measured characteristics. Therefore, if selection bias would have occurred, we have analyzed a more severe group of subjects. Secondly, the sensitivity of the CAM-ICU in daily practice may be low.[7] Yet, in contrast to studies where sensitivity of the CAM-ICU was studied at one point in time, we used all CAM-ICU screenings during the patients' entire ICU stay. As a result, we may have increased the sensitivity of the test, although this was not formally assessed.[26] We also used the prescription of haloperidol as a proxy measurement to reduce the risk of misclassification.[20] Thirdly, the duration of delirium as a measure for delirium burden is an important factor to incorporate in analyses,[10] which was unfortunately not possible in our study. Fourthly, because of lack of baseline assessment, it remains unclear from our data to what extend long-term cognitive problems are caused by delirium, and to what extend patients who experienced a delirium in the ICU had lower cognitive functioning before admission.[17] In a recent study on delirium and long-term cognitive impairment, this problem was addressed using the IQCODE for patients older than 50 years, excluding patients who were found to have severe dementia and stratifying according to age and burden of coexisting illness. This did not alter the observation that delirium increases the risk of long-term cognitive impairment.[10] Also, the response rate of the questionnaire was relatively low, which may have led to misclassification. Unfortunately, we were not able to address the issue of selective responsiveness. Furthermore, the assessment of problems with cognitive functioning with the EQ-6D is not detailed enough to examine specific functions or subdomains. The measure for cognitive functioning is based on a self-reported 3-level multiple choice question, which is minimal compared to extensive neuropsychological testing. However, because of self-reporting, the test measures how subjects experience their cognitive functioning, which is a relevant outcome in daily practice. Finally, the possibility of bias due to unmeasured confounders cannot be excluded, as with any observational study.

CONCLUSION

Delirium during ICU stay is not independently associated with long-term mortality and health related quality of life in ICU survivors when corrected for factors such as severity of illness throughout the course of ICU stay. In contrast, delirium in the ICU increases the risk of long-term problems with cognitive functioning, independent of severity of illness during ICU stay.

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9

LONG-TERM COGNITIVE PROBLEMS AFTER DELIRIUM IN THE INTENSIVE CARE UNIT AND THE EFFECT OF SYSTEMIC INFLAMMATION

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ABSTRACT

Purpose

To describe the association between intensive care unit (ICU) delirium and long-term cognitive problems in one year ICU survivors, and to investigate whether this association was mediated by exposure to systemic inflammation during ICU stay.

Methods

A prospective cohort study was conducted in subjects who survived up to one year after ICU discharge. Cognitive problems were measured with the cognitive failure questionnaire (CFQ). Exposure to systemic inflammation was based on all daily C-reactive protein (CRP) measurements during ICU stay, expressed as the area under the curve (AUC). Multivariable linear regression was conducted to evaluate the association between delirium and the CFQ. The effect of inflammation on the association between delirium and CFQ was assessed using mediation analysis, comparing the effect estimate (B) of delirium and CFQ between models with and without inclusion of the AUC of CRP.

Results

Among 567 one year ICU survivors, the CFQ was completed by 363 subjects. Subjects with multiple days of delirium during ICU stay reported more cognitive problems (adjusted B=5.10, 95%CI 1.01–9.20), whereas a single day delirium was not associated with higher CFQ scores (adjusted B=-0.72, 95%CI -5.75–4.31). Including the AUC of CRP did not change the association between delirium and the CFQ (ratio of effect estimates for a single and multiple days respectively, 1.00, 95%CI 0.59–1.44 and 0.86, 95%CI 0.47–1.16).

Conclusions

A single day of delirium was not associated with long-term self-reported cognitive problems, in contrast to multiple days of delirium. The exposure to systemic inflammation did not mediate this association

INTRODUCTION

Intensive care unit (ICU) survivors experience a substantial amount of long-term morbidity, including problems in cognitive functioning.[1] A pivotal risk factor for long-term cognitive problems after ICU stay seems to be the occurrence of delirium during critical illness.[2-5] Delirium has a multifactorial pathophysiology, and it is usually not possible to ascertain one specific cause to delirium in ICU patients. Previous studies found systemic inflammation to be a risk factor for delirium[6-8], and also for long-term cognitive impairment.[9,10] In rodent studies, neuroinflammation and neuronal loss was seen up to 10 months after systemic inflammation, induced by one peripheral injection of lipopolysaccharide.[11] Persistent neuroinflammation may thus explain why patients with exposure to acute systemic inflammation and resulting delirium, develop long-term cognitive impairment.[7] Delirium is, however, not exclusively associated with exposure to acute systemic inflammation and can also result from other causes, such as metabolic disturbances. Up till now, it is unclear whether the association between delirium and long-term cognitive problems is mediated by the degree of exposure to acute systemic inflammation.[7,8]

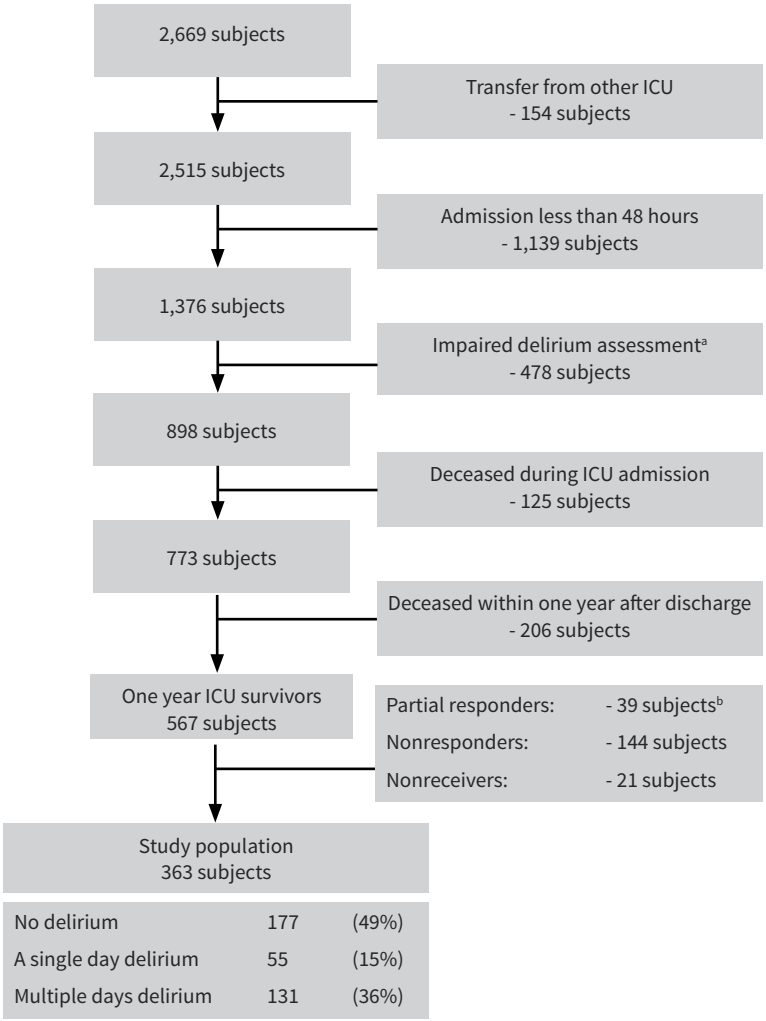
Recent literature shows that rapidly-reversible sedation-related delirium has a better outcome than persistent delirium.[12] It is plausible, but unstudied, that the prognosis of a very brief episode of delirium is also favorable, as compared to more delirium days. The aim of this study was to investigate the association of a single day or multiple days of ICU delirium with long-term cognitive problems in one year ICU survivors, and to assess whether this association was mediated by exposure to systemic inflammation during ICU stay.

METHODS

Setting and study population

This prospective, observational study was conducted in consecutively admitted adults, who stayed for at least 48 hours in the 32-bed mixed medical-surgical ICU of the University Medical Center Utrecht (UMCU) between January 2011 and June 2013, and who were alive one year after discharge. Survival status was determined by a query of the Dutch municipal register. Subjects who were transferred from an ICU of another hospital, as well as subjects with an acute neurological illness or another condition that could hamper delirium assessment were excluded. The Medical Research Ethics Committee of the UMCU waived the need for informed consent (protocols 12/421, 10/056 and 10/006).

FIGURE 9.1 STUDY FLOWCHART



[a] Neurological patients and/or other reasons for impaired delirium assessment e.g., mental retardation or a language barrier

[b] Partial responders sent the questionnaire back, with a partially completed CFQ. Nonresponders were subjects who did not sent the questionnaire back. To the nonreceivers we did not send a questionnaire because: they moved abroad (n=10), they died more than one year after discharge, but before the questionnaire was sent (n=6) or they declined any follow-up, and announced this in advance (n=5).

Data collection

A detailed description of the daily assessment of mental status was recently published.[13] In brief, an algorithm was used to evaluate daily mental status of each patient during the preceding 24 hours (awake without delirium, delirium, or coma).

For this assessment, the richmond agitation sedation scale (RASS[14]) and confusion assessment method for the ICU (CAM-ICU[15]) scores from the bedside nurses were used, next to initiation of delirium treatment, chart review, and an additional CAM-ICU by trained research nurses.[13]

All subjects who were alive one year after ICU discharge received a survey by mail containing multiple questionnaires, including the validated Dutch translation of the cognitive failure questionnaire (CFQ).[16,17] The CFQ consists of 25 questions, scored on a five-point Likert scale. The total score on the CFQ ranges from 0 to 100, with a higher score indicating more self-reported cognitive problems.[17] A reminder was sent and follow-up phone calls were made when subjects did not respond.

Systemic inflammation during ICU stay was quantified by daily C-reactive protein (CRP) levels (in milligrams per liter [mg/L]). CRP is an acute-phase reactant found to be elevated in blood in inflammatory and infectious conditions.[18] CRP levels in the ICU were measured at admission and daily thereafter. Daily CRP levels were used to calculate the area under the curve (AUC in mg*days/L), as a measure of total exposure to systemic inflammation during ICU stay.[19]

At ICU admission, we recorded data on age, gender, chronic disease burden according to the charlson comorbidity index (CCI[20]), and the acute physiology and chronic health evaluation IV (APACHE IV[21]) as a measure for severity of illness in the first 24 hours of ICU admission. Severity of illness on subsequent days was assessed by the sequential organ failure assessment (SOFA[22]) score.

Statistical analysis

To assess whether delirium during ICU stay was an independent risk factor for long-term self-reported cognitive problems, multivariable linear regression models were used. Results of these analyses were presented as unstandardized regression coefficients (B's), with accompanying 95% confidence intervals (95% CI). The presence of delirium was classified into three groups: (1) subjects with no delirium during ICU admission (used as the reference group), (2) subjects with a single day of ICU delirium, and (3) subjects with multiple days of delirium during ICU stay. In multivariable linear regression models, adjustments were made for covariables with the potency to be a confounder in the association between delirium and long-term self-reported cognitive problems. These covariables were chosen a priori based on clinical judgment and a recent systematic review[23], and included age, gender, CCI and the APACHE IV. Further, the maximal total SOFA score (leaving out the central nervous system component to prevent indirect adjustment for the presence of delirium) was entered in the models

as a measure for severity of illness during ICU stay. Trend imputation was used for missing values of daily measured variables, including the missing levels of CRP, given the availability of longitudinal data both preceding and following each measurement.[24]

We conducted mediation analysis to assess to which extent the degree of systemic inflammation was a mediator in the association between delirium and long-term cognitive problems. To this end, we used the following approach. From our study population 1,000 bootstrap samples were drawn with replacement. Within each bootstrap sample two models were developed: a model as described in the previous paragraph, including all potential confounders (model 1) and a model containing the same variables plus the amount of inflammation during ICU stay (expressed as the AUC of the daily CRP levels) (model 2). The effect estimates indicating the association between delirium (single and multiple days) and CFQ resulting from both models were compared by calculating their ratio and their absolute difference. Subsequently, these ratios were averaged over the bootstrap samples to obtain an overall estimate; a 95% CI around these estimates was obtained non-parametrically. The overall estimate for the absolute difference with accompanying 95% CI was calculated in a similar fashion. If the ratios were statistically significant different from 1 or the absolute differences were statistically significant different from 0, the amount of acute systemic inflammation could be considered as mediating the association between delirium and CFQ.[25]

In our cohort, subjects with at least one missing value in the CFQ were different from those with complete CFQ data with regard to age, gender, CCI and maximal SOFA score (Table S9.1, supplementary data). Missing data rarely occurs entirely at random, and excluding these subjects could potentially lead to biased results.[26] Therefore, next to analyzing data restricted to subjects who completed the full CFQ (i.e. complete case analysis) we also performed multiple imputation to assign values to missing answers to the questions of the CFQ in the one year ICU survivors, and analyzed the imputed dataset as a secondary analysis.[26] For multiple imputation we conducted 10 iterations and used subjects and ICU specific variables (e.g., gender, age, comorbidity score, severity of illness measures, and length of ICU stay), as well as answers to other questionnaires that were also included in the survey as predictors in the imputation model.

All data analyses were performed using IBM SPSS Statistics 21.0 for Windows and R version 3.1.1 for Windows (R Foundation for Statistical Computing Vienna, Austria). A significance level of 0.05 was used for all statistical inferences and the null hypotheses were tested against two-sided alternatives.

TABLE 9.1 CHARACTERISTICS OF THE STUDY POPULATION

Characteristic	Delirium during ICU stay						
	No		Single day		Multiple days		p-value[a]
	n=177 (49%)		n=55 (15%)		n=131 (36%)		
Age in years, mean (SD)	56	(16)	60	(14)	61	(15)	0.01
Male, n (%)	103	(58)	33	(59)	86	(66)	0.41
CCI, median (IQR)	4	(0–10)	6	(0–13)	6	(0–11)	0.07
APACHE IV score, mean (SD)	63	(25)	72	(26)	75	(23)	<0.001
Max SOFA score, median (IQR)[b]	5	(3–7)	7	(4–9)	8	(6–10)	0.002
ICU LOS in days, median (IQR)	3	(3–6)	6	(4–9)	9	(6–19)	<0.001
Type of admission, n (%)							
Medical	72	(41)	23	(45)	51	(39)	0.99
Acute surgical	51	(29)	16	(27)	37	(18)	
Elective surgical	54	(31)	16	(29)	43	(33)	
AUC of CRP in mg*days/L, median (IQR)	348	(179-646)	493	(340-911)	986	(535-2,127)	<0.001

[a] Group comparisons were made using the Chi^2 Test for categorical variables, one-way ANOVA for normally distributed continuous variables, or Kruskal-Wallis test for skewed distributed continuous variables.

[b] Maximal total SOFA score without the neurological component

Abbreviations: APACHE IV score = acute physiology and chronic health evaluation IV score, AUC = area under the curve, CCI = charlson comorbidity index, Max SOFA = maximal total sequential organ failure assessment, ICU = intensive care unit, IQR = interquartile range, LOS = length of stay, n = number, SD = standard deviation, CRP = c-reactive protein

RESULTS

Between January 2011 and June 2013 2,669 subjects were screened for delirium of whom eventually 567 persons were eligible for this study (i.e., the one year ICU survivors). Application of the exclusion criteria is described in Figure 9.1. In total, 546 subjects received a survey, of whom 402 individuals answered to the CFQ questionnaire (response rate 74%), and 363 (90% of the responders) completed the full CFQ (i.e., complete cases). These 363 subjects reported their CFQ scores after a median of 400 days (interquartile range [IQR] 380–415) following ICU discharge. Their characteristics are described in Table 9.1. Characteristics and differences between complete cases, subjects who completed the CFQ partially (i.e. partial responders), subjects who did not respond (i.e. nonresponders), and nonreceivers are outlined in Table S9.1 (supplementary data).

ICU delirium was present in 186 (51%) of the 363 patients, and the median duration of delirium when delirium was present was 3 days (IQR 1–5). The median CFQ scores for subjects who never had delirium, those who had a single day of delirium,

and subjects with multiple days of delirium were 23 (IQR 12–34), 20 (IQR 10–31) and 25 (IQR 16–35), respectively. Multivariable linear regression with adjustment for potential confounders showed that a single day of ICU delirium was not associated with worse CFQ scores, as compared to subjects with no delirium (adjusted B=-0.72,95%CI -5.75–4.31, Table 9.2). In contrast, subjects with multiple ICU delirium days reported more cognitive problems, than subjects with no delirium (adjusted B=5.10,95%CI 1.01–9.20, Table 9.2).

Of the daily measured CRP levels, 6% was missing and was therefore imputed using longitudinal imputation. The median AUC of the CRP was 545 (IQR 259–1,029 mg *days/L). The ratios of the effect estimates did not differ from 1 and the absolute differences were not different from 0, indicating that the AUC of the CRP levels was not a mediator in the association between delirium and CFQ scores.

Although the distribution of the CFQ scores was altered after multiple imputation, as compared to the CFQ scores of the complete cases (higher versus lower scores and bimodal versus right skewed, respectively), multivariable linear regression analysis after multiple imputation showed similar results on both the association between delirium and CFQ, and the absence of a mediating effect of systemic inflammation (Table S9.2, supplementary data).

TABLE 9.2 ASSOCIATION BETWEEN DELIRIUM AND COGNITIVE FAILURE QUESTIONNAIRE (CFQ) AND THE MEDIATING EFFECT OF SYSTEMIC INFLAMMATION

	Delirium during ICU stay				
	No	A single day		Multiple days	
Association between delirium and the CFQ[a]					
Crude	Reference	-1.96	(-6.95-3.03)	2.53	(-1.20-6.26)
Adjusted[b]	Reference	-0.72	(-5.75-4.31)	5.10	(1.01-9.20*
Mediation analysis of systemic inflammation on the association between delirium and CFQ[c]					
Ratio (95% confidence interval)	-	1.12	(0.89 – 1.49)	1.20	(0.81 – 1.76)
Difference (95% confidence interval)	-	0.88	(0.54 – 1.43)	1.15	(0.63 – 2.13)

* p-value = 0.02

[a] Unstandardized coefficient B with 95% confidence interval.

[b] Adjusted for: age, gender, charlson comorbidity index, acute physiology and chronic health evaluation IV score, and maximal total sequential organ failure assessment without the neurological component.

[c] Ratio and absolute difference between the effect estimates indicating the association between delirium and CFQ adjusted for the aforementioned covariables (model 1), and the effect estimates adjusted for the same covariables and including the AUC of CRP (model 2), calculated by averaging over 1,000 bootstrap samples and non-parametrically obtaining 95% confidence intervals.

DISCUSSION

This is the first study to explore the impact of a brief episode of delirium during ICU stay on cognitive outcome. We found that a single day of ICU delirium was not associated with long-term self-reported cognitive problems, in contrast to multiple days of delirium, which was associated with higher CFQ scores. With the distinction between a single day versus multiple days of delirium, we corroborated on previous research which revealed that rapidly-reversible sedation-related delirium does not affect long-term mortality, as compared to other types of delirium.[12] In addition, the association between delirium and long-term cognitive problems was not mediated by systemic inflammation during ICU stay. These findings suggest that not merely in the context of inflammation, but in the setting of other problems as well, delirium has worse long-term cognitive outcomes.

The association between delirium and long-term cognitive problems is consistent with previous research.[2-5] One earlier study investigated the association between inflammation during delirium onset and long-term self-reported cognitive problems.[27] In this previous study, no association was found between 'inflamed' delirium (i.e., systemic inflammation at the onset of delirium) and long-term cognitive problems as measured with the CFQ. Nevertheless, the sample size of this study was small (n=52).[27] Furthermore, inflammation was less well defined using systemic inflammatory response syndrome criteria, as these criteria have low sensitivity, and insufficient face and construct validity.[28,29]

We used a cumulative measure for inflammation during ICU stay (i.e., the AUC of the daily CRP levels) since we were interested in the mediating effect of the total burden of inflammation on the association between delirium and long-term cognitive problems. We did not take the temporal association between inflammation and delirium into account, and therefore did not investigate the causal influence of inflammation related to delirium, and subsequently, cognitive outcome. It is plausible that the effect of systemic inflammation on self-reported long-term cognitive problems is more pronounced in patients with multiple days of delirium than in those with only a single delirium day, as the absolute difference is larger. Nevertheless, this difference was not statistically significant and therefore this observation is merely speculative.

Our large prospective cohort study has several strengths. The study population consisted of mixed medical-surgical ICU patients, which contributes to the generalizability of our results. The validated delirium assessment conducted by research nurses reduced the risk of misclassifying subjects.[13] The response rate was relatively high thanks to careful follow-up of subjects using a postal reminder and follow-up phone calls. Furthermore, similar results were found in secondary

analyses with multiple imputation, indicating that the results were robust. Some potential limitations of our study should also be addressed. Differentiation between sedation-related and non-sedation related delirium could not be made in our cohort. Nevertheless, it is plausible that a single day of delirium during ICU stay reflects, at least in part, the rapidly-reversible sedation-related delirium. Our results cannot directly be compared with studies that used a neuropsychological test battery to assess objective cognitive impairment, as the CFQ estimates subjective self-reported cognitive problems. Furthermore, we did not have a baseline assessment of cognitive functioning. We also did not have information about events after ICU discharge, which may have influenced cognitive outcome, such as delirium after ICU discharge. As with all observational studies, residual confounding might have occurred. Hence, we could not causally relate ICU delirium to long-term self-reported cognitive problems. It is also important to realize that, as the domain of our study was subjects alive one year after ICU discharge, no inference can be made to subjects who died earlier.

CONCLUSION

In our study, a single day of ICU delirium was not associated with long-term self-reported cognitive problems, in contrast to multiple days of delirium during ICU admission. The cumulative exposure to systemic inflammation did not mediate this association.

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SUPPLEMENTARY DATA

TABLE S9.1 CHARACTERISTICS OF THE ONE YEAR ICU SURVIVORS; DIVIDED IN COMPLETE CASES, PARTIAL RESPONDERS, NONRESPONDERS, AND NONRECEIVERS

Characteristic	Complete cases		Partial responders		Nonresponders		Nonreceivers[a]		p-value[b]
	n=363 (64%)		n=39 (7%)		n=144 (25%)		n=21 (4%)		
Age in years, mean (SD)	59	(16)	65	(17)	54	(17)	50	(20)	< 0.001
Male, n (%)	222	(61)	22	(56)	84	(58)	6	(29)	0.03
CCI, median (IQR)	6	(0–10)	7	(0–11)	3	(0–9)	1	(0–9)	0.04
APACHE IV score, mean (SD)	69	(25)	74	(28)	65	(25)	71	(23)	0.27
Max SOFA score, median (IQR)[c]	7	(4–9)	7	(5–8)	6	(3–9)	5	(3–7)	0.03
ICU LOS in days, median (IQR)	5	(3–9)	6	(3–11)	5	(2–9)	6	(4–11)	0.70
Type of admission, n (%)									
Medical	146	(40)	17	(44)	67	(47)	11	(52)	0.66
Acute surgical	104	(29)	10	(26)	43	(30)	5	(24)	
Elective surgical	113	(31)	12	(31)	34	(24)	5	(24)	
AUC of CRP in mg*days/L, median (IQR)	545	(259–1,029)	753	(322–1,249)	643	(242–643)	576	(457–1,060)	0.36
Delirium, n (%)	186	(51)	22	(56)	80	(56)	9	(43)	0.62

[a] We refrained from sending a questionnaire to these subjects because: they moved abroad (n=10), they died more than one year after discharge, but before questionnaire was sent (n=6) or they declined any follow-up, and announced this in advance (n=5).

[b] Group comparisons were made using the Chi^2 Test for categorical variables, one-way ANOVA for normally distributed continuous variables, or Kruskal-Wallis test for non-normally distributed continuous variables. •

[c] Maximal total SOFA score without the neurological component

Abbreviations: APACHE IV score = acute physiology and chronic health evaluation IV score, AUC = area under the curve, CCI = charlson comorbidity index, CRP = c-reactive protein, Max SOFA = maximal total sequential organ failure assessment, ICU = intensive care unit, IQR = interquartile range, LOS = length of stay, n = number, SD = standard deviation.

TABLE S9.2 RESULTS AFTER MULTIPLE IMPUTATION FOR THE ONE YEAR ICU SURVIVORS (N=567)

TABLE S9.2.1 COGNITIVE FAILURE QUESTIONNAIRE (CFQ) TOTAL SCORES

	Delirium during ICU stay					
	No		A single day		Multiple days	
Number of subjects (%)	270	(48)	86	(15)	211	(37)
CFQ score, median (IQR)[a]	33	(16–64)	30	(15–65)	35	(20–65)

[a] Results from pooled imputed data after 10 imputation iterations.

TABLE S9.2.2 ASSOCIATION BETWEEN DELIRIUM AND COGNITIVE FAILURE QUESTIONNAIRE (CFQ) AND THE MEDIATING EFFECT OF SYSTEMIC INFLAMMATION

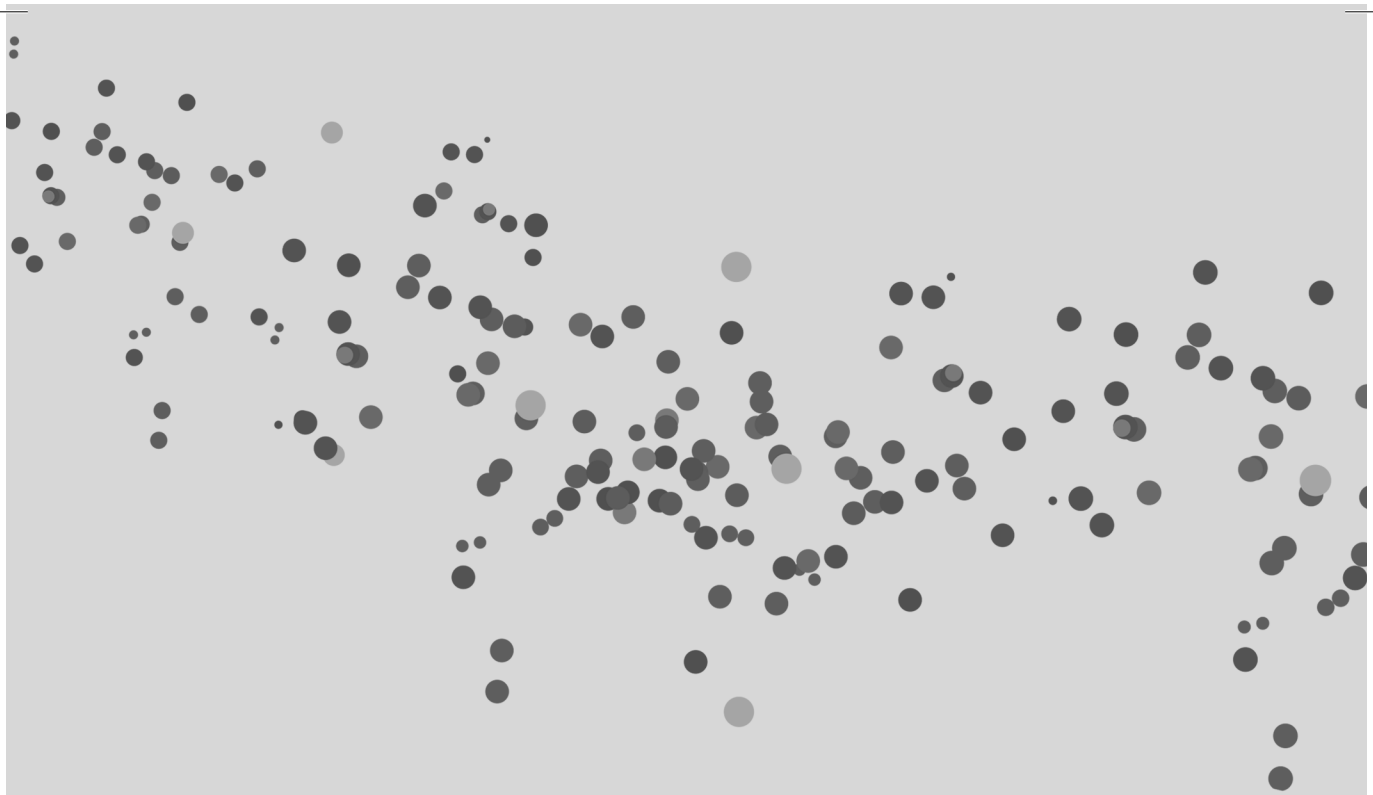
	Delirium during ICU stay				
	No	A single day		Multiple days	
Association between delirium and the CFQ[a]					
Crude	Reference	-0.98	(-6.79–4.82)	2.79	(-1.48–7.06)
Adjusted[b]	Reference	1.66	(-4.18–7.51)	7.31	(2.69–11.92)*
Mediation analysis of systemic inflammation on the association between delirium and CFQ[c]					
Ratio (95% confidence interval)	-	1.05	(0.63–1.45)	1.52	(0.89–1.93)
Difference (95% confidence interval)	-	0.10	(-0.11–0.47)	0.87	(-0.82–2.49)

* p-value = 0.002.

[a] Results from pooled data after 10 imputation iterations, presented as unstandardized coefficients B with 95% confidence interval.

[b] Adjusted for: age, gender, charlson comorbidity index, acute physiology and chronic health evaluation IV score, and maximal total sequential organ failure assessment without the neurological component.

[c] Ratio and absolute difference between the effect estimates indicating the association between delirium and CFQ adjusted for the aforementioned covariables (model 1), and the effect estimates adjusted for the same covariables and including the AUC of CRP (model 2), calculated by averaging over 1,000 bootstrap samples and non-parametrically obtaining 95% confidence intervals.



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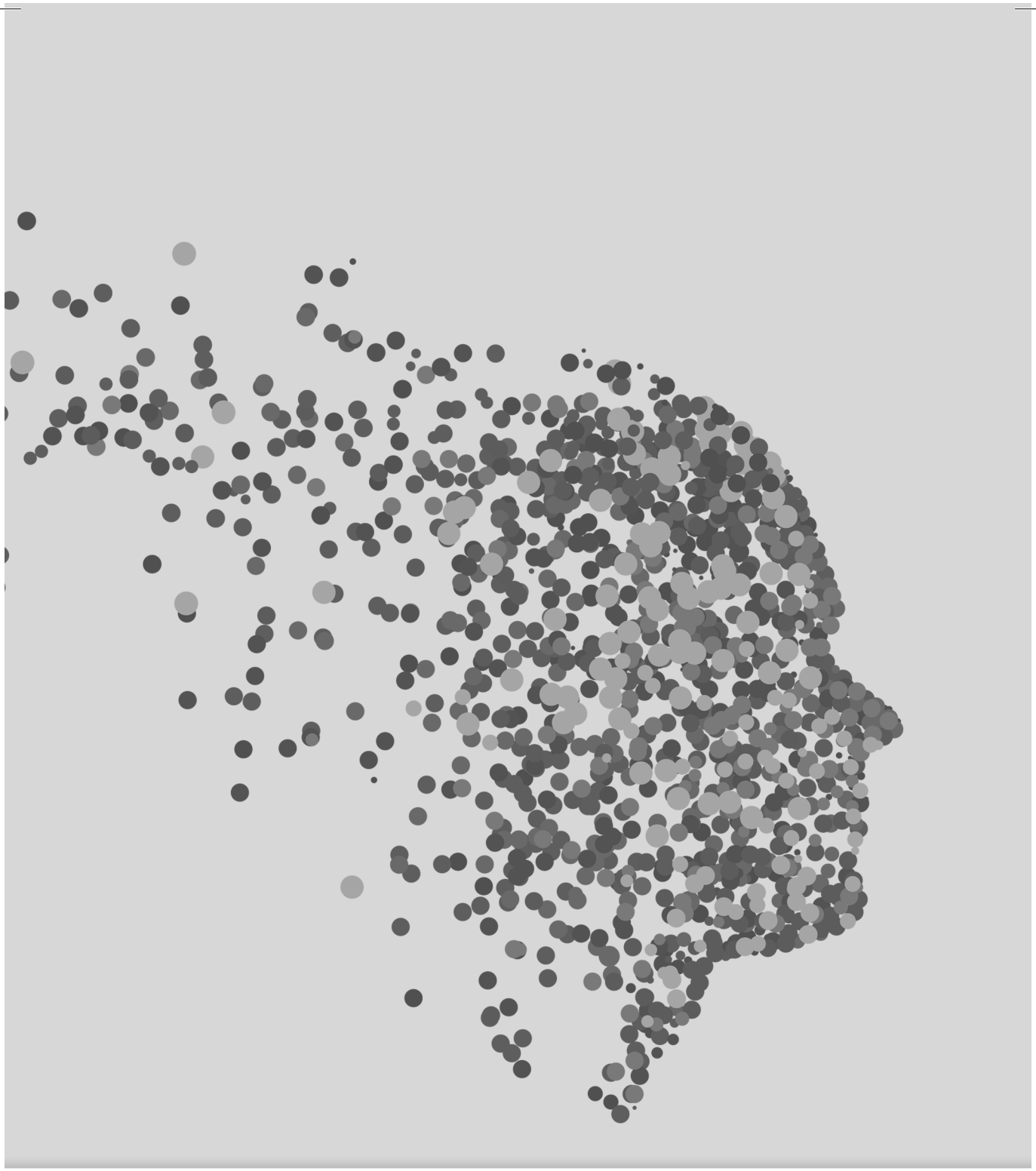

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SUMMARY AND GENERAL DISCUSSION

SUMMARY

In this thesis, risk factors for delirium are studied, an overview of long-term cognitive impairment and mental health problems is given, and the association between intensive care unit (ICU) delirium and long-term cognitive impairment, as well as mental health problems, is explored.

Part I Brain dysfunction during critical illness

In part I of this thesis, we search for etiological risk factors for delirium during critical illness, based on the important components of the etiology of ICU delirium, as proposed in the introduction (i.e., direct brain insults, and abnormal responses of certain pathways). The first two chapters (chapters 2 and 3) focus on iatrogenic, and thus potentially modifiable, factors. Chapter 2 investigates the effect of exposure to medication with anticholinergic properties on the daily probability of delirium occurrence, based on the hypothesis that anticholinergic medication exaggerates cholinergic deficiency leading to delirium.[1,2] A potential effect of age and the presence of inflammation is also examined, as these factors might cause an (aberrant) stress response and hence, aggravate the increased delirium risk.[1] No association between exposure to anticholinergic medication and delirium could be demonstrated, neither a significant effect of age or inflammation on this association was present. Yet, age and the presence of inflammation were both individually independent risk factors for transitioning to delirium. Subsequently, in chapter 3 we examine whether exposure to corticosteroids increase the daily probability of transitioning to delirium, as steroid-associated delirium has been described in previous literature.[2] No association between corticosteroid exposure and the occurrence of delirium could be demonstrated. Chapter 4 shows that psychopathology prior to hospital admission (e.g., an anxiety disorder or depression) did increase the risk of developing a delirium during critical illness. The mechanism by which psychopathology prior to admission increases the risk of delirium has to be elucidated in future studies, but hypothetically, this may be due to an aberrant stress response of the hypothalamic-pituitary-adrenal axis (HPA axis), as dysfunction of the HPA axis is sometimes seen in patients with psychopathology and in patients with delirium.[2] It could also be that, as a consequence of cytokine dysregulation, certain subjects with psychopathology have microglia that have become hypersensitive to stimulation, and thus, have an exaggerated response to peripheral inflammation. This would lead to a maladaptive sickness behavior response, clinically manifesting itself as a delirium.[1] Other factors that might also play a role are disturbances in neurotransmitters or neuronal network changes – both

factors are observed in persons with psychopathology, and in patients with delirium.[1,2]

In conclusion of part I, ageing, the presence of inflammation, and psychopathology prior to hospital admission are important factors in the etiology of delirium. Since the absence of evidence is not the same as evidence of absence, no definitive conclusions can be drawn about the association between the examined medications (i.e., anticholinergics and corticosteroids) and delirium, but no association was found. These factors might therefore not be the most promising modifiable factors worth focusing on, in terms of delirium prevention.

Part II Brain dysfunction after critical illness

Part II of this thesis assesses the occurrence of long-term brain dysfunction after critical illness and evaluates the association with ICU delirium and this long-term dysfunction. The systematic review in chapter 5 shows that a substantial number of patients experience cognitive problems after critical illness, although a wide range is reported (4–62%) and follow-up duration is diverse (2–156 months). Chapters 8 and 9 further elaborate on these cognitive problems after ICU stay, evaluating the association with delirium during ICU stay. An association between (multiple days of) ICU delirium and long-term self-reported cognitive problems was found in one year ICU survivors (chapters 8 and 9). Since systemic inflammation is both a risk factor for delirium during ICU stay (chapter 2),[1,3,4] and for long-term cognitive problems[5], a mediation analysis is conducted in chapter 9 to explore the potential mediating effect of exposure to systemic inflammation in the association between ICU delirium and long-term cognitive problems. No mediating effect was found, suggesting that the effect of ICU delirium on long-term cognitive problems is not merely driven by the exposure to systemic inflammation. Chapter 8 additionally assesses whether delirium is associated with long-term mortality and worse health-related quality of life (HRQoL). After adjustment for confounding, the association between ICU delirium and these outcomes did not remain, which showed for the first time that ICU delirium itself might not be etiologically related to these long-term outcomes.

Chapter 6 describes the occurrence of symptoms of the postintensive care syndrome, with a focus on symptoms of anxiety, depression, and posttraumatic stress disorder (PTSD), three months after critical illness in former patients and their families visiting an outpatient clinic. A substantial number of family members of former ICU patients seem to have mental health problems, an issue which is often overlooked. A lot of former ICU patients also experience mental health problems, three months after ICU discharge. In chapter 7, the association between delirium during ICU stay and symptoms of anxiety, depression and PTSD is assessed one year after

ICU stay. High frequencies of symptoms of anxiety, depression and PTSD in former ICU patients were demonstrated, also one year after ICU discharge. However, no association between ICU delirium and an increased risk for symptoms of anxiety or depression after one year was demonstrated, nor did it increase symptoms of PTSD.

In summary, part II of this thesis shows that a substantial number of former ICU patients and their families experience long-term cognitive and mental health problems. An association between ICU delirium and long-term cognitive problems was found. Nevertheless, no association with the other long-term outcomes could be demonstrated, when correcting for confounding.

GENERAL DISCUSSION

The work described in this thesis aims to contribute to a better understanding of brain dysfunction during and after critical illness. However, uncertainties persist and improvements remain necessary. It is important that medical research is designed and conducted in a manner that facilitates and supports clinical care. In my view, there are three topics which are of major importance in clinical care, related to ICU delirium and long-term brain dysfunction after critical illness (Box 10.1).

Box 10.1 Important topics related to ICU delirium and long-term brain dysfunction after critical illness

- How do we diagnose ICU delirium?
- What can we do about ICU delirium in terms of interventions?
- What is the prognosis of a critical illness with regard to long-term brain dysfunction?

These three issues all have their own clinical and research related difficulties, which will be discussed in the following sections.

Definition and diagnosis of ICU delirium

Even though not extensively discussed in this thesis, it is important to reflect on the phenomenology of ICU delirium, because a clear definition and reliable diagnosis is important for clinical care and is essential for delirium research. Delirium is a syndrome, which is defined by the criteria as described in the diagnostic statistical manual of mental disorders (DSM). In the fourth revised edition of the DSM (DSM-IV-R), delirium was characterized by a disturbance in consciousness and cognition that develops over a short period of time, which tends to fluctuate and, by definition, is a direct physiological

consequence of a medical condition.[6] Currently, the DSM-5 has been published.[7] In this thesis, the DSM-IV-R was used for delirium definition and diagnosis, as the majority of the patients were admitted before the DSM-5 was published and no validated screening tool based on the DSM-5 is available at this time.[6,8] The most prominent difference in the diagnostic criteria is that the term consciousness was removed and the focus shifted to attention and awareness. No major changes in the core elements were made. The diagnostic difference between the DSM-IV-R and the DSM-5 depends on the interpretation of the criteria. A flexible approach of DSM-5 criteria is recommended, as it renders a discordant number of delirium cases compared to the DSM-IV-R.[9]

Preferably, no false-positives nor false-negatives exist when a diagnosis is made by the gold diagnostic standard. The gold standard for diagnosing delirium is the application and evaluation of the DSM criteria by a delirium expert (usually a psychiatrist, geriatrician or neurologist). This makes diagnosing delirium complex, as even a diagnosis made by the gold standard will fall short of achieving 100% accuracy in clinical practice, due to interpretation differences. The fluctuating course of delirium makes the diagnosis even more difficult. In daily routine practice and in large prospective cohort studies, it is not feasible to assess delirium daily using the gold standard. For daily routine ICU delirium assessment, two screening tools are recommended by the Society of Critical Care Medicine – the confusion assessment method for the ICU (CAM-ICU), and the intensive care delirium screening checklist (ICDSC).[10] Both are based and validated on the DSM-IV-R criteria. In the ICU of the University Medical Center Utrecht, the CAM-ICU is implemented in daily routine practice because of its superior sensitivity compared to the ICDSC.[11] However, with daily routine screening the fluctuating tendency of delirium is not captured sufficiently. Therefore, for research purposes, a validated algorithm was designed which evaluates the mental status of the patient for the previous 24 hours.[8] This approach facilitates a more reliable delirium assessment compared to daily routine screening, as the fluctuating nature is captured more appropriately. Though, as it lags clinical decision making, it is merely useful in a research setting and not in clinical practice.

A promising future perspective in both daily routine screening and in research setting would be electroencephalography based delirium monitoring with a limited number of electrodes, which was demonstrated to distinguish post-cardiothoracic surgery patients with and without delirium.[12] Nevertheless, this potential promising delirium monitoring is not available yet. Important topics that should be addressed while moving from concept to clinical use are validation, inference to other study populations (such as critical care patients), and regulatory science.

Prevention and therapy of ICU delirium

Before elaborating on what needs to be done about ICU delirium, it is important to establish whether ICU delirium is an independent risk factor for worse outcomes. One might believe that delirium is only a reflection of illness severity, instead of being causally associated with worse short and long-term outcomes. This would implicate that by only focusing on treatment of the underlying illness, delirium and its related outcomes would also improve. Therefore, etiological studies relating ICU delirium to short and long-term outcomes are essential (e.g., chapters 7, 8 and 9). It is important to realize that a major limitation of observational research assessing the effect of delirium on outcomes is that causation cannot be established, but merely associations can be described. Delirium as a cause of adverse outcomes cannot be studied in randomized trials, as delirium cannot be randomly allocated. Hence, we are limited to observational studies. Therefore, it is important to apply adequate covariate adjustment to control for confounding (e.g., baseline assessment is essential), and the use of sophisticated methodology is necessary to adjust for other bias such as competing risks, the time varying nature of disease severity, and the selective responsiveness in long-term survey studies (e.g., with multiple imputation). With use of these methods, we can try to approximate causal inference.

In this thesis, no association between ICU delirium and long-term symptoms of anxiety, depression and PTSD could be demonstrated (chapter 7). In addition, after adjustments for confounding, the association between ICU delirium (of any duration) and long-term mortality and HRQoL did not hold. Nevertheless, current research does show that ICU delirium prolongs ICU stay, and persistent delirium is associated with attributable ICU mortality.[13,14] Multiple delirium days is also associated with cognitive impairment after discharge (chapter 9).[14] These findings implicate that particularly persistent ICU delirium is certainly a problem worth focusing on in terms of interventions, next to the underlying disease causing the ICU delirium.

The next step is exploring the etiology of ICU delirium further, as this will provide a basis for the development of appropriate therapeutic interventions. In this thesis, no association between anticholinergic medication or corticosteroids and delirium could be demonstrated (chapters 2 and 3) but the presence of systemic inflammation and age were both independent risk factors for delirium (chapter 2). Psychopathology prior to ICU admission was also associated with an increased risk of delirium (chapter 4). Direct brain insults, and aberrant responses of specific pathways in certain patients can be important components that might play a role in the way that the identified factors (i.e., age, inflammation, and a history of

psychopathology) increase the occurrence of delirium.[1] The exact mechanisms of how these factors are related to delirium etiology have to be elucidated in future studies.

The components in ICU delirium etiology are likely complementary, rather than competing, with many areas of reciprocal influence and intersections. This makes it very challenging to distinguish different etiological mechanisms, albeit emphasis in future research should be on subtyping the variations underlying the mechanisms of origin for delirium. Therapies can then potentially be tailored according to the different etiological mechanisms. Epidemiological studies and fundamental research can supplement each other in the pursuit for subtyping etiological mechanisms of delirium. Fundamental science studies should further identify different etiological mechanisms of delirium. Although complicated, focusing on the development of reliable animal models can be a vital step in discovering (new) pathways leading to delirium.[15,16] These pathways can represent novel leads in modifiable factors, and essential new drug targets. Additionally, neuroimaging studies involving serial measurements (before, during, and after episodes of delirium) would be highly desirable, to test whether delirium involved in certain etiological mechanisms reflects structural or functional changes of the brain.[17] Yet, we have to acknowledge the practical difficulties of imaging patients with a delirium. Future observational studies should also focus on factors with the potency to increase or decrease the risk of delirium, while using refined methodology to adjust for bias when randomization is not feasible or currently not desirable (e.g., chapters 2, 3 and 4). Potential risk factors for ICU delirium that could be of interest to be evaluated in observational studies are the use of various opioids and propofol, as it is currently hypothesized but unclear whether these medications may induce ICU delirium.

It is important to realize that after identifying risk factors, further studies are needed to assess whether decreasing exposure to these risk factors results in less delirium and improved outcome. Hence, observational studies identifying promising modifiable factors have to induce intervention studies. Currently, for reduction of incidence and duration of delirium early mobilization of critical care patients is recommended. No pharmacological prevention for ICU delirium is advised.[10] Although antipsychotics, such as haloperidol, are widely used for the prevention and treatment of ICU delirium, evidence of a beneficial effect is limited.[10] Atypical antipsychotics might reduce the duration of delirium, but evidence is currently weak and should be further evaluated.[10] Both the preventive as well as the therapeutic effect of haloperidol is uncertain, and assessment of these effects in a randomized setting is of major importance. Other promising therapy studies for ICU delirium treatment and prevention, which should be conducted in randomized studies include – but are not

limited to – the evaluation of dexmedetomidine, clonidine and the continuation of certain home medication during ICU stay, such as antipsychotics and statins.

Prognostication of brain dysfunction after critical illness

Former ICU patients experience substantial morbidities, summarized into two denominators; physical problems and brain dysfunction (chapters 5 and 6). The introduction of the umbrella term postintensive care syndrome (PICS) by the Society of Critical Care Medicine, as well as articles describing the occurrence of PICS (e.g., chapter 6), have increased clinical awareness for the morbidities experienced after critical illness.[18,19] Currently, a multistep approach addressing factors related to PICS is recommended for improving long-term outcome of ICU survivors.[19] When focusing on brain dysfunction after critical illness, it is still unresolved which preventive measures in which patients are most promising.[19] Enhancement of prediction of long-term brain dysfunction is necessary, as it has the potency to advance clinical decision making (e.g., tailored risk assessment and estimation of prognosis). This might in turn improve critical care patient outcomes, as interventions can subsequently be customized to certain patients. Therefore, an essential topic is the prognostication of patients with brain dysfunction after critical illness. One of the potential important predictors for long-term brain dysfunction is ICU delirium, as it is prognostically associated with worse outcomes such as mortality.[20] Other possible key predictors are severity of illness measures, such as the acute physiology and chronic health evaluation IV and the sequential organ failure assessment. Promising, but currently unstudied predictors of brain dysfunction after critical illness, are physical and cognitive functioning, as well as quality of life, prior to the ICU admission.

The typical approach for modeling prediction is based upon a population model, where a single predictive model is derived to predict outcomes for future individuals. This model is designed to have a good predictive performance on average on all members of the population, which means that it might not be the optimal model for a certain individual. A promising alternative is personalized modeling, with a model specialized to the features of the current critically ill patient, and optimized to predict especially well for that individual. When compared to population modeling, both approaches use a dataset to derive important predictors and both use features of the current patient. The difference lies in the approach on how the features are used to predict the outcome. The population model applies the features of an individual to a certain model, the personalized model uses the features to both derive the model and apply it. Further research is warranted, but personalization seems an interesting methodology in prognostic modeling of brain

dysfunction after critical illness.[21] The success of prognostic medicine eventually depends on having accurate (personalized) predictors that identify individuals who will (or will not) benefit from specific interventions. Hence, in prediction research personalized medicine is the ultimate goal, as it is in other research fields.

A final note on follow-up research is the awareness that a certain follow-up starting point has consequences on the generalizability of the results.[20] Follow-up can start for example at ICU admission, after ICU discharge, or after hospital discharge. When using for instance ICU discharge as the starting point, the minimal requirement is that the patient survives ICU stay, which introduces an important amount of selection as surviving ICU stay is already a marker for better outcome. Therefore, results of these studies will not be helpful for clinical decision making during critical illness. Hence, it highly depends on the aim of the study which follow-up starting point has to be chosen, and the limitation of generalizability to a certain domain should be recognized.

CONCLUSION

Brain dysfunction – in the broadest sense of the word – is frequently observed during as well as after critical illness. This thesis adds some understanding on the etiology of ICU delirium, morbidities in former ICU patients, and on the association between brain dysfunction during and after critical illness. However, there is still a considerable gap of knowledge on this topic. I would propose that future research focuses on three main issues: (1) the diagnosis of ICU delirium, (2) interventions for ICU delirium (following etiological studies identifying risk factors, providing a basis for these interventions), and (3) prognostication of long-term brain dysfunction after critical illness, and subsequently improvement of this prognosis. Our main goal should be to expand our knowledge to achieve increasing certainty about biological processes related to brain dysfunction during and after critical illness, and to establish promising interventions preventing negative outcomes.

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A

DUTCH SUMMARY
NEDERLANDSE SAMENVATTING

In Nederland worden jaarlijks ongeveer 80.000 kritiek zieke patiënten opgenomen op een intensive care afdeling (IC). Van deze patiënten overleeft 80–85% de IC opname. Een groot deel van deze patiënten heeft na ontslag last van het postintensive care syndroom (PICS). PICS is een verzamelterm voor alle nadelige lichamelijke, cognitieve en mentale gevolgen die een IC opname kan hebben. Het is belangrijk om inzicht te krijgen in hoe vaak deze nadelige gevolgen voorkomen, en bij welke patiënten dit met name een probleem is. Het lijkt bijvoorbeeld zo te zijn dat patiënten die een delirium doormaken tijdens IC opname meer last hebben van de genoemde nadelige cognitieve en mentale gevolgen. Een delirium, ook wel delier genoemd, is een plotseling optredende acute dysfunctie van de hersenen die vaak voorkomt op de IC. Kenmerkend voor een delirium is dat een patiënt niet helder kan nadenken, niet de aandacht vast kan houden en zich moeilijk kan oriënteren. Het is niet duidelijk of het delirium er (deels) voor zorgt dat een patiënt een slechtere uitkomst heeft na IC ontslag, of dat het delirium enkel een teken is dat de patiënt ernstig ziek is – patiënten die ernstiger ziek zijn krijgen eerder een delirium én hebben vaker een slechtere uitkomst. Het is belangrijk dat dit verder uitgezocht wordt. Ondanks dat delirium een veelvoorkomend probleem is op de IC en samen lijkt te hangen met slechtere uitkomsten, is niet goed bekend waardoor het delirium precies veroorzaakt wordt. Er is daarom ook meer inzicht nodig in welke factoren een oorzakelijke rol spelen bij het ontwikkelen van een delirium.

In dit proefschrift zijn factoren onderzocht die mogelijk een oorzakelijke rol spelen bij het ontwikkelen van een delirium tijdens een IC opname. Daarnaast wordt een overzicht gegeven van langetermijngevolgen van een IC opname, met de nadruk op mentale en cognitieve problemen welke samengevat worden onder de noemer hersendysfunctie na IC ontslag. Vervolgens wordt het verband gelegd tussen een delirium tijdens IC opname en de genoemde langetermijnuitkomsten.

Deel I Hersendysfunctie tijdens kritieke ziekte

In deel I van dit proefschrift worden risicofactoren onderzocht die een delirium zouden kunnen veroorzaken tijdens IC opname. In de hoofdstukken 2 en 3 worden factoren onderzocht waarvan de blootstelling potentieel te verminderen of te vermijden is. In hoofdstuk 2 wordt het effect van medicatie met een anticholinerge werking op de kans om een delirium te ontwikkelen bekeken. Dit onderzoek is gebaseerd op de gedachte dat medicatie met een anticholinerge werking een verstoring van het cholinerge neurotransmitter systeem in de hersenen verergeren en daarmee een delirium zouden kunnen veroorzaken. Het effect van leeftijd en de aanwezigheid van een ontsteking in het gehele lichaam (ook wel systemische inflammatie genoemd) is daarnaast onderzocht, omdat de aanwezigheid van deze factoren mogelijk het risico

op een delirium zouden kunnen versterken. Er is geen verband aangetoond tussen blootstelling aan medicatie met een anticholinerge werking en het optreden van een delirium tijdens opname op een IC. Ook leeftijd en systemische inflammatie hadden geen effect op het verband tussen de anticholinerge medicamenten en delirium. Een hogere leeftijd en de aanwezigheid van systemische inflammatie bleken beiden wel onafhankelijke risicofactoren voor het ontwikkelen van een delirium tijdens IC opname.

Aangezien er aanwijzingen zijn dat corticosteroïden een delirium zouden kunnen veroorzaken (in voorgaande literatuur het steroïde-geassocieerd delirium genoemd), wordt in hoofdstuk 3 bekeken of blootstelling aan corticosteroïden op de IC een verhoogde kans geeft op het ontwikkelen van een delirium. Er kon geen samenhang worden aangetoond tussen het gebruik van corticosteroïden en het optreden van een delirium tijdens IC opname.

In hoofdstuk 4 wordt onderzocht of patiënten met psychopathologie in de voorgeschiedenis (zoals een angststoornis of depressie) meer ontvankelijk zijn voor het ontwikkelen van een delirium tijdens IC opname dan patiënten die geen psychopathologie in de voorgeschiedenis hebben. Het blijkt dat patiënten met psychopathologie in de voorgeschiedenis een verhoogd risico hebben op het ontwikkelen van een delirium tijdens IC opname. Het mechanisme waardoor patiënten met psychopathologie een hoger risico op een delirium hebben moet nog worden uitgezocht, maar het zou bijvoorbeeld kunnen komen door een abnormale reactie van de hypothalamus-hypofyse-bijnier as, aangezien een verstoring in dit systeem in sommige patiënten met psychopathologie wordt gezien en ook lijkt voor te komen tijdens het optreden van een delirium. Het zou ook zo kunnen zijn dat bepaalde patiënten met psychopathologie overgevoelige cellen in de hersenen hebben. Deze cellen zouden bij inflammatie in het lichaam overactief kunnen reageren en een ernstige vorm van ziektegedrag kunnen opwekken, zich uitend als een delirium. Andere factoren die een rol zouden kunnen spelen zijn verstoringen in neurotransmittersystemen in de hersenen, of abnormale neuronale netwerken in de hersenen – beiden worden gezien in patiënten met psychopathologie in de voorgeschiedenis en in patiënten met een delirium.

Concluderend blijkt uit deel I van dit proefschrift dat een hogere leeftijd, de aanwezigheid van systemische inflammatie en psychopathologie in de voorgeschiedenis belangrijke factoren zijn in het ontwikkelen van een delirium tijdens IC opname. In dit proefschrift hebben we niet kunnen aantonen dat de onderzochte medicamenten (anticholinerge medicamenten en corticosteroïden) de kans op het optreden van een delirium tijdens IC opname verhogen. Het verminderen of vermijden van blootstelling aan deze medicamenten met als doel delirium te voorkomen lijkt gezien deze resultaten niet zinvol.

Deel II Hersendysfunctie na kritieke ziekte

Deel II van dit proefschrift beschrijft het optreden van cognitieve en mentale langetermijnproblemen na een IC opname. Ook wordt in dit deel de relatie van een delirium tijdens opname op een IC en het optreden van langetermijnproblematiek belicht. Uit het literatuuronderzoek in hoofdstuk 5 blijkt dat een substantieel deel van de mensen die een IC opname overleven cognitieve problemen ervaart. Desondanks blijft de exacte omvang van het probleem onduidelijk. In de studies welke zijn geïncludeerd in het literatuuronderzoek blijkt 4–62% van de voormalig IC patiënten last te hebben van cognitieve problemen, 2–156 maanden na IC ontslag. In hoofdstukken 8 en 9 wordt vervolgens het verband tussen een delirium tijdens IC opname en cognitieve problemen geëvalueerd. Er blijkt een verband tussen meerdere dagen delirium op de IC en het optreden van cognitieve langetermijnproblemen één jaar na IC ontslag (hoofdstukken 8 en 9). Systemische inflammatie is zowel een risicofactor voor het krijgen van een delirium tijdens het verblijf op een IC (hoofdstuk 2), als voor cognitieve langetermijnstoornissen. In hoofdstuk 9 wordt daarom onderzocht of het effect van het delirium op cognitieve langetermijnproblemen (deels) wordt verklaard door de blootstelling aan systemische inflammatie tijdens de IC opname. Dit kan in hoofdstuk 9 niet worden aangetoond, wat suggereert dat het effect van een delirium tijdens IC opname op cognitieve langetermijnproblemen niet afhankelijk is van de mate van blootstelling aan systemische inflammatie. In hoofdstuk 8 wordt, naast de cognitieve problemen, ook gekeken naar een verband tussen delirium op de IC en mortaliteit en kwaliteit van leven één jaar na IC ontslag. Wanneer gecorrigeerd wordt voor mogelijk verstorende variabelen, zoals de ernst van de ziekte, blijkt dat het verband tussen een delirium op de IC en deze uitkomstmaten niet overeind blijft.

Hoofdstuk 6 beschrijft het optreden van symptomen van PICS, met name gericht op symptomen van angst, depressie en posttraumatische stressstoornis (PTSS), drie maanden na IC ontslag bij patiënten en hun familieleden die een nazorgpoli bezochten. Een nazorgpoli is een polikliniek waar voormalig IC-patiënten en hun familieleden kunnen spreken met een zorgverlener die weet wat er met hen op de IC is gebeurd, zoals een IC-arts en/of IC-verpleegkundige. Het blijkt dat familieleden van voormalig IC-patiënten relatief veel mentale problemen ervaren, iets wat vaak over het hoofd wordt gezien. Veel voormalig IC-patiënten blijken ook last te hebben van symptomen van angst, depressie en PTSS, drie maanden na IC ontslag. In hoofdstuk 7 wordt vervolgens de samenhang beschreven tussen delirium op de IC en langetermijnsymptomen van angst, depressie en PTSS één jaar na IC ontslag. Een aanzienlijk deel van de mensen die een IC opname hebben overleefd geeft twaalf maanden na IC ontslag nog steeds aan

symptomen van angst, depressie en PTSS te ervaren. Het doormaken van een delirium op de IC blijkt echter geen verband te houden met een toename van deze symptomen.

Samenvattend blijkt uit deel II van dit proefschrift dat een aanzienlijk deel van de voormalig IC-patiënten en hun familieleden cognitieve en mentale problemen ervaren. Er bestaat een verband tussen het delirium op de IC en cognitieve langetermijnproblemen, welke niet lijkt te worden bepaald door de mate van blootstelling aan systemische inflammatie. Geen verband kon worden aangetoond met de overige onderzochte langetermijnuitkomsten.

Het laatste deel van dit proefschrift bestaat uit een Engelse samenvatting, gevolgd door een algemene discussie en conclusie over het onderzoek naar delirium op de IC en langetermijnproblematiek na IC ontslag. Hersendysfunctie – in de breedste zin van het woord – is een veelvoorkomend probleem, zowel tijdens als na een IC opname. Dit proefschrift heeft een bescheiden bijdrage geleverd aan dit onderwerp, waarbij we ons gericht hebben op het begrip van het optreden van delirium tijdens de IC opname, mentale en cognitieve problematiek na de IC, en het verband tussen deze twee. Desalniettemin is er nog heel veel wat we niet weten over deze onderwerpen en vervolgonderzoek is daarom essentieel. Mijn voorstel zou zijn dat vervolgonderzoek zich richt op drie klinisch belangrijke onderwerpen: (1) de diagnose van een delirium op de IC, (2) preventie en therapie van het delirium tijdens IC opname, en (3) factoren die het optreden van langetermijnproblematiek na IC ontslag kunnen voorspellen, zodat deze vervolgens meegenomen kunnen worden in het maken van klinische beslissingen. We moeten daarbij streven naar kennisvergaring over de biologische processen die ten grondslag liggen aan hersendysfunctie tijdens en na IC opname, en we zullen op zoek moeten naar veelbelovende interventies om slechte uitkomsten te voorkomen.

B

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C

ABOUT THE AUTHOR

LIST OF PUBLICATIONS

This thesis

- **Wolters AE**, Zaal IJ, Veldhuijzen DS, Cremer OL, Devlin JW, van Dijk D, Slooter AJC. Anticholinergic medication use and transition to delirium in critically ill patients: a prospective cohort study. Critical Care Medicine 2015, 43(9):1846–1852.
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  - Oral presentation 9th European Delirium Association (EDA) Conference, Cremona, November 2014
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- **Wolters AE**, Slooter AJC, van der Kooi AW, van Dijk D. Cognitive impairment after intensive care unit admission: a systematic review.
  - Oral presentation 7th EDA Conference, Bielefeld, October 2012
  - Poster presentation 25th ESICM Conference, Lisbon, October 2012
- **Wolters AE**, van Dijk D, Pasma W, Cremer OL, Looije MF, de Lange DW, Veldhuijzen DS, Slooter AJC. Long-term outcome of delirium in critically ill patients.
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CURRICULUM VITAE

Annemiek Elise Wolters was born on September 22nd, 1987 in Enschede. She grew up in Neede until the age of eight, and then moved to Bemmel. After completion of secondary school in 2005 (Over Betuwe College, Bemmel), she started her Bachelor of Pharmacy at the University of Utrecht. She became interested in research during her Bachelor graduating internship in 2008, at the National Institute of Public Health and the Environment in Bilthoven, under supervision of dr. C.A. Herberts and dr. J. van der Laan. Subsequently, she started the Selective Utrecht Medical Master (SUMMA) at the University of Utrecht. During her study, she did an extracurricular internship in surgery at the University of Santo Tomas in Manila, the Philippines. In 2011, she conducted a research internship at the Department of Intensive Care Medicine of the University Medical Center Utrecht (UMCU) under supervision of dr. A.J.C. Slooter and prof. dr. D. van Dijk. She graduated as a medical doctor and clinical researcher in 2012.

After her graduation, she worked as a resident at the Department of Intensive Care Medicine in Hospital Gelderse Vallei in Ede for a year. During her residency, she was a board member of the resident association of the Hospital Gelderse Vallei. In 2013, she returned to the UMCU to start her PhD program, which resulted from her earlier conducted research as a student (promotor: prof. dr. D. van Dijk, copromotors: dr. A.J.C. Slooter and dr. D.S. Veldhuijzen). During her PhD project, she obtained a masters' degree in Clinical Epidemiology at the University of Utrecht (cum laude).

In January 2016, she will start as a resident in Internal Medicine at the Canisius Wilhelmina Hospital in Nijmegen, as part of her residency training in Pulmonology which she will further continue at the Radboud University Nijmegen Medical Center.