Prediction and Non-pharmacological Prevention of Delirium in the Intensive Care Unit

Annelies Wassenaar

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The work presented in this thesis was funded by the 'Junior research round 2013' of the former Nijmegen Centre for Evidence Based Practice and carried out within the Radboud Institute for Health Sciences.

Cover & interior design: evelienjagtman.com
Printing: Ipskamp Printing
ISBN: 978-94-92896-25-4
Paper: 100 gr. G-Print

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Proefschrift

ter verkrijging van de graad van doctor
aan de Radboud Universiteit Nijmegen
op gezag van de rector magnificus prof. dr. J.H.J.M. van Krieken,
volgens besluit van het college van decanen
in het openbaar te verdedigen op woensdag 16 mei 2018
om 14.30 uur precies

door

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geboren op 19 oktober 1982
te Menaldum

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Doctoral Thesis

to obtain the degree of doctor
from Radboud University Nijmegen
on the authority of the Rector Magnificus prof. dr. J.H.J.M. van Krieken,
according to the decision of the Council of Deans
to be defended in public on Wednesday, May 16, 2018
at 14.30 hours

by

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CHAPTER 1

General introduction and outline of the thesis

General introduction

The number of patients who require treatment in the Intensive Care Unit (ICU) is extensive; in 2016 over 85.000 patients were admitted to Dutch ICUs for various reasons.(1) This number will continue to rise, as the elderly population is growing and medical technology in intensive care medicine advances. Due to the technical advances in ICU treatment, short term mortality after critical illness decreases.(2, 3) As a result, there has been a shift in emphasis from preventing mortality to preventing the devastating long-term consequences of critical illness in ICU survivors.(4) Following ICU discharge, patients often suffer from physical, mental, and cognitive impairments,(5, 6) which are referred to as postintensive care syndrome (PICS).(3, 7) In particular long-term cognitive impairment is a growing public health problem,(8) as it occurs in up to 60% of the ICU survivors.(9) An important risk factor for cognitive impairment is ICU delirium.(8)

Delirium

The history of the clinical syndrome delirium goes back over two millennia.(10, 11) First Hippocrates and later on Celsus used terms to describe mental disorders that still cover parts of the currently used definitions of delirium. Delirium is derived from the Latin 'delirare', which means the person is off the track.(10, 12) The definition of delirium that is currently most used, can be found in the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5).(13) In this manual five criteria are described to diagnose delirium:

a) Disturbance in attention (reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment);
b) The disturbance develops over a short period of time (usually hours to days), represents an acute change from baseline, and tends to fluctuate during the course of the day;
c) Disturbance in cognition (memory deficit, disorientation, language, visuospatial ability, or perception);
d) The disturbances are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma;
e) There is evidence from the history, physical examination or laboratory findings that the disturbance is caused by a medical condition, substance intoxication or withdrawal, or medication use.

Impact of delirium

Delirium is common in the ICU, burdening around a third of the critically ill patients.(14) The occurrence of delirium is associated with several adverse consequences including a longer duration of mechanical ventilation and length of stay in both the ICU and hospital.(14) Also, patients who were delirious during ICU admission are more likely to die or suffer from long-term cognitive impairment.(14) Next to the burden to the patient, delirium has a large economic impact due to both higher ICU and hospital costs, as well as additional costs due to rehabilitation after discharge.(15) Given these negative outcomes, delirium is recognized as a major public health problem.(16)

Subtypes and routine monitoring

In view of the negative consequences of delirium in ICU patients, systematic delirium monitoring is indispensable to deliver adequate patient care in the ICU. Routine monitoring of delirium in ICU patients using a reliable and valid delirium screening tool is therefore recommended in current clinical guidelines for delirium management in the ICU.(16, 17) The most valid and reliable tools are the Confusion Assessment Method for the ICU (CAM-ICU) (18, 19) and the Intensive Care Delirium Screening Checklist (ICDSC).(20) Regular delirium assessment may potentially improve patient outcome by earlier detection and treatment of delirium.(16)

When monitoring delirium in ICU patients, one should take the use of sedatives into account, as it is shown that delirium that abates after sedation interruption, known as rapidly reversible sedation-related delirium, is fundamentally different from persistent delirium.(21, 22) Where persistent delirium is associated with detrimental patient outcome, the prognosis of patients suffering from rapidly reversible, sedation-related delirium is comparable with the prognosis of ICU patients without delirium.(21)

Persistent delirium can present in different motoric subtypes consisting of hypoactive, hyperactive, and mixed states and may fluctuate between these types.(23) Delirium subtypes can be distinguished using a sedation assessment tool like the Richmond Agitation-Sedation Scale (RASS) or the Riker Sedation-Agitation Scale (SAS).(23-25) Hyperactive delirium, which is characterized by agitation, restlessness, and hallucinations, is present when the RASS assessment is persistently positive during the delirium episode (+1 to +4) or when the Riker SAS assessment is persistently 5, 6, or 7. Hypoactive delirium presents with depressed consciousness and is defined with persistently neutral or negative RASS assessments during the delirium episode (0 to -3) or with persistent Riker SAS assessments of 3 or 4. Mixed delirium involves both positive and negative RASS assessments or Riker SAS assessments varying between 3 to 7 during the delirium episode. These subtypes can influence the detection of delirium. Especially hypoactive delirium, which is present in a significant part of the ICU patients,(26-28) is often misdiagnosed and difficult to detect without the use of a screening tool.(27, 29)

Risk factors

Multiple risk factors are associated with delirium.(30-32) The presence of predisposing and precipitating risk factors determines patients' risk for delirium. Predisposing risk factors are baseline factors that are related to the underlying characteristics and co-morbidities of the patient, already present before ICU admission. These factors determine the patients' vulnerability to develop delirium. Examples are age, dementia, and alcohol use. Precipitating factors are related to the ICU admission, the patients' acute critical illness and the treatment. In other words, these factors are the insult that provokes delirium. Examples are infection, mechanical ventilation, metabolic acidosis, and medication including sedatives and analgesics.(31, 33, 34) Patients who are admitted to the ICU are exposed to many delirium risk factors, up to more than ten factors per patient.(35) As a result ICU patients are prone to delirium.

Delirium prediction in ICU patients

Identification of ICU patients at high risk for delirium may be important in the facilitation of delirium prevention,(36) since these are the most fragile patients who require maximum preventive efforts.(36) Restricting delirium prevention to high-risk patients prevents unnecessary exposure to potential harmful side-effects of pharmacological preventive measures and is likely more cost-effective; as stratification of patients based on the risk to develop delirium may positively influence efficient use of both the care for ICU patients and research. Moreover, the effectiveness of prevention seems more pronounced in patients with a higher risk for delirium.(37) Furthermore, family members can be provided with relevant information about the risk of their loved-one to develop delirium and involved in ICU care aimed at delirium prevention.(38) The use of an ICU delirium prediction model is warranted to identify those ICU patients at high risk for delirium, as it is shown that an ICU delirium prediction model provides more accurate risk scores compared to clinical judgment.(39)

Delirium risk stratification using a delirium prediction model enables healthcare professionals, as well as researchers, to focus on the most vulnerable group. Currently, an ICU delirium prediction model is available: the PRE-DELIRIC model which uses ten predictors obtained within 24 hours after ICU admission to reliably predict ICU delirium.(39, 40) This model was developed and validated in a large Dutch cohort of ICU patients (39) and was recently recalibrated in a multinational cohort.(40) However, a relevant limitation of the usefulness of this model is that it requires predictors obtained during the first 24 hours of ICU admission. As delirium develops within the first 24 hours of ICU admission in up to 25% of critically ill adults,(41, 42) preventive measures should be executed as soon as possible after ICU admission. This calls for an early delirium prediction model to reliably predict delirium at time of ICU admission.

(Non-)pharmacological delirium prevention

Delirium prevention is crucial because once delirium occurs efficacy of pharmacological therapy is limited.(43) Pharmacological interventions to prevent delirium, such as prophylactic use of dexmedetomidine for sedation, may have important beneficial effects in patients at high risk for delirium.(37, 44) However, currently no conclusive evidence is available showing that pharmacological interventions are effective in preventing delirium in ICU patients.(16) Therefore, there is a need to investigate alternative (non-pharmacological) interventions aimed to prevent delirium and its deleterious consequences.

As many risk factors are associated with delirium,(30, 31) a multicomponent non-pharmacological intervention (MCI) program targeting several modifiable risk factors may represent a promising strategy for delirium prevention.(45) In non-ICU patients, it has been shown that a program with standardized interventions focusing on cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment, resulted in a significant reduction of the delirium incidence and duration.(46, 47) Studies in ICU patients focusing on specific parts of the program also reported beneficial effects.(48-51) However, currently there is insufficient knowledge on the effects of an MCI program in ICU patients. Recent studies in the ICU yielded inadequate proof due to weaknesses in study design, a limited sample size, or problems with data collection.(52-54) Therefore, further research is needed to determine the effects of an MCI program on delirium in ICU patients. Before the effects of an MCI program on ICU delirium can be investigated using a rigorous design, the program should be tailored to ICU patients and studied for feasibility in the ICU. This is necessary because it is uncertain whether the MCI program that is developed and tested for non-ICU patients is complete for ICU patients and feasible in an ICU setting.

Measuring cognitive failure in ICU survivors

A significant number of ICU survivors develop long-term cognitive impairment following ICU-acquired delirium.(9) Post-ICU cognitive impairment is part of PICS and associated with depression, increased dependence and poor social functioning.(55) Further recognition of cognitive failure by both clinicians and researchers is required to allow for actions that are aimed at decreasing post-ICU cognitive impairment and its negative consequences.(55) To date there is a dearth of research into survivors' perception of their cognitive function. Having this knowledge could help to understand the functional implications of cognitive impairment, which is an essential step towards meeting the needs of ICU survivors.

Post-ICU cognitive impairment affects a person's attention, processing speed, memory, as well as executive function.(55) Seemingly simple tasks that a person normally should be able to perform without errors, suddenly become complicated.(56, 57) To assess a person's likelihood of making such errors in everyday life, multiple self-report measures are available.(57) The Cognitive Failures Questionnaire (CFQ) designed by Broadbent et al. (1982) is the most frequently used and most comprehensive measure in terms of covered

domains of daily life failures.(57, 58) This self-reported questionnaire consists of 25 items that cover failures of perception, memory, and motor function (58) and therefore is the designated questionnaire to identify ICU survivors' perception of their cognitive function.

Identification of cognitive failure following ICU delirium is essential to provide clinicians with important functional information necessary for the support of the ICU survivors during their recovery. Given that ICU survivors often develop a combination of cognitive, mental, and physical impairments (PICS) following ICU discharge, several questionnaires are needed to study the relevant issues related to these impairments, resulting in an overload of questions for ICU survivors. Paradoxically, given their problems with their concentration and attention they have a decreased capacity to fill out questionnaires, contributing to non-response of ICU survivors to questionnaires. So, introducing an optimal short form of the full 25-item CFQ (CFQ-25) for ICU survivors is desirable to prevent them for overburdening, as well as to reduce incomplete questionnaires or non-response.

Aims of the thesis

- To develop and validate an early ICU delirium prediction model, to determine if delirium can be reliably predicted immediately after ICU admission;
- To gain insight in the statistical performance and user convenience of different available ICU delirium prediction models;
- To develop a multicomponent non-pharmacological intervention program aimed to prevent delirium in ICU patients targeting the modifiable delirium risk factors cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment;
- To develop and validate an abbreviated self-reported questionnaire to easily measure cognitive failure in ICU survivors.

Outline of the thesis

The first part of this thesis focuses on the ***prediction*** of delirium in ICU patients. In **chapter two** we describe the development and validation of an early delirium prediction model, called the Early PREdiction model for DELIRium in ICu patients (E-PRE-DELIRIC model). This model uses nine predictors readily available at ICU admission to predict patients' risk to develop delirium during their complete ICU stay. The performance of a prediction model outside the development sample determines its generalizability and usefulness in daily clinical practice.(59) Thus, before the use of a delirium prediction model can be implemented as standard measure in the ICU, it is essential to confirm its predictive performance in a new dataset that is independent from the development dataset.(59) Therefore, in **chapter three** we externally validated the PRE-DELIRIC and E-PRE-DELRIC models. To enable clinicians to choose between both models, we compared the predictive performance and user convenience of the PRE-DELIRIC and E-PRE-DELIRIC models and determined the value of a two-stage calculation using both prediction models in **chapter four**.

The second part of this thesis focuses on the ***prevention*** of delirium in ICU patients. Delirium prevention is crucial since the efficacy of pharmacological therapy is limited once delirium has developed.(43) A multicomponent non-pharmacological intervention (MCI) program targeting several modifiable delirium risk factors represents a promising strategy for delirium prevention.(45) Since there is insufficient evidence available on the effects of an MCI program in ICU patients, further research is needed to determine the effects of an MCI program on delirium in ICU patients. In **chapter five and six** we describe the development of an MCI program consisting of nursing and physical therapy interventions, focusing on cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment. In **chapter five** we determined the feasibility and completeness of an MCI program to prevent ICU delirium using a modified RAND Delphi study. Apart from the cognitive training exercises aimed at maintaining cognitive function, group consensus on the MCI program was achieved. Therefore, we evaluated the feasibility of cognitive training exercises for critically ill patients, as well as the feasibility for ICU nurses (**chapter six)**. In **chapter seven** we describe the study protocol for the planned stepped wedge cluster randomized controlled trial, named the UNDERPIN-ICU study, in which the effect of the MCI program on the development of ICU delirium will be studied. ICU-acquired delirium is an important risk factor for developing long-term cognitive impairment following ICU admission.(9) Improved identification of ICU survivors' perception of cognitive impairment is required to allow for actions that are aimed at decreasing post-ICU cognitive impairment and its negative consequences.(55) In **chapter eight** we describe the development and validation of an abbreviated version of the CFQ-25 that may be used by ICU survivors as part of self-evaluation of their cognitive function. An abbreviated CFQ will be less of a

burden for the ICU survivors and may increase their response rates and compliance to fill out the complete questionnaires.

In **chapter nine**, the general discussion, we present the main results described in this thesis in a broader theoretical and practical context and reflect on the implications of our findings for ICU practice. Also, we discuss several methodological considerations and describe aims for future research and the general conclusions.

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PART

Prediction of delirium in ICU patients

CHAPTER 2

Multinational development and validation of an early prediction model for delirium in ICU patients

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Intensive Care Med. 2015;41(6):1048-56

Abstract

Rationale: Delirium incidence in Intensive Care Unit (ICU) patients is high and associated with poor outcome. Identification of high-risk patients may facilitate its prevention.

Purpose: To develop and validate a model based on data available at ICU admission to predict delirium development during a patient's complete ICU stay and to determine the predictive value of this model in relation to the time of delirium development.

Methods: Prospective cohort study in thirteen ICUs from seven countries. Multiple logistic regression analysis was used to develop the early prediction (E-PRE-DELIRIC) model on data of the first two-thirds and validated on data of the last one-third of the patients from every participating ICU.

Results: In total 2,914 patients were included. Delirium incidence was 23.6%. The E-PRE-DELIRIC model consists of nine predictors assessed at ICU admission: age, history of cognitive impairment, history of alcohol abuse, blood urea nitrogen, admission category, urgent admission, mean arterial blood pressure, use of corticosteroids, and respiratory failure. The area under the receiver operating characteristic curve (AUROC) was 0.76 (95% confidence interval (CI) 0.73-0.77) in the development data set and 0.75 (95%CI 0.71-0.79) in the validation data set. The model was well calibrated. AUROC increased from 0.70 (95%CI 0.67-0.74), for delirium that developed <2 days, to 0.81 (95%CI 0.78-0.84), for delirium that developed >6 days.

Conclusion: Patients' delirium risk for the complete ICU length of stay can be predicted at admission using the E-PRE-DELIRIC model, allowing early preventive interventions aimed to reduce incidence and severity of ICU delirium.

Introduction

Delirium is an acute organic brain dysfunction characterized by disturbances of attention and cognition with a fluctuating course, as a direct consequence of an underlying medical condition.(1) Delirium occurs frequently in Intensive Care Unit (ICU) patients,(2, 3) and is associated with poor outcome.(3-6)

Systematic delirium assessment in ICU patients is important to deliver adequate patient care by allowing clinicians to detect and treat delirium in an early stage.(7-9) Several promising interventions to prevent delirium are available that target cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment.(10-15) Although one study found no beneficial effects of haloperidol as prophylaxis and treatment for ICU delirium,(16, 17) other studies showed that prophylactic haloperidol may exert beneficial effects in critically ill patients.(18, 19)

As part of a process to improve delirium care and to further facilitate prevention of ICU delirium, identification of high risk patients is paramount,(20) since these are the most fragile patients who require maximum preventive efforts.(21) Also, when preventive measures can be restricted to high risk patients both the number of patients who will be unnecessarily exposed to potential harmful side-effects (22) and costs are likely less. Moreover, the effectiveness of prevention seems more pronounced in patients with a higher risk for delirium.(18) Finally, prediction of the ICU delirium risk provides relevant information for family members and caregivers and will facilitate stratification of patients in future delirium prevention studies. This stratification will positively influence the efficient use of research resources.

Currently, an ICU delirium prediction model is available.(23, 24) However, the usefulness of this model is limited by the fact that it requires predictors obtained during the first 24 hours of ICU admission. A relevant number of ICU patients develop delirium within 24 hours following admission,(25, 26) and preventive measures should ideally be applied as early as possible. This calls for a prediction model that can reliably predict delirium at the time of ICU admission. Therefore the objective of this multinational study was to develop and validate a model based on data available at ICU admission to predict the development of delirium during a patient's complete ICU stay and to determine the predictive value of this model in relation to the time of development of delirium.

Some results of this study have been previously presented at the ISICEM congress in Brussels, March 2014, ESICM congress in Barcelona, October 2014,(27) and the EDA congress in Cremona, November 2014.(28)

Methods

Design and Study population

A multinational prospective cohort study was carried out in thirteen ICUs from seven countries (Australia, Belgium, England, Germany, Spain, Sweden, and the Netherlands) (e-Table 1 online data supplement). Each participating ICU included all consecutive patients aged ≥18 years (surgical, medical, neurology/neurosurgical, or trauma patients) during a continuous period of approximately three months between October 2011 and June 2012. Patients were excluded if they: were delirious at ICU admission; had an ICU stay shorter than one day; were unable to reliably assess for delirium (e.g. coma during entire ICU stay; unable to understand the language spoken; severely mentally disabled; serious receptive aphasia; serious auditory or visual disorders) or if the compliance rate of the CAM-ICU for delirium screening was <80% during an individual patients' ICU stay. (Figure 1)

This study was approved by the medical ethical research committee Arnhem-Nijmegen region, the Netherlands (CMO Region Arnhem-Nijmegen, no. 2010/365) and conducted in accordance with the applicable rules concerning the review of research ethics committees and informed consent. All participating centers obtained ethics approval from their committees to conduct the study.

Data collection

Data of 18 candidate delirium predictors were collected at ICU admission in an electronic clinical report form using a secured website. Candidate predictors were selected based on the PRE-DELIRIC model,(23, 24) a systematic review about risk factors for delirium (29) and expert opinion (during the annual meeting of the working group Postoperative Delirium and Cognitive Dysfunction (PoDeCoD) of the European Society of Intensive Care Medicine (ESICM) a proposal with candidate predictors, based on the PRE-DELIRIC model and the systematic review, was presented and discussed. Candidate predictors were removed from/added to the final list based on consensus of the members of this working group). Candidate predictors available at time of ICU admission were: age, gender, history of cognitive impairment (history of dementia, mild cognitive impairment or delirium), history of alcohol-, nicotine- and drugs abuse, history of vascular disease, Glasgow Coma Scale (GCS)-score, diabetes, blood urea nitrogen (BUN), use of opiates in the 24 hours before ICU admission, use of anti-psychotics before ICU admission, admission category (surgery, medical, trauma, neurology/neurosurgery), urgent admission, mean arterial blood pressure (MAP), (strong suspicion of) infection, use of corticosteroids, respiratory failure (See e-Table 2 online data supplement for exact definitions). Data on sedation and illness severity (APACHE) were not collected, as these are not available at ICU admission.

Delirium assessment

All consecutive patients were screened for delirium by trained ICU nurses at least once every (8 or 12 hours) shift using the CAM-ICU. In accordance with previous prediction studies (23, 24) delirium was diagnosed when the CAM-ICU was positive,(7, 30) and/or when a patient was treated with haloperidol or other anti-psychotics because of delirium. (See e-Table 2) Patients were screened using the CAM-ICU as soon as delirium assessment was possible after awakening from sedation. To exclude a potential source of bias, assessors of the CAM-ICU were not made aware of the fact that they were collecting data for this study.(31)

In order to check the quality of the delirium assessments, compliance with the CAM-ICU was per participating centre calculated monthly as the percentage of assessments performed per day in relation to the total number of assessments that should have been performed. Also, inter-rater reliability (IRR) measurements of the CAM-ICU were performed by duplicate measurements of the CAM-ICU for all admitted ICU patients on one given day per month per centre, by comparing CAM-ICU scores assessed by the ICU nurse with the scores assessed by a CAM-ICU expert. CAM-ICU experts and ICU nurses were blinded to each others' delirium assessments. If per centre the CAM-ICU screening compliance was above 80% and the Cohen's kappa was above 0.80, their data were considered reliable. Centers that did not meet these criteria were per centre excluded from the analysis, after which re-analysis was performed. If exclusion of a centre did not significantly affected the performance of the E-PRE-DELIRIC model, the centre was included in the final analysis, as the data were considered to be of sufficient quality.

Sensitivity and specificity of the delirium assessments were calculated using the CAM-ICU outcomes obtained by CAM-ICU experts compared with those of the ICU nurses.(23, 24)

Outcome definition

The primary outcome of this study was the development of ICU delirium, defined as a positive assessment for delirium during a patient's complete ICU stay.

Statistical analysis

Statistical analyses, including information regarding missing values, are described in e-Supplement 1 online data supplement. The model was developed using multiple logistic regression analysis on data of the first two-thirds of the patients of all participating hospitals. Selection of the final predictors of the E-PRE-DELIRIC model took place through manual backward selection of the candidate predictors using a p-value of >0.10 for exclusion. The model was validated on data of the last one-third of the patients. Discriminative power was assessed using the area under the receiver operating characteristic curve (AUROC).(31) Calibration was assessed graphically by plotting the observed outcome frequencies against the mean predicted outcome probabilities or risks, within subgroups of

patients that were ranked by increasing estimated probability.(32) To evaluate the predictive value of the E-PRE-DELIRIC model related to the moment at which delirium first occurred, the database was divided in four groups based on the quartiles of the time to development of delirium at: day 0-1; day 2; day 3-6; >day 6.

Data were analyzed using IBM SPSS Statistics 20.01 and R statistics version R 3.0.1.(33) In this study we used the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD), a strict methodology for data reporting, to check our adherence to suggested optimal levels of transparency and completeness of reporting of a prediction model.(34)

Sample size calculation

The E-PRE-DELIRIC model was compiled from eighteen candidate predictors. For each candidate predictor at least ten patients with delirium were needed for the validation and calibration of the model.(35) With an anticipated delirium incidence of 15-30%, an expected attrition of 25%, we aimed to enroll at least (18*10/0.15)/0.75=1,600 patients.

Results

In total, 5,352 patients were screened, of whom 2,438 patients did not fulfill the inclusion criteria. (Figure 1) The cohort consisted of 2,914 patients of whom 1,962 patients were included in the development data set. The ICU delirium incidence was 24.5%. The remaining 952 patients were included in the validation data set with an ICU delirium incidence of 21.8%. The demographic characteristics of both groups were comparable. (Table 1)

Figure 1 Study flow chart

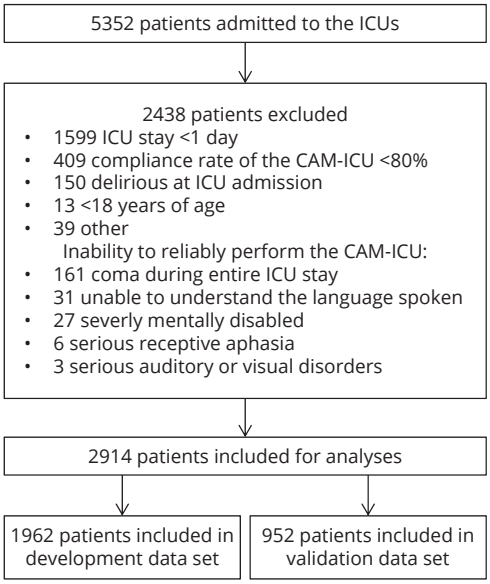


Table 1 Patient characteristics

Variable	Development data set (N=1962)	Validation data set (N=952)	Whole study population (N=2914)
Age in years Mean (Q1-Q3, min/max)	61.7 (53-74,18/95)	60.6 (51-73,18/94)	61.3 (52-73,18/95)
Male, N (%)	1166 (59.4)	550 (57.8)	1716 (58.9)
Admission category, N (%)			
Surgery	1019 (51.9)	476 (50.0)	1495 (51.3)
Medical	683 (34.8)	338 (35.5)	1021 (35.0)
Trauma	90 (4.6)	44 (4.6)	134 (4.6)
Neurology/neurosurgery	170 (8.7)	94 (9.9)	264 (9.1)
Urgent admission, N (%)	1163 (59.3)	570 (59.9)	1733 (59.5)
LOS-ICU in days Median (Q1-Q3, min/max)	2.0 (1-6,1/133)	2.0 (1-5, 1/125)	2.0 (1-5, 1/133)
Delirium, N (%)	481 (24.5)	208 (21.8)	689 (23.6)

CAM-ICU compliance and inter-rater reliability

As exclusion of the centers with a CAM-ICU screening compliance <80% and/or a Cohen's kappa < 0.80 did not significantly affect the performance of the E-PRE-DELIRIC model, all centers were subsequently included in the final analysis. The overall CAM-ICU compliance was 83% (Q1-Q3: 78-93). In total 648 inter-rater CAM-ICU measurements were performed. The mean IRR measurements were 0.83 (95% confidence interval (CI) 0.78-0.88) Cohen's kappa. (e-Table 3 online data supplement) The CAM-ICU had a sensitivity of 0.82 (95%CI 0.76-0.87) and a specificity of 0.98 (95%CI 0.96-0.99).

Discrimination and calibration of the E-PRE-DELIRIC model

The developed E-PRE-DELIRIC model consists of nine predictors: age, history of cognitive impairment, history of alcohol abuse, BUN at time of ICU admission, admission category, urgent admission, MAP at the time of ICU admission, use of corticosteroids, and respiratory failure. (Table 2) The discriminative power (AUROC) was 0.76 (95%CI 0.73-0.78) in the development data set. This database was divided in groups based on the quartiles of the predicted probabilities for delirium development: very low (0-10%), low (10-20%), moderate (20-35%), and high risk for delirium (>35%). For each of these groups the sensitivity, specificity and likelihood ratios were calculated. (Figure 2) At a cut-off of 24.5%, which was the ICU delirium incidence in the development data set, the sensitivity and specificity were 71% and 69%, respectively. The AUROC was 0.75 (95%CI 0.71-0.79) in the validation data set. See e-Figure 1 online data supplement for the calibration plot of the validation data set. Fitting the model Log(Odds)=b_0+b_1*LP on the observed data, showed that recalibration was not necessary. The slope of the model was 0.961 with an intercept of -0.094.

Prediction of early and late development of delirium

In patients who developed delirium at day 0-1 the AUROC was 0.70 (95%CI 0.67-0.74) with a sensitivity and specificity of 62% and 67%, respectively. This increased to 0.76 (95%CI 0.72-0.80) (development of delirium at day 2), 68% and 67%; 0.77 (95%CI 0.74-0.80) (development of delirium at day 3-6), 72% and 68%; and 0.81 (95%CI 0.78-0.84) (development of delirium after day 6), 78% and 68%, respectively. The predictive value of the model improved significantly over time. (Figure 3)

Table 2 Variables of the E-PRE-DELIRIC model and regression coefficients and formula for the E-PRE-DELIRIC model*

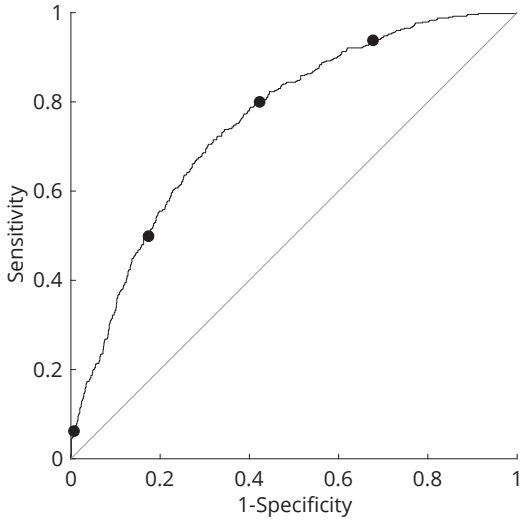
Variable	Regression coefficient	Odds ratio (95% C.I.)
age	0.025	1.025 (1.017-1.033)
history of cognitive impairment	0.878	2.406 (1.700-3.404)
history of alcohol abuse	0.505	1.657 (1.170-2.347)
admission category:		
surgery	RC	RC
medical	0.370	1.448 (1.058-1.982)
trauma	1.219	3.384 (1.997-5.735)
neurology/neurosurgery	0.504	1.655 (1.064-2.575)
urgent admission	0.612	1.843 (1.326-2.563)
MAP at the time of ICU admission	-0.006	0.994 (0.988-1.001)
use of corticosteroids	0.283	1.327 (0.996-1.768)
respiratory failure	0.982	2.670 (2.099-3.396)
BUN at time of ICU admission	0.018	1.018 (1.006-1.031)

RC = reverence category
*Data development set

Formula for the E-PRE-DELIRIC model

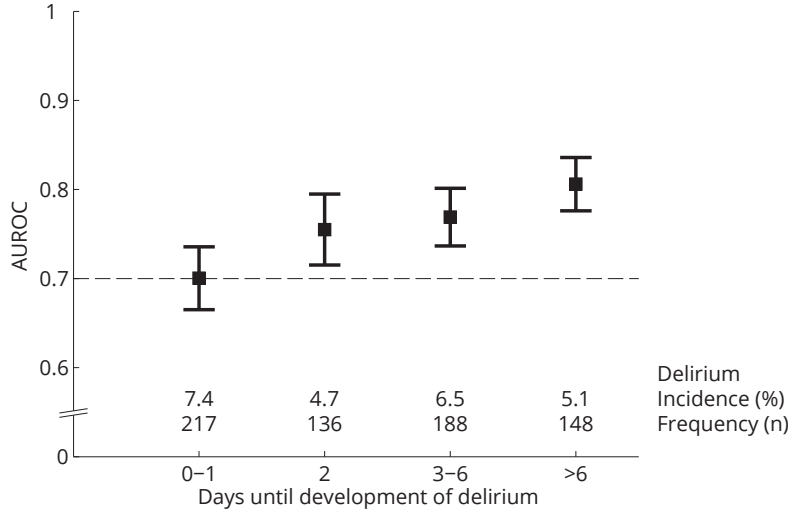
Risk of delirium =1/(1+ exp-(-3.907
+ 0.025 x age
+ 0.878 for history of cognitive impairment
+ 0.505 for history of alcohol abuse
+ 0 for surgery or 0.370 for medical or 1.219 for trauma or 0.504 for neurology/neurosurgery
+ 0.612 for urgent admission
- 0.006 x MAP at the time of ICU admission
+ 0.283 for use of corticosteroids
+ 0.982 for respiratory failure
+ 0.018 x BUN in mmol/l at time of ICU admission))

Figure 2 Area under the receiver operating characteristic curve (AUROC) of development data set (AUROC=0.76)



Cut-off	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio
10%	94	32	1.4	0.2
20%	80	58	1.9	0.4
35%	50	83	2.9	0.6
67.5%	6	99	8.9	0.9

Figure 3 Area under the receiver operating characteristic curve (AUROC) during ICU stay



Error bars show 95%CIs

Discussion

In this prospective, international multicenter study we developed and validated a model allowing early prediction of patients likely to develop delirium during ICU admission. Using nine predictors that are readily available at ICU admission, it is now possible to stratify ICU patients for delirium risk for the complete ICU length of stay with a high discriminative power. In contrast to the earlier prediction model,(23, 24) which reliably predicts delirium using data available only after 24 hours in the ICU, our E-PRE-DELIRIC model has a moderate-to-good performance using data available immediately at ICU admission. Of interest, the predictive accuracy of the model is higher for delirium that develops later compared to delirium that develops early following ICU admission.

In view of the high prevalence of delirium in ICU patients (2, 3) and its serious consequences,(3-6) prediction of ICU delirium is clearly of clinical relevance as early risk identification may serve different purposes. Both caregivers and patients' families can be informed early about the risk of developing delirium in the ICU and this may for example assist them in taking decisions related to the use of preventive measures. In addition, the model enables stratification for the risk to develop delirium, which may be helpful in future trials that aim to investigate preventive interventions. Our group previously reported the effects of prevention with low dose haloperidol in critically ill patients using a prediction model and demonstrated that patients with the highest risk appear to benefit most from prevention.(18) With the E-PRE-DELIRIC model, stratification is possible immediately after ICU admission. Various other preventive measures that target modifiable delirium risk factors have been found beneficial in non-critically ill patients (8, 10, 11) and need confirmation in ICU patients. In these confirmation trials, stratification of the a-priori risk to develop delirium should be determined to demonstrate that treatment groups are adequately randomized. As a consequence, possible interventions that may be expensive and/or labor-intensive can then be provided only to those patients with highest risk. In this way improved quality and efficiency of care may be achieved in a cost-effective manner.(36)

The predictors that build the E-PRE-DELIRIC-model are largely consistent with previously reported risk factors for delirium, including age, pre-existing dementia, history of alcoholism, and a high severity of illness at admission.(8, 37, 38) Other factors that confirm previously reported predictors include admission category, urgent admission, BUN,(23, 24) and respiratory failure.(37-39) While use of corticosteroids was not reported as a relevant factor in another study,(2) in our study use of corticosteroids was a significant predictor for delirium. In our study we only collected data about corticosteroids use at ICU admission, in contrast, Ouimet et al. (2007) collected daily data about corticosteroids use during the whole study period. Of importance, as relevant differences between countries may exist, the current study was a multinational study using data of ICUs from different countries for the development of a delirium prediction model which increases its generalizability.

Interestingly, while the delirium incidence remains stable over time in the four groups in this study, the predictive value of the model increases over time. However, examining differences between early and late delirium did not fall within the scope of this study, and therefore should be studied in future research.

Several limitations of this study need to be addressed. First, despite the fact that availability of candidate predictors at ICU admission and the effort it would take to collect the data in daily clinical practice were leading in determining candidate predictors, three of the predictors from the E-PRE-DELIRIC model (BUN, history of alcohol abuse, and cognitive impairment) had a fairly high rate of missing values. Probably due to unawareness of the importance of these predictors for delirium prediction, currently these predictors are not collected in a standardized manner in daily practice. When health professionals need the information about these predictors to be able to use the E-PRE-DELIRIC model they will (most often) be able to collect the information as they are readily available. We used imputation techniques to handle missing data. Multiple imputation helps to reduce bias and increases precision by including variation of data.(31) Second, the performance of the CAM-ICU in daily practice is not optimal.(40-42) However, in contrast to the evaluation study of Van Eijk at all,(40) in the current study ICU patients were screened for delirium at least two times daily and during the whole ICU length of stay. This increases the chance of correct delirium scores, because of the fluctuating course of delirium. The scores were determined in the same way in all participating ICUs, positively influencing possible measurement bias. In addition, data on the use of haloperidol and other anti-psychotics for delirium were used.(23) This usage was consistent among the different centers. Therefore, we may assume that sensitivity of the bedside nurse to recognize delirium anywhere during ICU admission is high. Quality of data of the CAM-ICU screening was further improved by determination of compliance and inter-rater reliability in each ICU. Third, although the full model approach to include all 18 candidate predictors in the predictive model is likely to avoid overfitting and selection data,(43) we chose to perform manual backward selection of predictors to improve the clinical feasibility. Fourth, based on the predetermined exclusion criteria a large number of patients had to be excluded. One of these exclusion criteria was an ICU stay shorter than one day. Since the E-PRE-DELIRIC model will be used prospectively following ICU admission one may not be able to anticipate a patient's ICU length of stay (LOS). Therefore for each patient admitted to the ICU the E-PRE-DELIRIC score will be calculated. Predictions for patients with an ICU LOS shorter than one day might be different than those for patients with an ICU LOS longer than one day. Therefore in future research it is recommended to include these patients to determine the influence on the performance of the E-PRE-DELIRIC model. Finally, it should be taken into account that selection of candidate predictors in the E-PRE-DELIRIC model might be biased. However, the candidate predictors were based on multiple scientific sources, including the previously published PRE-DELIRIC model,(23, 24) a systematic

review about delirium risk factors (29) and expert opinion. Although external validation of the E-PRE-DELIRIC model in new centers was not performed, this prediction model was internationally developed and prospectively validated in thirteen ICUs from seven different countries. The E-PRE-DELIRIC model is a result of a relevant sample from these ICUs, and therefore widely applicable and probably generalizable to other countries. ICUs should consider, however, that the prediction of delirium derived from the E-PRE-DELIRIC model is an approximation; there can always be some over- or underestimation in the predicted delirium risk. Therefore for future research it is recommended to test the external validity of the E-PRE-DELIRIC model in other centers to further improve its generalizability.

In conclusion, in this multinational study we developed and validated an early ICU delirium prediction model that revealed sufficient validity. It enables the clinician to identify those patients likely to develop delirium following ICU admission using only nine predictors. The model allows early delirium preventive interventions in ICU patients with a high risk of delirium.

An automatic version of the E-PRE-DELIRIC model (Excel and web based) will soon be available at https://www.radboudumc.nl/Research/Organisationofresearch/Departments/intensive%20care/Pages/vandenBoogaard.aspx (In multiple languages available). Furthermore the E-PRE-DELIRIC model will soon be integrated in the DeliriumICU app which makes it possible to use it bedside (http://itunes.apple.com/us/app/deliriumicu/id511306390 and https://play.google.com/store/apps/details?id=dotsdigits.deliriumicu)

Acknowledgments

The authors would like to thank all co-investigators, their research nurses, and their intensive care teams at each of the participating sites for their help in collecting the patient data.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interest.

Funding

There was no external funding for this study.

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Online data supplement

e-Table 1 Characteristics of participating hospitals

	Population	Number of beds for adults (annual admissions)
The Netherlands_Nijmegen[U]	Medicine, surgery, neurocritical care, and cardiothoracic surgery	33 beds (2000-2500)
The Netherlands_Utrecht[U]	Medicine, surgery, neurocritical care, and cardiothoracic surgery	32 beds (2000-2500)
The Netherlands_Leeuwarden*	Medicine, surgery, and cardiothoracic surgery	20 beds (1400-1500)
The Netherlands_Zwolle*	Medicine, surgery, neurocritical care, and cardiothoracic surgery	36 beds (2500-300)
The Netherlands_Den Bosch*	Medicine, surgery, and trauma	16 beds (750-850)
Belgium_Antwerp[U]	Medicine, surgery, neurocritical care, and cardiothoracic surgery	45 beds (2600-2800)
Germany_Berlin[U]	Medicine, surgery, trauma	35 beds (4000-4500)
Spain_Madrid[U]	Medicine, surgery, and neurocritical care	16 beds (1300-1500)
Sweden_Stockholm[U]	Medicine, surgery and trauma	13 beds (1000)
Australia_Brisbane*	Medicine, surgery, neurocritical care, cardiothoracic surgery, and trauma	25 beds (2000)
Australia_Canberra*	Medicine, surgery, neurocritical care, and cardiothoracic surgery	31 beds (1800-2000)
UK_Prescot*	Medicine, surgery	15 beds (800-850)
UK_Kent*	Medicine and surgery	9 beds (700-900)

[U]University hospital
*University affiliated teaching hospital

e-Table 2 Collected potential predictors of delirium immediately after ICU admission and outcome definition

Predictor	Explanation	Category
age	in years at time of admission	C
gender	male/female	D
history of cognitive impairment	known medical history of dementia, mild cognitive impairment or delirium	D
history of nicotine abuse	known medical history of nicotine abuse	D
history of drug abuse	known medical history of drug abuse	D
history of alcohol abuse	known medical history of alcohol abuse	D
history of vascular disease	brain (TIA/CVA), cardiac or other vascular disease	D
Glasgow Coma Scale (GCS)-score	at time of ICU admission according to APACHE II definition	C
diabetes	diabetes mellitus	D
blood urea nitrogen (BUN) at time of ICU admission	in mmol/l	C
use of opiates in the 24 hours before ICU admission	oral/iv/patches	Cat.
use of anti-psychotics before ICU admission	anti-psychotics other than for delirium	D
admission category	surgical, medical, trauma, neurology/ neurosurgical (trauma including brain damage was neurology)	Cat.
urgent admission	unplanned intensive care admission	D
mean arterial blood pressure (MAP)	at the time of ICU admission in mmHg	C
(strong suspicion of) infection	proven or strong suspicion of infection for which antibiotics were started	D
use of corticosteroids	oral/iv, used until time of ICU admission	D
respiratory failure	non-elective mechanically ventilation or non-invasive ventilation is necessary or expected <24hr	D

e-Table 2 Continued

Outcome	Explanation
delirium	delirium was diagnosed when the CAM-ICU was positive, and/or when a patient was treated with haloperidol or other anti-psychotics because of delirium. Treatment with anti-psychotics was considered indicative for delirium in patients without previous anti-psychotic medications, as in all participating centers haloperidol was only used to treat delirium. For example, if a patient who screened negative for delirium with the CAM-ICU was suddenly heavily agitated and therefore successfully treated with haloperidol, the next CAM-ICU would again be negative; in these cases the patient was considered positive for delirium

C = continuous
D = dichotomous
Cat. = categorical

e-Supplement 1 Methods Statistical analysis

Statistical analysis was pre-planned in collaboration with a statistician (RD). To determine if missing data were lacking systematically or at random, missing value analysis was performed. According to the IBM SPSS manual for missing values,(1) a significance value of the Little's MCAR test <0.05 indicates the data are not missing completely at random. Overall, candidate predictors with missing values at random were: GCS-score (1.5%), diabetes (6.4%), infection (6.3%), use of opiates (0.2%), BUN (10.5%), history of alcohol-, nicotine- and drugs abuse (19.7%), vascular diseases (5.1%), cognitive impairment (14.6%), use of anti-psychotics (6.6%). The missing values were imputed using two methods. First, imputation based on clinical judgment was used: where the GCS-score was missing, a normal score of 15 was assumed and imputed; where diabetes, infection and use of opiates were missing there was no reason to assume the value was abnormal and they were therefore imputed as normal or absence of disease; where BUN was missing there was no reason to assume the value was abnormal, and therefore the mean BUN value for that group, i.e. with or without delirium, was imputed.(2) Further, we performed multiple imputation using fully conditional specification implemented by Multivariate Imputation by Chained Equations algorithm (package mice: 40 imputation sets were created using the default imputation methods)(3) for the candidate predictors: history of alcohol-, nicotine and drugs abuse, vascular diseases, cognitive impairment, and use of anti-psychotics, because it was not possible to assume these values were (ab)normal when missing. As we wanted to develop a generally applicable model, a fixed centre effect was assumed. In addition, centre was included as a variable during multiple imputation.

The model was developed using multiple logistic regression analysis on data of the first two-thirds of the patients of all participating hospitals. Selection of the final predictors of the E-PRE-DELIRIC model took place through manual backward selection of the candidate predictors using a p-value of >0.10 for exclusion. The model was validated on data of the last one-third part of the patients, without multiple imputations. This so-called temporal validation, is a prospective evaluation of the model, external in time and independent of the development data set.(4) The validation was performed using the regression coefficients of the included predictors.

Discriminative power was assessed using the area under the receiver operating characteristic curve (AUROC).(5) Calibration was assessed graphically by plotting the observed outcome frequencies against the mean predicted outcome probabilities or risks, within subgroups of patients that were ranked by increasing estimated probability.(6) Also, a model was fit on the observed data in which the linear predictor (LP) was put in together with the intercept: $\text{Log(Odds)}=b_0+b_1*\text{LP}$.

To evaluate the predictive value of the E-PRE-DELIRIC model related to the moment at which delirium first occurred, the database was divided in four groups based on the quartiles of the time until the development of delirium at: day 0-1; day 2; day 3-6; >day 6. For each of these groups the AUROC, sensitivity and specificity, and delirium incidence were calculated.

Sample size calculation

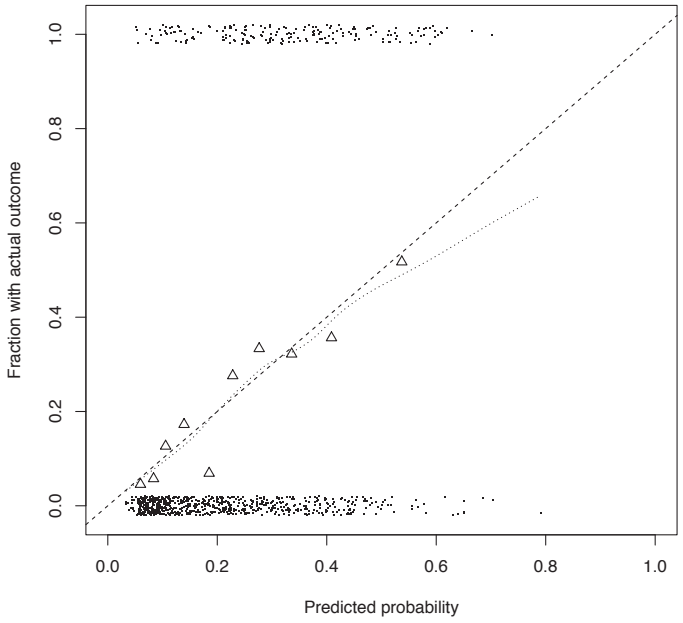
The E-PRE-DELIRIC model was compiled from eighteen candidate predictors. For each candidate predictor at least ten patients with delirium were needed for the validation and calibration of the model.(7) With an anticipated delirium incidence of 15-30%, an expected attrition of 25%, we aimed to enroll at least (18*10/0.15)/0.75=1,600 patients.

e-Table 3 CAM-ICU compliance and inter rater-reliability measurements

	CAM-ICU compliance (mean and SD in %)	Inter-rater reliability (mean Cohen's kappa)
The Netherlands_Nijmegen	81.7±1.5	0.81
The Netherlands_Utrecht	92.7±2.1	0.58
The Netherlands_Leeuwarden	92.1±5.2	0.88
The Netherlands_Zwolle	54.0±3.6	*
The Netherlands_Den Bosch	95.3±4.1	1.00
Belgium_Antwerp	78.0±7.0	#
Germany_Berlin	84.4±22.4	0.87
Spain_Madrid	92.5±8.7	0.89
Sweden_Stockholm	88.3±10.7	0.87
Australia_Brisbane	78.3±19.3	0.29
Australia_Canberra	100	^
UK_Prescot	60.8±1.0	0.79
UK_Kent	87.0±6.3	0.87

*Impossible to determine, due to the fact that the ICU nurses scored all patients negative for delirium, the experts scored one patient positive for delirium
#Not available
^In this center all CAM-ICU were assessed by two CAM-ICU experts, making this not applicable

e-Figure 1 Calibration plot validation data set



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for web-only publication

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CHAPTER 3

External validation of two models to predict delirium in critically ill adults

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Submitted for publication. 2017

Abstract

Objectives: To externally validate the E-PRE-DELIRIC model and the recalibrated PRE-DELIRIC model to predict delirium in critically ill patients.

Design: Multinational prospective cohort study.

Setting: Eleven ICUs from seven countries from the United States, Canada, Australia, and Europe.

Patients: Adults consecutively admitted to the ICU for ≥6 hours without delirium in whom delirium could be assessed reliably.

Interventions: None.

Measurements and Main Results: Predictors of each model were collected; for E-PRE-DELIRIC at the time of ICU admission, for PRE-DELIRIC within 24 hours of ICU admission. Delirium was assessed using the Confusion Assessment Method-ICU or Intensive Care Delirium Screening Checklist. Discrimination of both models was determined using the area under the receiver operating characteristic curve (AUROC) and compared with the original. Calibration was assessed graphically. A total of 2,178 patients were included. Delirium incidence was 21.4%. The AUROC of the E-PRE-DELIRIC model was 0.68 (95%CI 0.66-0.71) compared to the previously reported AUROC of 0.75 (95%CI 0.71-0.79). The AUROC of the recalibrated PRE-DELIRIC model was 0.74 (95%CI 0.71-0.76) compared to 0.77 (95%CI 0.74-0.79), respectively. Both models were well calibrated.

Conclusions: Using a large, heterogeneous, multinational cohort of critically ill adults we showed that both the E-PRE-DELIRIC and PRE-DELIRIC statistically perform moderate-to-good, which allows for generalization to ICUs around the world.

Introduction

Clinical prediction models are increasingly being developed and used to predict the occurrence of clinical events and outcomes both during and after Intensive Care Unit (ICU) stay.(1, 2) Delirium is common in the ICU, sometimes preventable, and is poorly predicted by ICU clinicians,(3, 4) warranting the use of a delirium prediction model in the ICU. Two ICU delirium prediction models are currently available to predict patients' risk to develop delirium over the duration of their ICU stay.(4-6) The recalibrated PRE-DELIRIC model incorporates 10 predictors available within the first 24 hours after ICU admission.(5) The E-PRE-DELIRIC model includes nine predictors available at the time of ICU admission.(6)

Before any ICU prediction model can be used outside the developmental setting, it is essential to confirm its predictive performance in a new cohort of patients, independent from the dataset used during development and initial validation, and to determine its generalizability among critically ill adults who may have different risk factors for an event, across different ICUs from different countries where clinical practices and health care systems may vary.(7) The study aim was to externally validate the E-PRE-DELIRIC model and the recalibrated PRE-DELIRIC model to predict delirium in ICU patients.

Methods

This multinational prospective cohort study was conducted as part of the The *DE*lirium predi*CT*/on in the inten*SI*ve care unit: comparis*ON* of two delirium prediction models (DECISION) study, in eleven ICUs from Australia, Belgium, Canada, Denmark, Portugal, the Netherlands, and the United States. Between September 2015 and June 2016, adult ICU patients were consecutively included and evaluated for up to three months (or until 300 patients were enrolled at a particular hospital). Patients with delirium at ICU admission, a barrier to reliable delirium assessment or an expected ICU stay <6 hours were excluded. The Medical research ethics committee (MREC) Arnhem-Nijmegen region, The Netherlands (no. 2015-1782) and the local MRECs of the participating ICUs approved the study and waived the need for informed consent.

Data for the E-PRE-DELIRIC model were collected immediately after ICU admission,(6) data for the PRE-DELIRIC model within 24 hours of ICU admission.(4, 5) See online data supplement e-Appendix 1&2 for the models' predictors and corresponding definitions.

Data were collected for each ICU day up to 14 days after ICU admission. Delirium was defined as at least one positive delirium assessment using either the Confusion Assessment Method-ICU (CAM-ICU) or Intensive Care Delirium Screening Checklist (ICDSC) and/or when a patient received anti-psychotic medication for delirium treatment. Each patient was screened for delirium by a trained nurse at least once every 12 hours. To exclude potential bias, the nurses were not informed about this study. Level of sedation was assessed using the Richmond Agitation-Sedation Scale (RASS) or Riker Sedation-Agitation Scale (SAS) prior to delirium assessment.

For each prediction model at least 200 events, i.e. positive delirium assessments, were needed. With an anticipated delirium incidence of 20%, we aimed to enroll: (400/0.20)=2000 patients.

Complete-case analysis was performed. No imputation techniques were used to handle missing data. To minimize missing values, we provided clear definitions and instruction manuals for data collection.(4-6) The original models with their predictors and assigned linear predictor weights were applied in this study.(5, 6) Subsequently the predictor and delirium outcome values were used to quantify the predictive performance of both models. Discriminative power was assessed using the area under the receiver operating characteristic curve (AUROC). Calibration was assessed graphically.(7) Differences from the development data in setting, outcome and predictors were identified. We used the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) for data reporting.(8)

Results

From 2,802 patients screened, 2,178 were included for analysis. In the 624 patients excluded, a barrier to reliable delirium assessment (46.3%) and delirium at the time of ICU admission (25.9%) were the most frequent reasons for exclusion. A total of 14 patients (2.2%) were excluded because of missing model data. No patients were excluded due to missing data on delirium diagnosis.

Patients' mean (standard deviation (SD)) age was 62.1 (15.2) years and their APACHE-II score 17.4 (7.1). A total of 467 (21.4%) patients developed delirium. For patient characteristics see Table 1. The AUROC of the E-PRE-DELIRIC model was 0.68 (95%CI 0.66-0.71), compared to the previously reported AUROC of 0.75 (95%CI 0.71-0.79).(6) The AUROC of the recalibrated PRE-DELIRIC model was 0.74 (95%CI 0.71-0.76) compared to the previously reported 0.77 (95%CI 0.74-0.79),(5) respectively. (Online data supplement e-Figure 1) Both models were well calibrated. (Figure 1)

Figure 1 Calibration plot of E-PRE-DELIRIC and PRE-DELIRIC

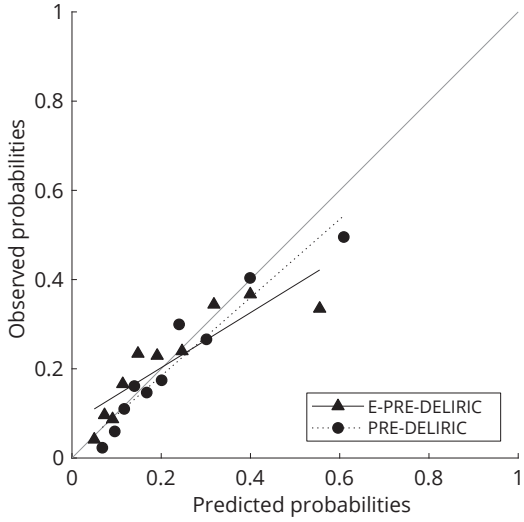

Table 1 Patient characteristics of both the present and original studies according to TRIPOD criteria

Variable	External validation cohort (N=2178)	Recalibration PRE-DELIRIC cohort (5) (N=1824)	Original E-PRE-DELIRIC cohort (6) (N=2914)
Male, N (%)	1324 (60.8)	N.A.	1716 (58.9)
Age in years, Mean (SD)	62.1 (15.2)	60 (17)	61.3 (16.1)
History of cognitive impairment, N (%)	53 (2.4)	N.A.	437 (15.0)
History of alcohol abuse, N (%)	146 (6.7)	N.A.	524 (18.0)
Admission category, N (%)			
Surgery	1079 (49.5)	869 (48)	1495 (51.3)
Medical	856 (39.3)	654 (36)	1021 (35.0)
Trauma	86 (3.9)	99 (5)	134 (4.6)
Neurology/neurosurgery	157 (7.2)	202 (11)	264 (9.1)
Urgent admission, N (%)	1345 (61.8)	1147 (63)	1733 (59.5)
Mean arterial blood pressure, Mean (SD)	80 (18.5)	N.A.	82.4 (18.8)
Use of corticosteroids, N (%)	453 (20.8)	N.A.	465 (16.0)
Respiratory failure, N (%)	796 (36.5)	N.A.	1270 (43.6)
BUN at ICU admission (mmol/L) Median (Q1-Q3, min/max)	7.9 (5-13, 1/277)	N.A.	7.5 (5-12, 0/95)
APACHE-II score, Mean (SD)	17.4 (7.1)	19 (9)	N.A.
No coma, N (%)	1792 (82.2)	1405 (77)	N.A.
Coma:			
1. With use of medication, N (%)	237 (10.9)	295 (16)	
2. Other (i.e. intra cerebral bleeding, post-resuscitation), N (%)	21 (1.0)	21 (1)	
3. Combination (1+2), N (%)	128 (5.9)	103 (6)	
Infection, N (%)	681 (31.3)	516 (35)	N.A.
Metabolic acidosis, N (%)	782 (35.9)	525 (29)	N.A.
No morphine use, N (%)	1571 (72.2)	1333 (77)	N.A.
Cumulative use of morphine:			
1. 0.01-7.1mg/day	210 (9.6)	77 (6)	
2. 7.2-18.6mg/day	274 (12.6)	115 (8)	
3. 18.7mg or more/day	122 (5.6)	135 (9)	
Sedative use, N (%)	882 (40.5)	774 (42)	N.A.
BUN (mmol/L), Mean (SD) Median (Q1-Q3, min/max)	8.0 (56-14, 0.6/287)	11.2 (8.2)	N.A.
Delirium, N (%)	467 (21.4)	410 (22.5)	689 (23.6)
LOS-ICU in days, Median (Q1-Q3, min/max)	3.0 (2-6, 1/96)	N.A.	2.0 1-5, 1/133)

N.A. = Not Available in the original studies (5, 6)

Discussion

Given that most prediction models show an optimistic performance in their development sample, the use of a prediction model in daily clinical practice should be preceded by external validation.(7, 9) In the present large multinational study we externally validated two ICU delirium prediction models, the E-PRE-DELIRIC model and PRE-DELIRIC models, showing that both have a moderate-to-good statistical performance in a new and independent sample of ICU patients. Consistent with the results from other primary external validation studies,(9) the discrimination of both models was lower in the present study than in the original studies.(4-6) However, despite this somewhat lower predictive value, the models still provide a more accurate risk score compared to prediction by clinicians.(4)

The lower statistical performance observed is not surprising. First, a difference in case-mix between the development and external validation sample may have affected the models' discriminative performance. The difference in case-mix is indicated by a difference in delirium incidence, which was lower in the current study compared to development samples, as well as by the distribution of the predictor values. For example, history of cognitive impairment and alcohol abuse and respiratory failure, predictors of the E-PRE-DELIRIC model, had a lower incidence in the current cohort. Second, different predictor effects might have influenced the models' performance due to overfitting of the regression coefficients of their formula in the development sample, which is probably less present in PRE-DELIRIC due to the fact that this model was recalibrated previously using an external sample.(5) Also, changes over time may have influenced the models' performance; since data collection in 2008-2009 for de PRE-DELIRIC and 2011-2012 for the E-PRE-DELIRIC models, daily clinical practice in the ICU has changed. For example, due to the implementation of the ABCDEF-bundle, that has been shown to positively affect delirium outcome.(10) As a result, in the current study sedative exposure was less and the frequency of medication associated coma and morphine administration was lower. Still, despite these differences, both ICU delirium prediction models showed a well calibration in the current study with plots that were comparable to those in the original studies.

An important strength of this study is its multinational design and the fact that patients were evaluated with one of two different recommended delirium screening tools. The majority of the participating ICUs in this study, nine out of eleven, were different from those of the recalibration study of PRE-DELIRIC and six out of eleven ICUs were different compared to those of the development study of E-PRE-DELIRIC. This resulted in an independent dataset and improves the generalizability. To prevent bias due to an overrepresentation of one of the participating ICUs in the dataset, each ICU included patients for three consecutive months with a maximum of 300 patients per ICU. Naturally, also limitations of the current study are present. One might argue that adjusting the ICU delirium prediction models to a specific center to account for differences in ICUs may improve both

models' performance. However, this would obviously limit the generalizability. Therefore, we prefer a general prediction model that can be widely used rather than an ICU specific model.

In conclusion, this study shows that both available ICU delirium prediction models have moderate-to-good statistical performance in a new and independent sample of ICU patients, which allows for generalization to other ICUs in the world. Future research should focus on the improvement of ICU delirium prediction.

Acknowledgments

The authors would like to thank all involved research nurses and the intensive care teams of each of the participating sites for their help in collecting the patient data.

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Online data supplement

e-Appendix 1 Collected delirium predictors immediately after ICU admission (E-PRE-DELIRIC)*

Predictor	Explanation	Category
Age *(years)*	In years at time of admission	C
History of cognitive impairment	Known medical history of dementia, mild cognitive impairment or delirium *(normal value = no history of cognitive impairment)*	D
History of alcohol abuse	Known medical history of alcohol abuse *(normal value = no history of alcohol abuse)*	D
Admission category	1. Surgical 2. Medical 3. Trauma 4. Neurology/neurosurgical	Cat
Urgent admission	Unplanned intensive care admission *(normal value = no urgent admission)*	D
Mean arterial blood pressure *(MAP in mmHg)*	At the time of ICU admission	C
Use of corticosteroids	Oral/iv, the corticosteroids should be used until time of ICU admission *(normal value = no use of corticosteroids)*	D
Respiratory failure	Non-elective mechanical ventilation or non-invasive ventilation is necessary or expected <24hr after ICU admission *(normal value = no respiratory failure)*	D
Blood urea nitrogen (BUN) *(mmol/L)*	BUN value at time of ICU admission or max 12 hours before ICU admission *(normal value at admission = 8 mmol/l)*	C

C = continuous
D = dichotomous
Cat. = categorical

*IMPORTANT NOTE: When no data is available about the predictors for the E-PRE-DELIRIC model (after asking the patient, the patient's family or general practitioner, or by assessment of the patient's medical record), there is no reason to assume the value is abnormal and therefore the predictor can be filled out as normal/absence of disease. [see *italic font* in the Table]. Age, admission category and MAP = no normal value available (these values are always available, therefore no missing values are expected).

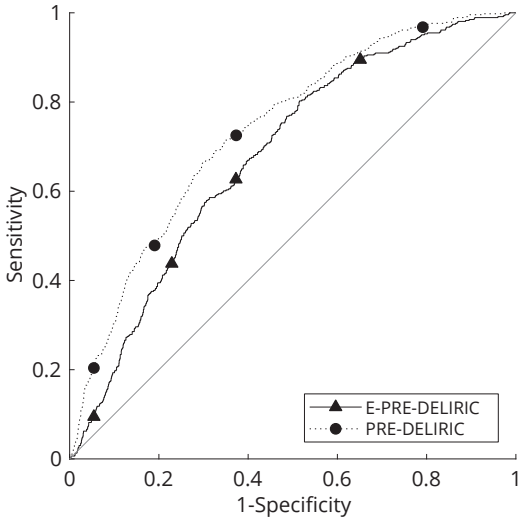
e-Appendix 2 Collected delirium predictors within 24 hours after ICU admission (PRE-DELIRIC)*

Predictor	Explanation	Category
Age *(years)*	In years at time of admission	C
APACHE-II score *(per point)*	Calculated 24 hours after ICU admission *(no normal value available (when APACHE-II is missing this patient will be excluded from analyses))*	C
Coma	No coma: RASS -4/-5 maximum 8 hours RASS -4/-5 for longer than 8 hours: OR No coma: Riker SAS 1/2 maximum 8 hours Riker SAS 1/2 for longer than 8 hours: 1. With use of medication 2. Other (i.e. intra cerebral bleeding, post-resuscitation) 3. Combination (1+2) *(normal value = no coma)*	Cat
Admission category	1. Surgical 2. Medical 3. Trauma 4. Neurology/neurosurgical	Cat
Infection	Proven or strong suspicion of infection for which antibiotics were started *(normal value = no infection)*	D
Metabolic acidosis	pH <7.35 with bicarbonate <24mmol/L *(normal value = no metabolic acidosis)*	D
Morphine use	No morphine: no use of any morphine Cumulative use of any form of morphine: 4. 0.01-7.1mg/day 5. 7.2-18.6mg/day 6. 18.7mg or more/day *NOTE: This only concerns morphine, no other opiates. (Do **not** use any converting formulas to calculate the morphine dose of other opiates).* *(normal value = no use of morphine)*	Cat
Sedative use	Any iv use of propofol, midazolam, lorazepam or combination *(normal value = no use of sedatives)*	D
Urgent admission	Unplanned intensive care admission	D
Blood urea nitrogen (BUN) *(mmol/L)*	Highest BUN the first 24 hours after ICU admission or max 12 hours before ICU admission *(normal value the first 24 hours after ICU admission or max 12 hours before ICU admission = 8 mmol/l)*	C

C = continuous
D = dichotomous
Cat. = categorical

*IMPORTANT NOTE: When no data is available about the predictors for the PRE-DELIRIC model (after asking the patient, the patient's family or general practitioner, or by assessment of the patient's medical record), there is no reason to assume the value is abnormal and therefore the predictor can be filled out as normal/absence of disease. [see *italic font* in the Table].
Age and admission category = no normal value available (these values are always available, therefore no missing values are expected).

e-Figure 1 Discriminative performance of E-PRE-DELIRIC and PRE-DELIRIC



CHAPTER 4

Delirium prediction in the intensive care unit: Comparison of two delirium prediction models

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Submitted for publication. 2017

Abstract

Background: Accurate prediction of intensive care unit (ICU) delirium may facilitate efficient use of early preventive strategies as well as stratification of ICU patients by delirium risk in clinical research, but the optimal delirium prediction model to use is unclear. We compared the predictive performance and user convenience of the PRE-DELIRIC and E-PRE-DELIRIC models and determined the value of a two-stage calculation.

Methods: This seven-country, 11 hospitals, prospective cohort study evaluated consecutive adults admitted to the ICU who could be reliably assessed for delirium with the Confusion Assessment Method-ICU or the Intensive Care Delirium Screening Checklist. The models' predictive performance was measured using the Area under the Receiver Operating Characteristic curve. Calibration was assessed graphically. A physician questionnaire evaluated user convenience. For the two-stage calculation we used E-PRE-DELIRIC immediately after ICU admission and updated the prediction using PRE-DELIRIC after 24 hours.

Results: In total 2,178 patients were included. The Area under the Receiver Operating Characteristic curve was significantly greater for PRE-DELIRIC [0.74 (95% confidence interval 0.71-0.76)] compared to E-PRE-DELIRIC [0.68 (95% confidence interval 0.66-0.71)] [Z-score of -2.73 ($p<0.01$)]. Both models were well calibrated. The sensitivity improved when using the two-stage calculation in low-risk patients. Compared to PRE-DELIRIC, ICU physicians (n=68) rated the E-PRE-DELIRIC model more feasible.

Conclusions: While both ICU delirium prediction models perform moderate-to-good, the PRE-DELIRIC model predicts delirium better. However, ICU physicians rated the user convenience of E-PRE-DELIRIC superior to PRE-DELIRIC. In low-risk patients the delirium prediction further improves after an update with the PRE-DELIRIC model after 24 hours.

Trial registration: ClinicalTrials.gov no. NCT02518646.

Introduction

Delirium, defined as an acute brain dysfunction featured by disturbances of attention, awareness and cognition with a fluctuating course caused by an underlying medical condition,(1) occurs frequently in the intensive care unit (ICU), is associated with impaired patient outcome, and substantially increases healthcare costs.(2, 3) Given these deleterious consequences, delirium prevention is crucial.

Delirium-prevention efforts should generally be focused on those critically ill patients at greatest risk for delirium,(4) given that nonpharmacologic reduction strategies require substantial health professional time and some medication-based strategies have high acquisition costs and may lead to unwanted side effects. Also, the use of a delirium prediction model facilitates patient selection for studies on delirium prevention, and family members can be informed and engaged to help provide strategies to reduce delirium (e.g. cognitive activities) if it is known that their loved one is at higher risk for developing delirium.(5)

Two delirium prediction models have been validated for use in critically ill adults admitted to the ICU.(6-8) The PRE-DELIRIC model was developed and validated in a large cohort of Dutch ICU patients.(6) This model, which was recently recalibrated in a multinational cohort,(7) reliably predicts ICU patients' risk for delirium using ten predictors obtained within the first 24 hours of ICU admission.(7) However, given that up to 25% of critically ill adults develop delirium within the first 24 hours of ICU admission,(9, 10) and delirium prevention strategies should be deployed as early as possible, an early prediction model (E-PRE-DELIRIC) was developed to predict the risk for delirium the moment a patient is admitted to the ICU.(8) This E-PRE-DELIRIC model was developed and validated in a multinational cohort and uses nine predictors to predict ICU patients' risk for delirium.(8)

It remains unclear which ICU delirium prediction model might be recommended for daily clinical practice, because both the comparative predictive performance of the PRE-DELIRIC and E-PRE-DELIRIC models and clinicians' preferences have not been assessed.(11) Therefore, the objective of this study was to compare the predictive performance and user convenience of the PRE-DELIRIC and E-PRE-DELRIC models. Second, we sought to determine the value of the use of both models in a two-stage calculation of patients' risk for ICU delirium (i.e. the E-PRE-DELIRIC model immediately after ICU admission with an updated delirium risk score after 24 hours of ICU admission using the PRE-DELIRIC model) to see if we could expand on current models, since it is well known that dynamic variables over time as opposed to variables at admission only tend to perform better in prediction models.

Methods

Design and Study population

The *DE*lirium predi*CT*/on in the inten*SI*ve care unit: comparis*ON* of two delirium prediction models (DECISION) study was a multinational prospective cohort study conducted in 11 ICUs from seven different countries (Australia, Belgium, Canada, Denmark, Portugal, United States, and the Netherlands). Each study site had a well-established delirium screening protocol and similar delirium treatment practices. All consecutive, critically ill adults admitted to the ICU were enrolled. Patients were excluded if they had delirium at the time of ICU admission, were discharged from the ICU within 6 hours, or were unable to be reliably assessed for delirium (e.g. sustained coma, inability to understand the predominant language spoken in the ICU, severe cognitive dysfunction, receptive aphasia, or serious auditory or visual disorders).(6-8) Each institution enrolled patients for up to three months or until data on 300 patients was collected.

Data collection

Data over the first 14 days of the ICU stay was collected. Data for each delirium predictor (nine for the E-PRE-DELIRIC model; ten for the PRE-DELIRIC model) were collected in consecutive patients immediately after ICU admission (E-PRE-DELIRIC)(8) and within 24 hours of ICU admission (PRE-DELIRIC)(6, 7) and entered in a validated web-based, data management system Castor.(12) Severity of illness was estimated at ICU admission using the Acute Physiology and Chronic Health Evaluation (APACHE) II score (13) and daily using the Sequential Organ Failure Assessment (SOFA) score.(14)

The presence of ICU delirium was evaluated at least every 12 hours by the trained bedside nurse using either the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)(15) or Intensive Care Delirium Screening Checklist (ICDSC).(16) Development of ICU delirium was defined as at least one positive assessment for delirium using the CAM-ICU or ICDSC. Patients were also deemed to have delirium whenever they were administered haloperidol or an atypical antipsychotic for treatment of delirium, to prevent from false negative delirium screenings. To eliminate bias, nurses were kept unaware of the fact that their delirium assessments were used for a study.(17)

Level of sedation (using either the Richmond Agitation-Sedation Scale (RASS) or the Riker Sedation-Agitation Scale (SAS)(18, 19), and current intravenous (IV) sedative therapy was documented at the time each delirium assessment was completed. Delirium was preferentially evaluated when patients were maximally awake (e.g. after a spontaneous awakening trial). When coma was present (i.e., RASS = -4 or -5 or Riker-SAS = 1 or 2) patients were designated as unable to be assessed for delirium.

To help ensure that the nurse delirium assessments were of high quality,(20) a trained investigator (or research nurse) independently and sequentially evaluated patients for

the presence of delirium using the same tool as the bedside nurse (i.e., CAM-ICU or ICDSC) during one daytime shift each month and nurse-expert inter-rater reliability (IRR) was calculated. A delirium assessment compliance rate (i.e. delirium assessments documented/delirium assessments that should have been completed) was calculated for one day monthly in each ICU. If the Cohen's kappa for the paired delirium assessments was ≥0.80 and delirium screening compliance was ≥80% then the delirium assessment was considered to be reliable in that ICU. Prior to the study it was determined that centers that did not meet these two reliability criteria and whose outcomes significantly affected the performance of the (E-)PRE-DELIRIC model in the primary analysis, would be described separately.

Evaluation of the user convenience of the delirium prediction model

To estimate delirium model user convenience, the preferences of ICU physicians regarding the two delirium prediction models was determined by electronically administering a short, optional, and anonymous web-based survey (four, 5-point Likert scale questions) to all physicians working in each study ICU. (e-Appendix 1) A completed questionnaire indicated that a physician provided consent for their data to be used.

Statistical analysis

For each delirium prediction model at least 200 events, i.e. positive delirium assessments, were needed.(21) With an anticipated delirium incidence conservatively set at 20%, we aimed to enroll: (400/0.20)=2000 patients in total.

Discriminative power of both models was assessed using the Area under the Receiver-Operating Characteristic curve (AUROC).(17) The database was divided in groups based on the quartiles of the predicted probabilities for delirium development: very low (0.00-0.10), low (0.10-0.20), moderate (0.20-0.30) and high risk for delirium (≥0.30).

Sensitivity, specificity and likelihood ratios were calculated for these four groups. Calibration was assessed graphically by plotting the observed outcome frequencies against the mean predicted outcome probabilities or risks, within subgroups of patients that were ranked by increasing estimated probability.(22) The predictive performance of both models was compared using the Hanley & McNeil method.(23) It is estimated that approximately a third of the ICU patients will develop ICU delirium.(3) We therefore rated patients with a predicted probability for delirium of <0.30 as low-risk patients and ≥0.30 as high-risk patients for delirium. The additional value of a two-stage calculation in low-risk patients was determined using the E-PRE-DELIRIC model to calculate a patient's risk for delirium immediately after ICU admission. Subsequently we used data of the first 24 hours in ICU to update the prediction with the PRE-DELIRIC model to determine how many patients with a predicted probability for delirium of <0.30 with the E-PRE-DELIRIC model would

subsequently be labeled high risk for developing delirium using the PRE-DELIRIC score. Both risk calculations were compared to the patients' delirium outcome.

The questionnaires for ICU physicians were analyzed using the Wilcoxon Signed Ranks Test for non-parametric statistical testing of two dependent samples.

Statistical significance was defined as $p<0.05$ and the null hypotheses were tested against two-sided alternatives. Data were analyzed using SPSS® Statistics version 22 and R statistics R3.2.4.(24)

Results

A total of 2,802 patients were screened for inclusion; 2,178 (78%) were included. Among the 624 patients excluded, inability to reliably assess for delirium (46.3% (289/624)) and delirium at the time of ICU admission (25.9% (162/624)) were the most common reasons for exclusion. (See Figure 1 for study flowchart) Among the 83 patients that were excluded for other reasons, severe neurological injury and confidential file were the most common reasons. Patients were 62.1 ± 15.2 years old, 60.8% male, and had a baseline APACHE-II score of 17.4 ± 7.1. During the ICU-stay, 21.4% (467/2,178) developed delirium. Patient characteristics are presented in Table 1. For patient and hospital characteristics per participating ICU see e-Table 1.

Figure 1 Study flowchart

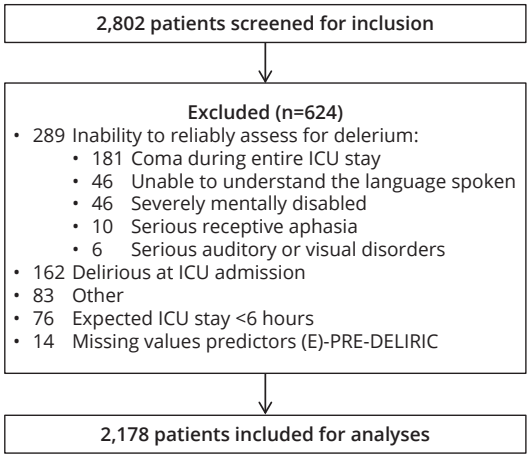


Table 1 Patient characteristics

Variable	Total cohort (N=2,178)
Age in years, Mean (SD)	62.1 (15.2)
Male, N (%)	1324 (60.8)
Admission category, N (%)	
– Surgery	1079 (49.5)
– Medical	859 (39.3)
– Trauma	86 (4.0)
– Neurology/neurosurgery	157 (7.2)
Urgent admission, N (%)	1345 (61.8)
≥1 day use of sedatives during ICU stay, N (%)	992 (45.5)
≥1 day comatose during ICU stay, N (%)	873 (40.1)
E-PRE-DELIRIC score, Median (Q1-Q3, min/max)	16.7 (9-32, 2/99)
PRE-DELIRIC score, Median (Q1-Q3, min/max)	18.4 (12-30, 3/98)
SOFA, Median (Q1-Q3, min/max)	4.5 (3.0-6.6, 1/20)
APACHE-II score, Mean (SD)	17.4 (7.1)
Delirium, N (%)	467 (21.4)
LOS-ICU in days, Median (Q1-Q3, min/max)	3.0 (2-6, 1/96)

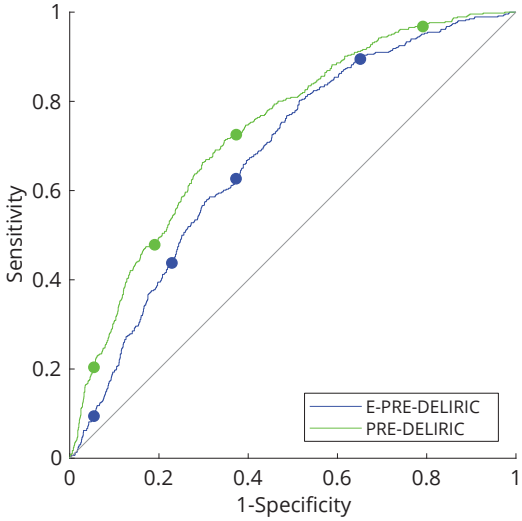
Sedatives = IV sedative therapy
Level of sedation = assessed using either the Richmond Agitation-Sedation Scale (RASS) or the Riker Sedation-Agitation Scale (SAS) (31, 32)
Coma = RASS = -4 or -5 or Riker-SAS = 1 or 2
SOFA = the Sequential Organ Failure Assessment score (33)
APACHE-II = the Acute Physiology and Chronic Health Evaluation score (34)
LOS-ICU = length of stay in the intensive care unit

Model performance

The AUROC of the PRE-DELIRIC model [0.74 (95%CI 0.71-0.76)] was significantly higher than that for the E-PRE-DELIRIC model [0.68 (95%CI 0.66-0.71)] [Z-score of -2.73 ($p<0.01$)]. (Figure 2) Both models were well calibrated. (Figure 3)

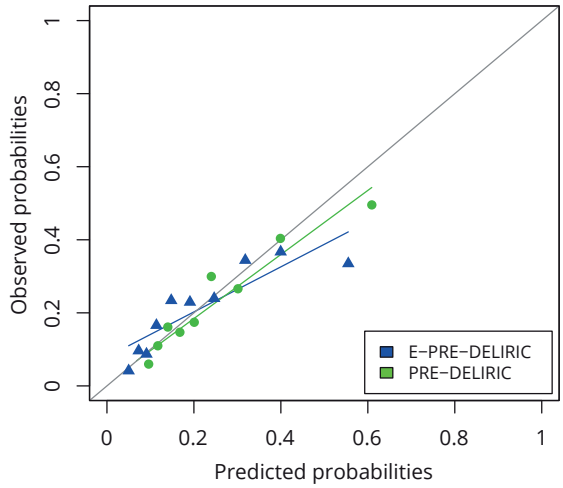
At a cut-off of 0.214, the delirium incidence of 21.4% in the total sample, the sensitivity and specificity were 60 and 65% for the E-PRE-DELIRIC model and 69 and 66% for the PRE-DELIRIC model.

Figure 2 AUROC E-PRE-DELIRIC and PRE-DELIRIC



Cut-off	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio
			E-PRE-DELIRIC	
0.10	90	35	1.4	0.3
0.20	63	63	1.7	0.6
0.30	44	77	1.9	0.6
0.50	10	95	2.0	0.9
			PRE-DELIRIC	
0.10	97	21	1.2	0.1
0.20	73	63	2.0	0.4
0.30	48	81	2.5	0.6
0.50	20	95	4.0	0.8
			Two-stage calculation	
0.30	58	71	2.0	0.6

Figure 3 Calibration plot E-PRE-DELIRIC and PRE-DELIRIC



Two-stage calculation

A total of 1,586 patients had a predicted probability for delirium of <0.30 with the E-PRE-DELIRIC model and therefore were not deemed to be at high risk for delirium based on the cut-off of 0.30. However, 262 of these patients eventually did experience delirium during their ICU stay, despite an initial low predicted risk for delirium calculated with the E-PRE-DELIRIC model. Using data of the first 24 hours in the ICU, the PRE-DELIRIC model identified 64 (24%) of these 262 patients to be at high risk for delirium (i.e. a predicted probability for delirium of ≥0.30). The two-stage calculation improved the sensitivity of the prediction with 14% compared to the E-PRE-DELIRIC model alone and with 10% compared to the PRE-DELIRIC model alone. (Figure 2)

User convenience

In total, 68 (41%) ICU physicians completed the user convenience questionnaire. Of the ICU physicians who participated in this study 52 (76%) were intensivists, 11 (16%) were intensivist trainees, 4 (6%) were specialists other than intensivist, and 1 (2%) was a physician without specialization. Fifty-six (82%) of the ICU physicians had no prior experience with a delirium prediction model; only 1 physician had experience with the E-PRE-DELIRIC model and 11 with the PRE-DELIRIC model. None of the physicians used a prediction model regularly, although 6 (9%) physicians stated a prediction model had been implemented in the ICU where they work. Physicians perceived that the PRE-DELIRIC model (vs. the E-PRE-DELIRIC model) took more 'time and effort to collect data' ($p<0.05$) and was a greater 'burden for the physician to collect the model data' ($p<0.01$). In contrast, for the E-PRE-DELIRIC model, physicians perceived that 'the predictors were more available'

(p<0.05) and that they were more likely 'to use this model (vs. the PRE-DELIRIC model) in daily practice' (p<0.05). The 'clearness of the definitions' and the 'reliability of the outcome' between the E-PRE-DELIRIC and PRE-DELIRIC model were perceived to be similar. (Table 2 and e-Table 2)

Table 2 Outcome user convenience questionnaire

Question	Negative Ranks^ (N)	Ties^ (N)	Positive Ranks^ (N)	Significance*
Time and effort needed to collect data to calculate a patient's risk	4	45	16	p<0.05
Burden for the physician to collect data about the predictors to calculate a patient's risk	3	42	20	p<0.01
Availability of predictors	11	50	4	p<0.05
Clearness of the definitions of the predictors	5	56	4	p=1.00
Reliability of the outcome (predicted risk) of the prediction model	2	62	1	p>0.5
Are you going to use the delirium prediction model in daily practice	9	55	1	p<0.05

^PRE-DELIRIC compared to E-PRE-DELIRIC: *negative ranks* mean number of ICU physicians who scored PRE-DELIRIC lower, *ties* mean no difference, *positive ranks* mean number of ICU physicians who scored PRE-DELIRIC higher
*Null hypotheses were tested against two-sided alternatives

Quality check delirium assessment

The overall quality of delirium assessment and screening compliance were strong (see e-Table 3 for all IRR and compliance rates for each participating ICU). When the ICUs that did not fully meet all delirium assessment reliability criteria were removed from the analysis, as was determined a priori, neither E-PRE-DELIRIC or PRE-DELIRIC models' performance was significantly affected. Consequently all centers were included in the primary analysis.

Discussion

This large, multinational prospective cohort study provides insight regarding the comparative performance of two available ICU delirium prediction models [i.e. the E-PRE-DELIRIC model that estimates the risk for delirium at the time of ICU admission and the PRE-DELIRIC model that estimated the risk for delirium 24 hours later].(6-8) Both models show a moderate-to-good statistical performance. Although the predictive accuracy of the E-PRE-DELIRIC model is somewhat lower, its user convenience appears to be better compared to the PRE-DELIRIC model. To allow for an optimal implementation of a delirium prediction model in daily practice, involvement and the opinion on user convenience of the target group, i.e. the ICU physicians, is very important.(19, 20) Based on these results, the E-PRE-DELIRIC model is likely the model that can be implemented most successfully in daily ICU practice. Moreover, our analysis indicates that when the E-PRE-DELIRIC model predicts a low risk for delirium, an additional calculation using the PRE-DELIRIC model after 24 hours in the ICU increases the model's sensitivity to detect patients that will develop delirium who are incorrectly identified as low-risk patients. Thus, this method will prevent deprivation of delirium preventive measures in the false negative patients (i.e. the patients with a predicted probability <0.30 who develop delirium during ICU admission).

The routine use of delirium preventive measures in the ICU is widely endorsed given the high prevalence of delirium and its deleterious effects on patient outcome.(21, 22) The routine use of a delirium prediction model allows ICU clinicians to focus delirium prevention efforts on those patients at greatest risk for delirium and avoid delirium-prevention interventions, that in some cases can be risky or costly, on patients whom are at low risk for delirium.(23) Preventive measures should be initiated as soon as possible after ICU admission; therefore an early ICU delirium prediction model is preferred.

The performance of a prediction model outside the development sample determines its generalizability in clinical practice.(24) External validation of many other clinical prediction models is lacking.(25) Of note, both the E-PRE-DELIRIC and recalibrated PRE-DELIRIC model are validated externally and showed moderate-to-good statistical performance in independent data sets, allowing for generalization to non-study ICUs around the world. (26)"Wassenaar et al. 2017, External validation of two models to predict delirium in intensive care unit patients. Unpublished data."

Our study has important strengths. The use of a cohort design without strict eligibility criteria helped boost its generalizability.(11) Its prospective nature allowed us to carefully measure and document the predictors and outcomes, thereby improving its applicability and reproducibility into non-study ICUs.(11, 15, 27) The large number of patients enrolled, their mixed nature and the multinational character of our study allows the results to be applied in the vast majority of ICUs in the developed world. The proportion of ICU physicians responding was better than response rates shown in other physician surveys.(28) No imputation techniques were used to handle missing data, as we wanted to determine

the clinical performance of both delirium prediction models and the use of a prediction model in daily clinical practice does not allow for imputation. Our efforts to provide clear definitions and instruction manuals to all study sites resulted in the exclusion of only fourteen patients due to missing values on the predictors.

Several limitations are also present. It might be possible that the two delirium prediction models evaluated might need to be updated in the future as new risk factors for delirium in the ICU may emerge. Of course, this also offers an opportunity to further improve the discriminative performance of each model, of which in particular the E-PRE-DELIRIC could benefit from. For an update, referred to as model revision, one needs to have insight in new risk factors for delirium, both available at ICU admission or within 24 hours of ICU admission. Subsequently, a new prediction study is needed to determine which of the new risk factors improve the models' performance and should be used for model revision.(29) It is important to realize that when a model is used to predict a patient's risk for an event that it should always be considered an approximation no matter how strong a predictive accuracy is documented. This is particularly important in the case of medical decision making. Two, well-validated, delirium screening instruments (i.e. the CAM-ICU and the ICDSC) were used in this study. Naturally, the sensitivity and specificity of each instrument differs.(30) Realizing that the sensitivity of either screening tool is not 100%, we also defined delirium to be present when haloperidol or an atypical antipsychotic was administered for delirium treatment. While each ICU had similar delirium treatment protocols, we cannot exclude that antipsychotic therapy may have been initiated in patients who did not have delirium.

It is well established that ICU clinicians' predictions are less accurate than those of an ICU delirium prediction model.(6) We believe that routine prognostic delirium evaluation in the ICU is important in the clinical setting to identify those patients who may benefit the most from early preventive measures and in the research setting to ensure that delirium risk is well characterized and stratified in controlled studies. To achieve the best predictive performance and user convenience currently possible, we suggest a two-stage calculation by using the E-PRE-DELIRIC model in all ICU-admitted patients to predict patients' risk for delirium immediately after ICU admission and to update the risk scores of the patients at low risk for delirium after 24 hours by using the PRE-DELIRIC model. This way, the chance to miss a patient that will develop delirium during ICU admission is further attenuated. Future research should focus on the clinical impact of the use of both delirium prediction models, since this is the only way to determine whether their use improves usual care.(29) In addition, such an impact analysis also provides the opportunity to study the acceptance of the models in daily practice.(29)

Conclusion

This study shows that both ICU delirium prediction models statistically perform moderate-to-good. Although the predictive accuracy of the PRE-DELIRIC is greater, the E-PRE-DELIRIC model scores significantly better on user convenience. Moreover, the PRE-DELIRIC model needs data obtained during 24 hours, while the E-PRE-DELIRIC can be obtained at ICU admission, allowing direct preventive measures in patients at high risk for delirium as well as stratified randomization in studies as soon as ICU admission. In patients who appear to be at low risk for delirium at ICU admission, it is of additional advantage to update their predicted risk scores using the PRE-DELIRIC model after 24 hours in ICU.

Declarations

Ethics approval and consent to participate

The study was reviewed by the Medical Research Ethics Committee (MREC) Arnhem-Nijmegen region, The Netherlands (CMO Region Arnhem-Nijmegen, no. 2015-1782) and the local MRECs/ Institutional Review Boards (IRBs)/ Research Ethics Boards (REBs) of the participating ICUs. Each institutional MREC/IRB/REB waived the need for informed consent. Only de-identified data were entered into the study database and used for analysis. Trial registration: ClinicalTrials.gov no. NCT02518646.

Acknowledgments

The authors would like to thank Alexandra Cheng (ICU pharmacist, Mount Sinai Hospital) for her help in collecting the patient data and all involved research nurses and the intensive care teams of each of the participating sites for their help in collecting the patient data.

Competeting interests

The authors declare that they have no competeting interests related to this study.

Funding

We received no external funding for this study.

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Online data supplement

e-Appendix 1 Physician Questionnaire DECISION study

Hospital:	.....
Date:	.....

By means of this questionnaire we want to determine your opinion about the *user convenience* of both delirium prediction models (E-PRE-DELIRIC and PRE-DELIRIC).

E-PRE-DELIRIC: Delirium prediction immediately after ICU admission	**PRE-DELIRIC:** Delirium prediction within 24 hours after ICU admission
Predictors*:	
Age (years)	Age (years)
Blood urea nitrogen (BUN) (mmol/L)	Blood urea nitrogen (BUN) (mmol/L)
Admission category	Admission category
Urgent admission	Urgent admission
History of alcohol abuse	*Coma*
History of cognitive impairment	*Infection*
Mean arterial blood pressure	*Morphine use*
Use of corticosteroids	*Sedative use*
Respiratory failure	*APACHE-II score (per point)*
	Metabolic acidosis (pH <7.35, with bicarbonate <24 mmol/L)

**Italic fond in Table: predictors that differ from each other per prediction model*

1. *What is your profession in ICU?*
   - ☐ Intensivist
   - ☐ Intensivist trainee
   - ☐ Specialist, other than intensivist
   - ☐ Physician without specialization

2. *Have you previously worked with a delirium prediction model?*
   - ☐ no, no prior experience with a delirium prediction model
   - ☐ yes, in this unit (E-PRE-DELIRIC)
   - ☐ yes, in this unit (PRE-DELIRIC)
   - ☐ yes, elsewhere (E-PRE-DELIRIC)
   - ☐ yes, elsewhere (PRE-DELIRIC)

If yes

- ☐ implemented in daily practice
- ☐ use on occasion

3. *What do you think of the user convenience of both delirium prediction models, in terms of:* (Please place for both delirium prediction models an X in the box behind the answer of your choice)

	Possible answers	**E-PRE-DELIRIC**	**PRE-DELIRIC**
Time and effort needed to collect data to calculate a patient's risk	Very low		
	Low		
	Neutral		
	High		
	Very high		
Burden for the physician to collect data about the predictors to calculate a patient's risk	Very low		
	Low		
	Neutral		
	High		
	Very high		
Availability of predictors	Never available		
	Unavailable		
	Neutral		
	Available		
	Always available		
Clearness of the definitions of the predictors	Very vague		
	Vague		
	Neutral		
	Clear		
	Very clear		

Reliability of the outcome (predicted risk) of the prediction model	Very unreliable		
	Unreliable		
	Neutral		
	Reliable		
	Very reliable		
Are you going to use the delirium prediction model in daily practice	Not		
	Probably not		
	Neutral		
	Probably		
	Sure		
	Depends on this study		

4. *Do you have other information you like to add concerning the delirium prediction models?*

.....

.....

Thank you for your response!.

e-Table 1 Patient and hospital characteristics

Variable	Total cohort (N=2,178)	University Medical Centre Utrecht (UMCU) (N=292)	Jeroen Bosch Ziekenhuis (JBZ) (N=146)	Antwerp University Hospital (AUH) (N=288)	The Canberra Hospital (TCH) (N=299)
Age in years, Mean (SD)	62.1 (15.2)	62.8 (14.2)	63.0 (15.2)	62.6 (14.6)	63.6 (16.5)
Male, N (%)	1324 (60.8)	193 (66.1)	78 (53.4)	171 (59.4)	172 (57.5)
Admission category, N (%) Surgery Medical Trauma Neurology/neurosurgery	 1079 (49.5) 859 (39.3) 86 (4.0) 157 (7.2)	 191 (65.4) 58 (19.9) 10 (3.4) 33 (11.3)	 41 (28.1) 100 (68.5) 3 (2.0) 2 (1.4)	 159 (55.2) 112 (38.9) 17 (5.9) -	 129 (43.1) 134 (44.8) 19 (6.4) 17(5.7)
Urgent admission, N (%)	1345 (61.8)	108 (37.0)	126 (86.3)	173 (60.1)	216 (72.2)
≥1 day use of sedatives during ICU stay, N (%)	992 (45.5)	72 (24.7)	74 (50.7)	158 (54.9)	109 (36.5)
≥1 day comatose during ICU stay, N (%)	873 (40.1)	60 (20.5)	46 (31.5)	155 (53.8)	102 (34.1)
E-PRE-DELIRIC score, Median (Q1-Q3, min/max)	16.7 (9-32, 2/99)	10.2 (7-23, 2/68)	25.1 (15-37, 4/100)	16.4 (9-33, 2/75)	19.0 (11-31, 3/65)
PRE-DELIRIC score, Median (Q1-Q3, min/max)	18.4 (12-30, 3/98)	18.0 (11-28, 4/84)	19.4 (13-31, 5/68)	17.6 (11-41, 4/94)	16.7 (11-27, 4/78)
SOFA, Median (Q1-Q3, min/max)	4.5 (3.0-6.6, 1/20)	4.0 (3.0-6.0, 1/16)	N.A.	6.0 (4.0-8.0, 1/19)	4.0 (3.0-5.8, 1/13)
APACHE-II score, Mean (SD)	17.4 (7.1)	17.3 (6.0)	19.2 (7.7)	17.2 (6.9)	16.2 (6.7)
Delirium, N (%)	467 (21.4)	58 (19.9)	36 (24.7)	64 (22.2)	37 (12.4)
LOS-ICU in days, Median (Q1-Q3, min/max)	3 (2-6, 1/96)	2 (2-4, 1/45)	3 (2-6, 1/36)	3 (2-6, 1/85)	3 (2-5, 1/96)
Delirium assessment: Tool Number of assessments/ day Implementation	 N.A.	 CAM-ICU 2/day 2010	 CAM-ICU 3/day 2009	 ICDSC 3/day 2015-2016	 CAM-ICU 3/day 2012
Number of beds Yearly admission rate	N.A.	30 2000 Mixed ICU	16 850 Mixed ICU	45 2800 Mixed ICU	31 2000 Mixed ICU

Sedatives = IV sedative therapy
Level of sedation = assessed using either the Richmond Agitation-Sedation Scale (RASS) or the Riker Sedation-Agitation Scale (SAS) [17, 18], coma = RASS = -4 or-5 or Riker-SAS =1 or 2
SOFA = the Sequential Organ Failure Assessment score [13]
APACHE-II = the Acute Physiology and Chronic Health Evaluation score [12]
LOS-ICU = length of stay in the intensive care unit

	Medisch Spectrum Twente (MST) (N=64)	Hospital Espírito Santo (HES) (N=48)	Erasmus Medical Center (EMC) (N=222)	Tufts Medical Center (TMC) (N=274)	Radboud university medical center (RUMC) (N=298)	Rigs hospitalet (RHL) (N=139)	Mt Sinai Hospital/U of Toronto (SHT) (N=108)
	61.5 (12.4)	69.4 (13.0)	56.1 (15.7)	63.1 (15.2)	63.1 (14.0)	62.2 (14.6)	57.4 (17.5)
	44 (68.8)	43 (89.6)	141 (63.5)	169 (61.7)	189 (63.4)	92 (66.2)	43 (39.8)
	17 (26.6) 42 (65.6) 2 (3.1) 3 (4.7)	12 (25.0) 33 (68.8) 2 (4.1) 1 (2.1)	89 (40.1) 66 (29.7) 14 (6.3) 53 (23.9)	101 (36.9) 164 (59.8) 1 (0.4) 8 (2.9)	208 (69.8) 56 (18.8) 11 (3.7) 23 (7.7)	72 (51.8) 43 (30.9) 7 (5.0) 17 (12.2)	60 (55.6) 48 (44.4) - -
	57 (89.1)	48 (100)	112 (50.5)	241 (88.0)	104 (34.9)	88 (63.3)	72 (66.7)
	56 (87.5)	40 (83.3)	142 (64.0)	128 (46.7)	105 (35.2)	67 (48.2)	41 (38.0)
	46 (31.5)	39 (81.3)	73 (32.9)	91 (33.2)	158 (53.0)	77 (55.4)	24 (22.2)
	30.4 (20-40, 5/56)	48.7 (37-62, 22/82)	12.7 (7-22, 3/58)	18.8 (13-28, 3/71)	10.4 (8-18, 2/76)	29.8 (19-48, 10/100)	10.7 (6-21, 3/96)
	29.7 (20-40, 7/51)	43.4 (33-58, 12/83)	21.0 (14-29, 5/80)	18.5 (13-25, 5/59)	14.0 (11-23, 3/78)	39.6 (27-52, 7/99)	12.3 (9-21, 4/96)
	6.5 (3.0-6.5, 3/10)	6.4 (5.3-8.3, 2/14)	5.9 (4.0-7.9, 1/20)	3.4 (2.0-5.1, 1/15)	N.A.	N.A.	3.0 (1.6-5.0, 1/15)
	18.7 (6.0)	24.3 (8.0)	18.6 (6.6)	15.0 (6.2)	16.1 (5.5)	23.9 (7.7)	14.8 (8.7)
	24 (37.5)	5 (10.4)	59 (26.6)	66 (24.1)	71 (23.8)	32 (23.0)	14 (13.0)
	7 (3-17, 1/81)	6 (3-12, 2/19)	3 (2-7, 1/57)	3 (2-6, 1/14)	2 (2-3, 1/71)	4 (2-8, 2/38)	3 (2-5, 1/49)
	CAM-ICU 3/day	CAM-ICU 2/day	ICDSC 3/day	ICDSC 2/day	CAM-ICU 3/day	CAM-ICU 2-3/day	ICDSC 2/day
	2013	2015	2012-2014	2005	2008	2012-2015	2010
	18 900 Mixed ICU	5-6 200 Medical ICU	30 1200-1300 Mixed ICU	30 3300 Mixed ICU	34 2500 Mixed ICU	40 2600 Mixed ICU	16 800-850 Mixed ICU

e-Table 2 Quality check delirium assessment[#]

Center	Inter-rater reliability (mean Cohen's kappa)	CAM-ICU or ICDSC compliance (mean in %)
1 'University Medical Centre Utrecht (UMU)'	0.50	82
2 'Jeroen Bosch Ziekenhuis (JBZ)'	1.00	100
4 'Antwerp University Hospital (AUH)'	*	89
5 'The Canberra Hospital (TCH)'	0.69	74
6 'Medisch Spectrum Twente (MST)'	0.60	100
8 'Hospital Espírito Santo (HES)'	1.00	86
9 'Erasmus MC (EMC)'	1.00	95
10 'Tufts MC (TMC)'	0.84	85
11 'Radboudumc (RMC)'	0.60	91
12 'Rigshospitalet (RHL)'	1.00	87
13 'Mt Sinai Hospital/U of Toronto (SHT)'	*	*

*Not available
[#]Four ICUs were not able to perform the quality check of their delirium assessment completely according to the description in the method section

e-Table 3 Outcome user convenience questionnaire for ICU physicians

Question	Score	E-PRE-DELIRIC % of ICU physicians	PRE-DELIRIC % of ICU physicians
Time and effort needed to collect data to calculate a patient's risk	Very low	4.5	6.2
	Low	37.9	27.7
	Neutral	40.9	40.0
	High	15.2	20.0
	Very high	1.5	6.2
Burden for the physician to collect data about the predictors to calculate a patient's risk	Very low	1.5	1.5
	Low	36.4	24.6
	Neutral	37.9	36.9
	High	21.2	29.2
	Very high	3.0	7.7
Availability of predictors	Never available	3.0	6.2
	Unavailable	1.5	6.2
	Neutral	24.2	23.1
	Available	59.1	58.5
	Always available	12.1	6.2
Clearness of the definitions of the predictors	Very vague	1.5	1.5
	Vague	3.0	1.5
	Neutral	18.2	21.5
	Clear	69.7	67.7
	Very clear	7.6	7.7
Reliability of the outcome (predicted risk) of the prediction model	Very unreliable	1.5	1.5
	Unreliable	1.5	3.1
	Neutral	68.2	69.2
	Reliable	27.3	23.1
	Very reliable	1.5	3.1
Are you going to use the delirium prediction model in daily practice	Not	6.1	12.3
	Probably not	31.8	30.8
	Neutral	22.7	24.6
	Probably	24.2	18.5
	Sure	9.1	7.7
	Depends on this study	6.1	6.2

PART II

Non-pharmacological prevention of delirium in ICU patients

CHAPTER 5

Determination of the feasibility of a multicomponent intervention program to prevent delirium in the intensive care unit: A modified RAND Delphi study

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Aust Crit Care. 2017;30(6):321-7

Abstract

Background: Delirium is common in Intensive Care Unit (ICU) patients and associated with poor outcome. In non-ICU patients a multicomponent intervention program with non-pharmacological interventions has shown to reduce delirium. Currently, there is insufficient evidence regarding the effects of such a program in ICU patients. We developed a draft program based on a review. As most studies were conducted in non-ICU patients, the feasibility of the program in ICU patients needs to be assessed before investigating its effectiveness.

Objectives: To determine experts' opinion and to achieve group consensus on the feasibility and completeness of the multicomponent intervention program for ICU patients.

Methods: A modified RAND/UCLA appropriateness Method Delphi study was used. A total of 38 experts were selected following purposive sampling. Round one informed the experts about the draft program and asked for their opinion about its feasibility and completeness. In round two the experts were asked to reconsider their opinion based on changes made, and to rank the interventions in order of importance. The feasibility was scored using a 9-point Likert scale. A disagreement index (DI) and panel median were calculated to determine the level of agreement.

Results: During Delphi round one 100% of the questionnaires was completed, during round two 79%. After two rounds the experts agreed on the feasibility of the interventions targeting sleep deprivation (panel median 7.00, DI 0.26), immobility (panel median 8.00, DI 0.22), visual and hearing impairment (panel median 8.00, DI 0.19), and cognitive impairment (panel median 8.00, DI 0.23), except for cognitive training (panel median 5.00, DI 0.52).

Conclusions: During this study a feasible multicomponent intervention program to prevent ICU delirium was developed based on expert consensus. As no consensus was reached on cognitive training, a pilot study is planned to determine the feasibility of cognitive training in the ICU.

Introduction

Delirium is a common acute brain disorder in Intensive Care Unit (ICU) patients associated with serious short- and long-term consequences, including a higher rate of mortality, re-intubations, and ICU readmissions, longer ICU and hospital length of stay, longer duration of ventilation, increased risk for use of physical restraints and long-term cognitive problems.(1-6) In addition, delirium is a financial burden due to increased ICU and hospital costs.(7) These negative consequences emphasize the need for strategies to prevent delirium.(8)

As multiple risk factors are associated with delirium in critically ill adults,(9-11) it is plausible that delirium prevention strategies should target multiple risk factors.(12, 13) Nonpharmacologic approaches that target modifiable risk factors to prevent delirium appear promising.(12, 14-19) In non-ICU patients it has been shown that a multicomponent non-pharmacological intervention (MCI) program targeting several delirium risk factors can significantly reduce delirium incidence and duration.(15, 18) Studies in ICU patients that focus on specific parts of the program also showed beneficial effects.(14, 16, 17, 20, 21) However, there is currently insufficient evidence for the effects of an MCI program in ICU patients due to weaknesses in study design, sample size or problems with data collection.(13, 22) Therefore, further research is needed into the effects of an MCI program on delirium in ICU patients.

In preparation of a randomized controlled trial to study the effects of an MCI program on delirium in ICU patients, a draft MCI program was developed based on a review of existing literature which mainly included studies in non-ICU patients. The draft MCI program, consisting of nursing and physical therapy interventions, focuses on the modifiable delirium risk factors cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment. In view of the fact that the draft MCI program contains several interventions with interacting components, the MCI program is considered to be a complex intervention according to the MRC framework.(23, 24)

Since it is uncertain whether the draft MCI program is feasible in an ICU setting, the aim of this current study is to determine experts' opinion and to achieve group consensus on the feasibility and completeness of the draft MCI program for ICU patients. Assessing the feasibility of a complex intervention is an important element in the development and evaluation of an intervention according to the MRC framework.(23, 24)

Methods

A modified RAND/UCLA appropriateness Method (RAM) Delphi study was used.(25) This method was chosen since it allows to include experts from diverse regions and expertise, without the need to meet physically. As a result the experts stay anonymous for each other, eliminating the influence of dominant persons during the consensus forming.(26, 27) Multiple stages from RAM were used, including a literature review and individual feasibility rating and ranking of the interventions. A panel meeting was not part of this study for reasons of feasibility and logistics, like travel time and irregular shifts.

A literature review was conducted to develop a draft of the MCI program in the form of an intervention protocol. The review mostly included studies conducted in non-ICU patients, supplemented with studies conducted in ICU patients. The latter category only consisted of studies focusing on single interventions from the MCI program. Each intervention aimed at cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment was included if it was considered feasible to be carried out by an ICU nurse. Interventions aimed at dehydration and feeding were not included as these items are incorporated in daily clinical ICU practice already. See e-Appendix 1 for the references used.

Feasibility of the individual interventions was scored using a 9-point Likert scale. This Delphi study consisted of two rounds and an anonymous expert panel. After the last round the experts received a final report with the results and conclusions of the Delphi study.

Participants

Purposive sampling was conducted based on predetermined selection criteria,(28) to recruit experts who were representative for the clinical ICU practice in the Netherlands in which the MCI program will be tested in the future, and who have the appropriate knowledge about delirium and nursing interventions.(29, 30) Inclusion criteria for panel members were: membership of a delirium working group in their ICU and/or having special interest in the subject delirium; registered critical care nurse, intensivist or physical therapist working in a representative ICU from both academic and general hospitals, or work as a delirium researcher; appropriate knowledge about nursing interventions. One independent contact person per hospital, which guaranteed voluntary participation, recruited experts for the panel according to the inclusion criteria.(29) The participating hospitals in this Delphi study have ICUs equipped for surgical, medical, neurology/neurosurgical, or trauma ICU patients. Three experts, including a registered critical care nurse, an intensivist and a physical therapist, from each of the eleven Dutch hospitals that expressed an interest in participating in the planned randomized controlled trial, and from one non-participating hospital were invited to participate in the Delphi study. Also two senior nurse scientists from the field of delirium research were invited to participate as an expert.

Data collection

Data were collected using LimeSurvey, an online Software survey tool.(31) Each of the experts received a private invitation to the questionnaire by email. Each Delphi round started with an information letter concerning the aim and content of that specific round, the estimated time investment, and a deadline for completion. The experts were able to save answers and complete the questionnaire at a later time if necessary. To optimize the response rate, the experts received a maximum of two reminders per round about the deadline for completion. In the first round, an information paragraph per delirium risk factor was presented to the participants. The experts were asked to give their opinion about the completeness of the interventions per risk factor and to explain their answer and include suggestions for modifications and/or improvements. Per intervention the expert was asked to indicate her/his opinion about the feasibility of that specific intervention on a 9-point Likert scale. The experts were asked to explain their answers and the reason why they chose their answer. All information from the experts' explanations about both the completeness and feasibility was used in the decision making process on the modification of the interventions. The interventions that scored 'feasible' in round one and did not need any modifications were accepted and not presented as a question to the experts again in round two. The second round started with a general summary and explanation about the results and analysis of Delphi round one. Subsequently an information paragraph per delirium risk factor was described. This paragraph included the modified or newly added interventions based on the first Delphi round. The experts were asked to rank the interventions that were part of that risk factor in order of importance for delirium prevention, with the most important intervention on the first place, followed by the intervention that was second important and so on. Per intervention the experts received the following information: the intervention as presented in the draft MCI program, the overall group results of the feasibility rating during Delphi round one and the modified or new intervention. The experts were asked to reconsider their opinion based on this information (29, 30) and to rate the feasibility of the modified or new intervention. Similar to Delphi round one the experts were asked to explain their answers.

Ethical considerations

This study was evaluated by the medical research ethics committee Arnhem-Nijmegen region, the Netherlands (No.2014/1487). Participants' consent was assumed by return of the completed questionnaire. This study was conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act. Handling of the data complied with the Dutch Personal Data Protection Act.

Data analysis

For each intervention a disagreement index (DI) and panel median was calculated to determine the level of agreement.(25) A panel median of 1-3 without disagreement indicates 'not feasible', a panel median of 4-6 or any median with disagreement indicates 'uncertain', and a panel median of 7-9 without disagreement indicates 'feasible'.(25) Disagreement means a lack of consensus; ratings of the experts are spread over the entire 9-point Likert scale. To detect disagreement, the interpercentile range (IPR: 0.3-0.7) and the IPR adjusted for symmetry (IPRAS) was calculated. An IPR lower than the IPRAS indicates disagreement. After calculating the ratio, a DI <1 indicates agreement.(25)

After each of the two Delphi rounds, one researcher (AW) read and assessed all the explanations of the experts for the need to be used to modify or newly add any interventions. Afterwards two researchers discussed the results (AW, MvdB) and decided which modifications the interventions needed. In case of disagreement or questions two other researchers (LS, PP) were consulted to make a final decision.

The ranking by the experts in order of importance was rated as follows. Per delirium risk factor the maximum achievable number of points for an intervention rated on rank one was identical to the number of interventions that were part of that specific risk factor. The number of points for an intervention rated on rank two was identical to the number of interventions minus one and so on, until one point for an intervention ranked on the lowest possible rank for that risk factor. For each intervention that was part of that risk factor we counted how many experts rated that specific intervention, and this number was multiplied by the maximum achievable number of points per rank. These points achieved per possible rank were added up, resulting in a total score per intervention. These scores ultimately resulted in the ranking of the interventions per risk factor.

This ranking was used as additional information in the process of determining whether or not to exclude an intervention based on the level of agreement. If there was no consensus on the feasibility of an intervention, and the ranking of that intervention was low, this was a reason to exclude that intervention from the MCI program.

Validity and reliability

A high response rate is important for the validity of the results.(29) Sumsion suggested a response rate of 70% for each round in order to maintain rigor of the Delphi technique.(32) To reach commitment in the study and to optimize the ownership of the panel, we chose to invite experts from the ICUs that expressed an interest in participating in the planned randomized controlled trial in order to ultimately increase the response rate.(30) Also, the experts were informed exactly about the content, aim and the time investment for the study, and reminders about the deadline of completion were sent.(29, 30) A Delphi study usually consists of two to four rounds.(29, 30) The number of Delphi rounds was predetermined as two, to prevent exhaustion and reduction of the response rate of the experts, so as to ultimately limit attrition bias.(30, 33)

Results

In total, 38 experts participated in the Delphi study. (Table 1) During the first Delphi round 100% (N=38) of the questionnaires was completed, and during the second round 79% (N=30). After two rounds the expert group agreed on the feasibility of the interventions targeting sleep deprivation (panel median 7.00, DI 0.26), immobility (panel median 8.00, DI 0.22), visual and hearing impairment (panel median 8.00, DI 0.19), and cognitive impairment (panel median 8.00, DI 0.23). Despite the modifications based on Delphi round one, the score of the expert group for cognitive training remained 'uncertain' (panel median 5.00, DI 0.52). (Table 2) Every risk factor includes interventions related to direct patient care such as 'explain to the patient who you are to improve the patient's orientation', and indirect unit based interventions such as 'noise reduction strategies or use of flyers to highlight the importance of sleep'. See e-Appendix 1 for the complete interventions of the MCI program.

Table 1 Participants characteristics

Characteristics	Delphi round 1	Delphi round 2
Response rate, N (%)	38 (100)	30 (79)
Age, years (mean ± SD)	42 ± 7.7	41 ± 7.7
Male, N (%)	18 (47.4)	13 (43.3)
Education, N (%)		
Higher professional education	23 (60.5)	19 (63.3)
Academic level	15 (39.5)	11 (36.7)
Profession, N (%)		
ICU nurse	12 (31.6)	9 (30.0)
Physical therapist	12 (31.6)	11 (36.7)
Intensivist	12 (31.6)	9 (30.0)
Delirium researcher	2 (5.2)	1 (3.3)

Table 2 Panel median and disagreement index (DI)

Risk factor Interventions as part of the risk factor	Round 1 Panel median# (DI)	Round 2 Panel median# (DI)
Visual and hearing impairment	8.00 (0.35)*	8.00 (0.19)*
Ensure use of visual aids when awake	8.00 (0.08)	8.00 (0.22)
Provide adapted material	7.00 (0.37)	7.00 (0.22)
Ensure hearing aids are functioning	8.00 (0.13)	-
Ensure use of hearing aids when awake	8.00 (0.16)	8.00 (0.08)
Resolve any reversible cause	6.00 (0.97)	5.00 (0.32)
Use special communication techniques	8.00 (0.37)	8.00 (0.16)
Ensure note of impairment is in patient's file	-	9.00 (0.08)
Ensure visual aids are clean	-	9.00 (0.13)
Approach patient from good vision side	-	7.00 (0.28)
Prevent dehydration cornea	-	9.00 (0.08)
Extra attention verbal communication	-	8.00 (0.13)
Ask family to bring hearing aids, batteries and instructions	-	8.00 (0.13)
Speak clear, limit background noise	-	7.00 (0.37)
Approach patient from good hearing side	-	7.00 (0.37)
Sleep deprivation	7.00 (0.31)*	7.00 (0.26)*
Noise reduction strategies	6.50 (0.30)	7.00 (0.22)
Avoiding procedures during sleep time	6.50 (0.30)	7.00 (0.16)
Reduction of ICU lights	8.00 (0.13)	8.00 (0.16)
Using earplugs	7.00 (0.50)	8.00 (0.16)
Providing relaxation music	7.00 (0.37)	7.00 (0.12)
Ask family what patient does at home to promote sleep	7.00 (0.65)	7.00 (0.60)
Discouraging daytime sleep	7.00 (0.22)	-
Strive to use sedation as less as possible	8.00 (0.16)	8.00 (0.09)
Encouraging (early) mobilization	8.00 (0.16)	-
Be cautious with use of sleep medication	-	7.00 (0.48)
Use flyers to highlight importance sleep	-	8.00 (0.37)
Provide clear day structure	-	8.00 (0.28)
Cognitive impairment (orientation protocol)	8.00 (0.16)*	8.00 (0.23)*
Place information board for patient	8.00 (0.16)	8.00 (0.28)
Provision of clock and calendar in room	9.00 (0.13)	-
Presence of familiar object in room	8.00 (0.00)	-
Facilitation of regular visiting hours	8.00 (0.29)	-
Discuss with family which name to use to call the patient	9.00 (0.13)	-
Provide appropriate lightning	7.00 (0.37)	7.00 (0.65)
Ensure appropriate use of glasses	8.00 (0.08)	-
Ensure patient is provided with information	8.00 (0.16)	8.00 (0.16)
Stimulate patient's orientation	8.50 (0.13)	8.00 (0.16)
Explain who you are	8.00 (0.16)	8.00 (0.00)
Provide continuity of nurses	-	6.00 (0.52)
Compile poster with information about patient	-	7.00 (0.37)

Table 2 Continued

Risk factor Interventions as part of the risk factor	Round 1 Panel median# (DI)	Round 2 Panel median# (DI)
Cognitive impairment (cognitive training)	6.00 (0.58)*	5.00 (0.52)*
Digit span	6.00 (0.52)	6.00 (0.45)
Digit game	7.00 (0.35)	6.00 (0.22)
Memory task	7.00 (0.45)	6.00 (0.52)
Symbol searching	6.00 (0.49)	6.00 (0.45)
Digit cancellation task	6.00 (0.85)	5.00 (0.85)
Blocks task	6.00 (0.52)	5.00 (0.51)
First and second names	6.00 (0.84)	5.00 (0.32)
Executive functioning	6.00 (0.32)	6.00 (0.45)
Bells test	5.00 (0.85)	5.00 (0.85)
Picture guess	4.00 (0.52)	5.00 (0.60)
Difference searching	6.00 (0.65)	5.00 (0.45)
Immobility	8.00 (0.28)*	8.00 (0.22)*
Optimize patients' sedation	8.00 (0.16)	8.00 (0.16)
Physical therapy at least once daily	8.00 (0.29)	-
Physical therapy dependent on tolerance	8.00 (0.00)	8.00 (0.16)
Initiation, encouraging and reminding patients to mobilize	8.00 (0.29)	7.00 (0.37)
Promote and facilitate mobilization	6.00 (0.65)	7.00 (0.37)
Reduce pain and fear as hampering factor	-	8.00 (0.05)
Set and register clear goals per patient	-	7.00 (0.16)

#A panel median of 1-3 indicates 'not feasible', a panel median of 4-6 or any median with disagreement indicates 'uncertain', and a panel median of 7-9 indicates 'feasible'. DI <1 indicates agreement
*The panel median and DI per delirium risk factor
Italic interventions are new interventions added based on the results of Delphi round 1 and therefore only the panel median (DI) of Delphi round 2 is available. The interventions without panel median (DI) in Delphi round 2 are those that did not require modifications and scored 'feasible' in round one. These interventions were accepted and not presented as a question to the experts again

Delphi round one

All interventions scored a DI <1.00, indicating agreement. In total, thirteen interventions scored 'uncertain' based on the median, 28 interventions scored 'feasible' and none of the interventions scored 'not feasible'. (Table 2)

Of the interventions that were part of the risk factor 'visual and hearing impairment', five were modified based on the experts' opinions about completeness and feasibility. Also eight new interventions were added. Seven of the interventions that were part of the risk factor 'sleep deprivation' were modified based on the experts' explanations and three new interventions were added. Of the interventions that were part of the risk factor 'cognitive impairment', five were modified based on the experts' explanations and two new interventions were added. All eleven cognitive training interventions were modified based on the experts' explanations. And of the interventions that were part of the risk factor 'immobility' four were modified based on the experts' explanations. Also two interventions were newly added. The modifications consisted of (textual) changes to the intervention

itself and adding notes to the intervention to make it more clear and complete. (See Figure 1 for an example) Nine interventions were not modified at all.

Figure 1 Example questionnaire item in Delphi round two*

Intervention in Delphi round 1:
Immobilizing equipment (e.g., bladder catheters, continuous fluid therapy or physical restraints) should be removed as much as possible to facilitate patients to mobilize.

Panel medial (overall group result of feasibility rating): 6 without agreement, uncertain about the feasibility of the intervention.

Modified intervention based on the experts feedback:
To promote and facilitate mobilization: the location of central lines and tubes should allow mobilization (preferably not in the groin). Daily evaluation of the necessity of immobilizing equipment (e.g., central lines, tubes, bladder catheters, or physical restraints). This equipment should be removed whenever possible. If necessary central lines, tubes or catheters are temporary disconnected or blanked off. In consultation with the patient's family fixation can be disconnected in their presence.

Notes added to the intervention: presence of the family is stimulated.

Question: How do you rate the feasibility of this intervention? Please explain your answer.

	Not feasible 1	2	3	4	Neutral 5	6	7	8	Feasible 9
Feasibility	o	o	o	o	o	o	o	o	o

*This is an example of an intervention targeting immobility that was modified based on the explanations of the experts during Delphi round one

Delphi round two

All interventions scored a DI <1.00, indicating agreement. In total, thirteen interventions scored 'uncertain' based on the median, 34 interventions scored 'feasible' and none of the interventions scored 'not feasible'. (Table 2) No interventions needed a modification or needed to be newly added, based on the experts' explanations and answers during Delphi round two. See Table 3 for the ranking of the interventions. Two interventions 'Resolve any reversible cause' and 'Provide continuity nurses' were removed from the intervention program based on their panel median ('uncertain') and the ranking of the interventions. (Table 2 and 3) During both Delphi rounds the cognitive training interventions scored 'uncertain'. Reasons for scoring cognitive training as 'uncertain' or 'not feasible' were: too difficult, complex and burdening for ICU patients, dependent on the capabilities of individual patient, and too labor-intensive for ICU nurses. See e-Appendix 1 for the intervention program after Delphi round two.

Table 3 Ranking of the interventions

Risk factor **Ranking interventions**	**Total score**
Visual and hearing impairment	
1. Ensure use of visual aids when awake	222
2. Ask family to bring hearing aids, batteries and instructions	201
3. Ensure note of impairment is in patient's file	190
4. Ensure use of hearing aids when awake	185
5. Ensure hearing aids are functioning	171
6. Prevent dehydration cornea	155
7. Ensure visual aids are clean	140
8. Speak clear, limit background noise	131
9. Approach patient from good vision side	125
10. Use special communication techniques	118
11. Approach patient from good hearing side	114
12. Extra attention verbal communication	102
13. Provide adapted material	78
14. Resolve any reversible cause	47
Sleep deprivation	
1. Reduction of ICU lights	175
2. Noise reduction strategies (including avoiding procedures during sleep time)	172
3. Provide clear day structure	135
4. Encouraging (early) mobilization	124
5. Discouraging daytime sleep	118
6. Strive to use sedation as less as possible	114
7. Using earplugs	98
8. Be cautious with use of sleep medication	88
9. Ask family what patient does at home to promote sleep	84
10. Use flyers to highlight importance sleep	72
11. Providing relaxation music	71
Cognitive impairment (orientation protocol)	
1. Explain who you are	197
2. Provision of clock and calendar in room	161
3. Stimulate patient's orientation	138
4. Provide appropriate lightning	135
5. Ensure patient is provided with information	121
6. Place information board for patient	116
7. Provide continuity nurses	114
8. Ensure appropriate use of glasses	111
9. Discuss with family which name to use to call the patient	110
10. Facilitation of regular visiting hours	99
11. Presence of familiar object in room	97
12. Compile poster with information about patient	85

Table 3 Continued

Risk factor **Ranking interventions**	**Total score**
Cognitive impairment (cognitive training)	
1. Digit span	142
2. Memory task	135
3. Symbol searching	128
4. Digit game	121
5. First and second names	119
6. Executive functioning	113
7. Picture guess	113
8. Digit cancellation task	108
9. Difference searching	94
10. Blocks task	92
11. Bells test	87
Immobility	
1. Optimize patients' sedation	159
2. Reduce pain and fear as hampering factor	149
3. Physical therapy dependent on tolerance	143
4. Physical therapy at least once daily	139
5. Set and register clear goals per patient	91
6. Promote and facilitate mobilization	85
7. Initiation, encouraging and reminding patients to mobilize	70

Discussion

In this modified RAND/UCLA appropriateness Method Delphi study, a multidisciplinary expert panel agreed on the feasibility of a multicomponent non-pharmacological intervention (MCI) program aimed at preventing delirium in ICU patients. During the preset two Delphi rounds the expert group reached consensus on the feasibility and completeness of the interventions targeting sleep deprivation, immobility, visual and hearing impairment, and cognitive impairment, but not on cognitive training. Although the Delphi technique proved to be an appropriate design for the aim of our study, during both Delphi rounds the cognitive training interventions scored 'uncertain' meaning no consensus was reached on their feasibility. We believe that adding an extra Delphi round would not have resulted in consensus on the feasibility of cognitive training, as the 'uncertain' score for cognitive training was most likely due to unfamiliarity of the experts with performing cognitive training in their clinical practice. Because of the necessity of consensus before adding an intervention to the final MCI program, an additional prospective cohort pilot study is planned to determine the feasibility of cognitive training in ICU patients.(34) During this pilot study ICU patients, ICU nurses and delirium researchers will test the cognitive training interventions in clinical practice which allows a proper decision to be made about whether or not to include cognitive training in the MCI program. Former pilot studies suggest that cognitive training combined with physical therapy is feasible and safe for the rehabilitation of ICU patients.(35, 36)

In view of the high delirium incidence and the serious consequences related to delirium,(1-5) the use of an MCI program in ICU patients is promising and relevant for the daily clinical ICU practice.(14, 16, 17, 20, 21, 37) Currently, there is in insufficient evidence regarding the effectiveness of an MCI program in ICU patients.(13, 22) Because a more rigorous design is needed to prove effectiveness, we have planned a stepped wedge cluster randomized controlled trial, called the UNDERPIN-ICU study (nUrsiNg DEliRium Preventive INterventions in the Intensive Care Unit), which aims to determine the effect of the MCI program on delirium in ICU patients, to ultimately increase the number of delirium free days in the ICU.

To facilitate delirium prevention, the identification of ICU patients at high risk for delirium is important, since these are the most fragile patients who require the maximum preventive efforts.(38) Patients' risk for delirium in the ICU can be predicted using a delirium prediction model, allowing early delirium prevention in high risk patients.(39-41) As many delirium risk factors are present in the ICU,(42) prevention strategies target multiple modifiable delirium risk factors. Recent studies (13, 22) aimed at reducing ICU delirium by the implementation of a non-pharmacological protocol targeted mostly the same risk factors as our MCI program. Despite the fact that dehydration and feeding were targeted by the MCI program studied in non-ICU patients,(15, 18) they are not targeted by our MCI

program, nor by the intervention protocol of two recent ICU delirium prevention studies conducted in ICU patients,(13, 22) as these items are incorporated in daily clinical ICU practice. In contrast to recent ICU delirium prevention studies,(13, 22) our Delphi study provides a clear insight into how the intervention program was developed, on which specific sources the interventions were based, and an exact description of the interventions including clarifying notes. (e-Appendix 1 in the online data supplement) This is important for future studies into the effects of an MCI program on delirium in ICU patients and ultimately the use of the MCI program in clinical practice, as it allows for transparency and implementation of the interventions.

Strengths and limitations

For this study we used the research guidelines of Hasson et al. for performing and reporting the Delphi technique.(29) An important strength of this study is the high response rate of the expert panel during the different Delphi rounds, which positively influences the validity of the results.(29, 32) A frequent issue in Delphi studies aimed at achieving group consensus is the question what level of agreement equals consensus.(30) In order to avoid having to choose an arbitrary cut off we used the RAM, as this method provides clear rules for determining the level of agreement.(25) Furthermore, to ultimately limit attrition bias, the maximum number of Delphi rounds was predetermined.(30, 33) In addition, to improve the interpretation of the results of a previous Delphi round by the experts, we returned the results accompanied by an explanation on for example the meaning of a group median and DI.(30)

However, our results should be interpreted considering some limitations. First, we used purposive sampling which most likely resulted in selection bias.(28) We did this to include a representative sample for the clinical ICU practice in which the MCI program will be implemented during the future UNDERPIN-ICU study. This was important for the sense of ownership to stimulate the response rate during the Delphi study.(30) Second, in regard to the generalizability of the results it should be taken into account that our sample was limited to one country. However, we did select a heterogeneous and representative sample of experts from ICUs from both academic and general hospitals spread all over the Netherlands. In addition, we based the final MCI program on the expertise of ICU nurses, intensivists, physical therapists as well as delirium researchers, to make sure the MCI program included all important interventions.

Conclusion

In this study a feasible multicomponent non-pharmacological intervention (MCI) program aimed at preventing delirium in the ICU was developed based on expert consensus. The use of a literature review provided a sound scientific base for the draft MCI program, and during the Delphi rounds the MCI program was tailored to be tested in ICU patients. This Delphi study represents an essential step towards future research consisting of a stepped wedge cluster randomized controlled trial, the UNDERPIN-ICU study, to determine the effects of the MCI program on ICU delirium.

Conflict of interests

None declared.

Funding

This study was not funded.

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Online data supplement

e-Appendix 1 Intervention program after Delphi round two

The UNDERPIN-ICU program (nUrsiNg DEliRium Preventive INterventions in the Intensive Care Unit), consisting of nursing and physical therapy interventions, will focus on the modifiable delirium risk factors cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment.

1 Visual and hearing impairment

This protocol aims to prevent or treat sensory deprivation and ultimately the loss of orientation. The intervention will consist of:

Ensure there is a clear note in the patients' file in case of visual and/or hearing impairment and what types of visual or hearing aids the patient is using.
Notes added to the intervention: whenever an electronic patient data management system is available a reminder should be built in to make sure visual and hearing impairment is discussed during the admission interview and the patient's family is asked to bring any visual or hearing aids including an instruction on how to use them to the ICU.

Visual protocol:

A. Ensure that the patients use their visual aids whenever they are awake.
   Notes added to the intervention: e.g. use glasses or magnifier, in case a patients wants to use contact lenses the patient should be able to insert and remove the lenses by themselves. Pay attention to pressure spots due to glasses during repositioning.(1-6)
B. Ensure that visual aids are clean before use.
C. Approach the patient from the side at which he or she has good vision.
D. Provide material adapted to visually impaired patients, like large-print books, electronic books (iPad) or fluorescent tape on call bell.(1-6)
E. Prevent dehydration of the cornea during sedation.
F. Pay extra attention to verbal communication about the execution of (nursing) activities and the patient's surroundings, in case a patient is severely visually impaired.

Hearing protocol:

G. Ask the patient's family to bring the patient's hearing aids, including enough batteries and an instruction on how to use them, to the ICU.
H. Ensure that the hearing aids are fully functional before use.
I. Ensure that the patients use their hearing aids whenever they are awake, remove the hearing aids in consultation with the patient during the night or moments of rest.
   Notes added to the intervention: pay attention to pressure spots due to the hearing aids

during repositioning.(1-6)

J. Speak clear and limit background noise.

K. Approach the patient from the side at which he or she has good hearing.

L. Use special communication techniques, like easy (hand)gestures, writing, pictures/ symbols, letter cards or new communication devices like an iPad.(1-6)

2 Sleep deprivation

Aim: to minimize/avoid sleep deprivation.

A. Unit-wide noise-reduction strategies (1, 2, 4-12):
   1. Quiet hallways, closed doors, no loud talking, provide colleagues with noise feedback. Vibrating beepers or telephones. Use of headphone when a patient listens to music or is watching television. Decrease alarm volume, expansion of alarm boundaries of the mechanical ventilator or monitor within safe levels.
      Notes added to the intervention: close doors of the patient's room or other rooms like the staff room or utility room depending on the building and possibilities of the ICU.
   2. Avoid nursing and medical procedures during sleep time, taking into account the patient's medical condition.
      Notes added to the intervention: use a schedule to make adjustments to allow sleep. These adjustments include a rescheduling of medication rounds (adjustment of the default time for medication gifts), blood draws, scheduling vital signs measurement (minimize use of non invasive blood pressure measurements) and bundling of necessary nursing activities.

B. Reduce ICU lights to a minimum when it is time to sleep, unless necessary.(2, 7, 9-12)
   Notes added to the intervention: automatically dim (turn off) the lights in (communal) rooms after a certain time. Use of a flashlight by nurses during the nightshift. Dim monitor screens and turn the machines out of the patient's sight. Fend light by the use of curtains, luxaflex or lamellae.

C. After consultation with the patient, apply earplugs (unless contra indicated), from start of the night shift until the end of the night shift.(11, 13)

D. Provide relaxation music when it is time to sleep, pay attention to noise disturbance. (1, 11)
   Notes added to the intervention: ask the patient's family for help and advice regarding the patient's music preference and if necessary to bring any devices.

E. Ask the patient/family what the patient does at home to promote sleep and whenever permissible provide this to the patient.(12)
   Notes added to the intervention: for example, read to the patient (by nurse, family or audio book), or when the patient has particular sleep objects, such as a certain pillow provide these. Keep hygiene rules in mind. You can ask this question during the admission interview.

F. Be cautious with the use of sleep medication, use a ward protocol in case you use sleep mediation.
Notes added to the intervention: the ward protocol provides information regarding the choice of sleep medication, for example do not use sedation like midazolam or propofol, and the time of administration.
G. Highlight the importance of good sleep in your ward by the use of flyers that ask attention for the reduction of light and noise during the night.
H. Provide a clear day structure by compiling a personal day program for the patient.
I. Discourage daytime sleep, by improving the sleep-wake cycle using bright light during the day.(4, 8, 11, 14, 15)
Notes added to the intervention: whenever necessary a short rest moment can be planned in a personal day program.
J. Whenever fitting the patient's individual treatment plan: strive to use sedation as less as possible. In case of sedation, perform a daily wake-up (reduce or stop sedation once a day) and pursue a Richmond Agitation-Sedation Scale (RASS) score of > -3 en < +2. Pursue a RASS of 0 in patients without sedation.(9, 10)
Notes added to the intervention: in case the patient is having a RASS score outside the target levels: evaluate the cause and if possible take care of it. Use the ward protocol for this.
K. Encourage (early) mobilization.(11)

3 Cognitive impairment

Aim: to (re)orientate patients with regard to time, place and person to prevent or minimize decline.

Orientation protocol:

A. Place a board with the name of the patient's nurse, intensivist and a day schedule in the patient's sight.(1)
Notes added to the intervention: the day schedule is compiled using key words and symbols for activities like mobilization, sleeping, visiting hours.
B. Provide a clock and calendar in the patient's room in the patient's sight.(1, 3, 5-7, 16)
Notes added to the intervention: it is important to keep track of whether the clock is working and the time and date are correct.
C. In consultation with the patient's family, take care of the presence of familiar objects in the patient's room like own pillows, pictures or family photographs.(3, 8, 16) Let the patient watch television, listen to preferred music or read the paper or a magazine. (7, 17, 18)
Notes added to the intervention: if necessary let the family bring visual or auditory media from home (labeled with a name). It is important to follow the hygiene rules and have availability of WIFI.

D. Facilitate regular visits from family and friends. Give the family a letter to explain preventive measures like reorientation and the presence of family or friends.(3, 6)
Notes added to the intervention: provide wide visiting hours. Important is to inform the family about the care, treatment and rest moments of the patient and when the specific consultation meetings with healthcare staff are planned. Make clear arrangements about who may visit the patient and how many and how long visitors are allowed. Translate the letter into different languages.

E. Discuss with patient's next of kin how to call the patient (use of the first or last name). (7)
Notes added to the intervention: this subject might be part of the admission interview and should be documented in the patient's file and on the board in his room (see intervention A).

F. To get to know the patient his/her family and nurse compile a poster containing information about the patient's preferred calling name, which devices the patient is using to support vision/hearing, what the patient does at home to promote sleep, favorite music, television programs, books, and hobbies, and other things important to the patient.

G. Orient the patient's bed so they can perceive daylight/darkness (8) and provide appropriate lighting fitting the time of the day.(5) Place patients with a long ICU length of stay in the rooms with most daylight.
Notes added to the intervention: during the day time bright light, in the course of the evening dim the light and during the night as dark as possible. Decisive in the possibilities to be able to execute this intervention is the construction of the ICU.

H. Ensure appropriate use of glasses(contact lenses) and hearing aids.(16)

I. Ensure daily during the day shift that the patient is provided with simple and short information about the ward, hospital (i.e., hospital name, ICU length of stay), reason for hospitalization, and their illness progression (e.g. concerning diagnostic and therapeutic measures).(1, 7, 8)
Notes added to the intervention: it is important to provide uniform information (registered in the patient's file). The nurse should also ask the patient what he or she already knows. Based on their own discretion nurses can repeat the information.

At least every shift:

J. Stimulate the patient's orientation as part of the daily routine by asking or explaining them what day is it and where they are.(1, 7, 8)

K. Health care professionals explain to the patient who they are, and what their role is, answer the patient's questions and discuss the patient's concerns whenever necessary.(2, 5, 6)

Preliminary cognition training protocol:
Aim: to minimize/avoid cognitive decline.

Cognitive training will be described in the article describing the pilot of cognitive training.(19)

- Digit span: to train attention and short term memory
- Digit game: to train selective attention and (verbal) working memory
- Memory task: to train attention, working memory and long-term memory
- Symbol searching: to train speed of information processing using visual perception and selective attention
- Digit cancellation task: to train selective attention and visual perception
- Blocks task: to train selective attention and (visual) working memory
- First and second names: to train speed of daily life memory
- Executive functioning: to train working memory and attention
- Bells test: to train selective attention
- Picture guess: to train reasoning and working memory
- Difference searching: to train selective attention and working memory

4 Immobility
Aim: to improve patients' functional mobility in the ICU and to stimulate patients' cognition.

A. With the exception of contra indications: optimize ICU patients' sedation (pursue RASS 0) to permit (active) physical therapy, while retaining their comfort.(20)
   Notes added to the intervention: for this stimulation of the day- and night rhythm is important.
B. Reduce pain and fear as a hampering factor for mobilization, by taking care of adequate analgesia and proper guidance of the patient.
C. Physical therapy or mobilization supported by nurses should be performed at least once daily.(6, 16, 20, 21).
   Notes added to the intervention: whenever possible more often.
D. With the exception of contra indications: patients who are unresponsive due to coma (RASS -3/-4/-5), who are at risk for contractures, will receive passive motion exercises for all their limbs.(21) In addition, their position in bed should be changed every three to four hours to prevent the occurrence of pressure ulcers.(6) When patients are able to interact (RASS > -3 and < +2), physical therapy can consist of active (independent) exercises while the patient is lying on his back. When the patient tolerates these exercises the therapy can be extended to bed mobility activities, including upright sitting, sitting balance activities and exercising on a cycle movement device. These activities can be followed by participation in activities of daily living and exercises

that encourage increased independence with functional tasks (e.g. sit-to-stand transfers from bed to chair), and finally pre-gait exercises and walking (if necessary with mechanical ventilation). Progression of activities should depend on patient tolerance and stability.(21, 22)

E. Whenever feasible, nurses and instructed family should initiate, encourage and remind patients to mobilize early or do motion exercises multiple times a day.(1, 4, 5, 8-10) In addition, nurses stimulate active involvement during daily care activities.
Notes added to the intervention: the physical therapist plays a stimulating and informing role in this.

F. To promote and facilitate mobilization: the location of central lines and tubes should allow mobilization (preferably not in the groin). Daily evaluation of the necessity of immobilizing equipment (e.g., central lines, tubes, bladder catheters, or physical restraints). This equipment should be removed whenever possible.(1, 6) If necessary central lines, tubes or catheters are temporarily disconnected or blanked off. In consultation with the patient's family fixation can be disconnected in their presence.
Notes added to the intervention: presence of family is stimulated.

G. Per patient clear goals targeting mobilization are set and registered in the patient's medical record. In addition, multi disciplinary consultation takes place to take care of the right timing of physical therapy regarding sedation and the day program.
Notes added to the intervention: it should be known what mobilization is allowed and/or if the patient needs any devices for security reasons like a collar, corset or plaster helmet. Whenever possible the patient is informed about this and receives the necessary instructions.

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for web-only publication

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CHAPTER 6

Feasibility of cognitive training in critically ill patients: A pilot study

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Am J Crit Care. 2018;27(2):124-135

Abstract

Background: Delirium occurs frequently in the intensive care unit and is associated with detrimental consequences. Cognitive training is a promising nonpharmacologic, preventive intervention, but it is unknown whether cognitive training is feasible for patients in intensive care units.

Objectives: To examine the feasibility for both the patients and nurses of using cognitive training exercises for intensive care unit patients.

Methods: A pilot study of a set of cognitive training exercises in a large, academic intensive care unit. Feasibility of the exercises, operationalized as practicability and burden for both the ICU patient and the nurse, was tested using Likert scales and open-ended questions, patients' vital signs, and time investment.

Results: In total, 75 ICU patients were included. During the first round, 11 exercises were separately tested by nursing researchers in 44 cooperative patients (50% with delirium). Four exercises were evaluated as burdensome and were excluded. Vital signs did not alter during execution. In a second round, the remaining exercises were tested in 31 patients (52% with delirium) by their attending ICU nurse. All exercises were rated as practicable and not burdensome by the patients and the nurses. Total time investment per exercise was median 4.5 [interquartile range; 3.0-5.0] minutes.

Conclusion: Cognitive training exercises used in this study were feasible for intensive care unit patients (including cooperative patients with delirium) and their nurses. More research is needed to determine the clinical effect of the exercises on delirium outcome.

Introduction

Delirium is defined as an acute brain dysfunction, characterized by a disturbance in attention, awareness, and cognition. It fluctuates during the course of the day and is caused by an underlying medical condition.(1) Delirium occurs frequently in the Intensive Care Unit (ICU), burdening around one-third of the patients.(2) It is associated with several adverse short-term consequences, including prolonged mechanical ventilation, increased length of stay in the ICU and hospital, and an increased mortality rate.(2, 3) In addition, patients who were delirious during ICU admission were significantly more likely to suffer from cognitive impairment in the long term.(2, 4-6) Because of these sequelae, the use of strategies to prevent ICU delirium is paramount.

Current delirium management guidelines (7, 8) emphasize prevention by performing nonpharmacologic interventions, in which ICU nurses may play a central role. In studies of non-ICU patients, a multicomponent nonpharmacologic intervention (MCI) program focusing on modifiable delirium risk factors has had positive effects on delirium. These modifiable risk factors include cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment.(9-11) In ICU patients, results of studies targeting specific parts of the MCI program separately, including mobilization,(12, 13) reorientation,(14) and sleep,(15) have shown beneficial effects. Although the use of an MCI program to prevent ICU delirium seems promising, the evidence for the effects of such a program on delirium-related ICU outcomes is insufficient.(16-18) Therefore, additional research is necessary to study the effects of an MCI program tailored to ICU patients with delirium.

In preparation for a randomized, controlled, nonpharmacologic delirium-prevention trial,(19) a draft MCI program was developed. To determine the feasibility of the program in ICU patients, a Delphi study was performed to determine experts' opinion and to achieve group consensus on the feasibility and completeness of the MCI program in ICU patients. Subsequently, a feasible MCI program was developed.(20) However, no consensus was reached on the MCI part 'cognitive training', which consists of daily cognitive training exercises to maintain cognitive function.(20, 21) To cover different cognitive domains that are affected by delirium,(1) cognitive training is focused on skills in the area of attention, different forms of memory, and executive functioning to stimulate the patients' cognitive processing.(22) In view of the unclear feasibility of cognitive training exercises in critically ill patients, we evaluated the practicability and burden of cognitive training exercises for critically ill patients and the nurses caring for them.

Methods

Design and study population

A prospective, multiphase pilot study was performed between August 2014 and August 2015. Patients admitted to the ICU of a large university medical center in the Netherlands were enrolled. Inclusion criteria were age at least 18 years, a surgical, medical or trauma admission diagnosis, and a Richmond Agitation Sedation Score (RASS)(23) from -2 to +1. Patients were approached for consent when they were in a stable respiratory and hemodynamic state. Patients were excluded if they had an expected ICU stay of less than 1 day, or were unable to be reliably assessed for delirium because of an inability to understand Dutch, severe mental disability, serious receptive aphasia, or serious auditory or visual disorders.

Ethical considerations

This study was conducted according to the principles of the 2013 revised World Medical Associations' Declaration of Helsinki and the Medical Research Involving Human Subjects Act. This study was evaluated by the Medical Research Ethics Committee Arnhem-Nijmegen region (No. NL2013/567). Because a certain degree of cognitive training exercises is already offered in an unstructured way to ICU patients in our daily practice, the need to obtain written informed consent was waived. Nevertheless, all participants were informed and gave their verbal or nonverbal consent before participation.

Sampling

Because the aim of the study was to determine feasibility, no formal power calculation was performed. The cognitive training exercises were tested separately, which is according to the anticipated daily practice. We intended to include at least 2 delirious and 2 patients who were not delirious for the test of each exercise during each round, which resulted in including 44 patients during the first round. This number was based on the assumption that each of the eleven cognitive training exercises needed to be tested at least four times, with equal distribution of delirious and nondelirious ICU patients to enable a reliable conclusion. The sample size of the second round was based on the same assumption.

Data collection and procedures

In order to detect delirium, all patients were screened using the validated Confusion Assessment Method (CAM)-ICU,(24) which is part of the daily ICU care.(25) In the first round, nursing researchers (AW, PR, MvdB) executed 1 of the 11 cognitive training exercises per patient. Each exercise was tested for feasibility in 4 ICU patients. In the second round, a similar procedure was followed for the remaining exercises, but instead of the researchers, the attending ICU nurse was asked to conduct the cognitive training exercise

with the patient and evaluate its feasibility for the patient and for the nurse. The execution of a cognitive training exercise by the ICU patient and nurse is the anticipated daily practice; therefore, this method also provided insight in the health care workers' experiences and was expected to be useful for future implementation purposes.

Feasibility of the cognitive training exercises was defined as the degree to which the exercise is rated as practicable and not burdensome. Practicability and burden were evaluated by having patients and nurses use a 5-point Likert scale to answer questions about practicality, clarity, difficulty, burden, exhaustion, and the fun factor. For example,: for burden, a score of 1 represented 'very burdensome', a score of 3 'neutral', and a score of 5 'not burdensome at all'. In addition, after each question, the respondents were asked via open ended questions, to identify the motivation for their response.

After the first round the data were analyzed and exercises were selected based on their degree of practicality and burden. Cognitive training exercises only progressed to round two when deemed practical and not burdensome for the patients, operationalized as a median rank higher than three (neutral). In addition, during the first round, to assess the physical burden of the cognitive training exercises, vital signs of each patient, consisting of the mean arterial pressure, heart rate, respiration rate, and blood oxygen saturation, were registered directly before, during, and after the exercise. A significant change in vital signs would result in exclusion of the exercises after the first round. During both rounds, the time investment was registered. The allocation of an exercise per patient took place randomly during both rounds, stratified for the presence of delirium.

Cognitive training exercises

The preliminary cognition training protocol was compiled by a multidisciplinary team of ICU nursing researchers (AW, PR, LS, MvdB), a clinical neuropsychologist (DB) and a critical care physician (PP) and was based on scientific literature (22, 26-31) and the expertise of the multidisciplinary team. The reason for choosing the 11 specific cognitive training exercises was their match with the different cognitive domains that are affected by delirium, including attention, memory and executive function (Table 1, e-Appendix 1and 2).(22) Orientation, another important domain affected by delirium, is already included as a separate protocol in the MCI program.(20) Besides the wish of the multidisciplinary team to target various skills, important considerations during the compilation of cognitive training exercises were the inclusion of different levels of difficulty and of recreational activities to allow the nurse to fit the exercises to the capabilities and personal interests of ICU patients and to increase the profitability of cognitive training.(22, 26)

Testing procedures

Patient enrolment took place during day shifts between 8:00 AM and 4:00 PM. Effort was made to minimize disturbance while executing the cognitive training exercise with the patient. All awake (RASS score, -2 to +1)(23) and cooperative patients (nondelirious and delirious) were approached for participation by 2 researchers (combinations of AW, PR, MvdB). The aim of the study was explained, and it was emphasized that the goal was execution of the exercise rather than achieving a high score. After receiving verbal or non-verbal consent, 1 training exercise was drawn randomly from two bundles of envelopes (1 for delirious and 1 for non patients without delirium), which contained each training 2 times. The training exercises (Table 1) were executed using cleanable plasticized cards in A5 format (210mm x 148 mm or [8.27 x 5.83 in]) containing a short instruction (e-Appendix 1). The attending ICU nurses did not receive additional training to conduct the exercises with the patients.

During the exercise, the use of visual and hearing aids, adequate lightening, and a proper posture of the patient in bed were taken into account. The execution of the exercise was tailored to the patients' limitations (e.g. patients receiving mechanical ventilation were asked to point or answer nonverbally, according to their functional level).

As the cognitive training exercise started, a short explanation was given. The exercise was performed for a maximum of 5 minutes or until patients expressed verbal or physical signs of refusal or fatigue. Afterwards, the feasibility was systematically assessed using predefined evaluation forms (e-Appendix 3). The total duration of the execution and evaluation took between 10 and 15 minutes.

Table 1 Summary of preliminary cognitive training exercises

Exercise	Targeted cognitive function
Digit span	Attention and working memory
Digit game	Selective attention and (verbal) working memory
Memory task	Attention, working memory and long-term memory
Symbol searching	Speed of information processing using visual perception and selective attention
Digit cancellation task	Selective attention and visual perception
Blocks task	Selective attention and (visual) working memory
First and second names	Daily life memory
Executive functioning	Working memory and attention
Bells test	Selective attention and visual perception
Picture guess	Reasoning and working memory
Difference searching	Selective attention and working memory

Data analysis

Baseline characteristics of both the ICU patients and nurses; duration of the training, including preparation; and questions regarding practicability and burden requiring responses on a 5-point Likert scale were analyzed using descriptive statistics. It was decided beforehand that a median score higher than 3 (neutral) per cognitive training exercise in the first round indicated feasibility and lack of burden for the patient, and these exercises would advance to the second round. The answers to the open-ended questions (e-Appendix 3) were used to determine the need for any modifications (e.g. textual, visual) of the remaining cognitive training exercises.

Continuous and normally distributed variables are described as mean and standard deviation. Non-normally distributed data are given as median and interquartile range (IQR), and categorical values as number and percentage. The patients' vital signs (ie., mean arterial pressure, heart rate, respiration rate, and blood oxygen saturation) were analyzed using one-way analysis of variance (F-test) for normally distributed data and using the Kruskal-Wallis test by ranks (H-test) for data that were not normally distributed. The feasibility scores of delirious and nondelirious patients were compared by using the Mann-Whitney U-test. SPSS software, version 22 (IBM) was used for statistical analyses. Statistical significance was defined as a P less than .05.

Results

Over two rounds, in total 75 ICU patients were included. Two patients were excluded from analysis and replaced: a patient fell asleep within 30 seconds and was therefore unable to execute the exercise, and 1 patient refused cooperation because she already experienced high mental burdening due to her sickness. During round 1, 11 cognitive training exercises were tested in 44 patients of whom 50% were delirious. Their mean age was 69 (SD, 10), and 29 (66%) were male. The median length of ICU stay (LOS ICU) before the start of the exercises was 6 (IQR, 2-18) days. During round 2, the remaining 7 cognitive training exercises were tested in 31 patients of similar mean age, and with similar LOS-ICU. (Table 2) Of these 31 patients, 16 (52%) were delirious. The mean age of the attending ICU nurses was 37 (SD 11) and five (16%) were male. (Table 2)

Table 2 Participant characteristics

ICU patients	**Round 1 N=44**	**Round 2 N=31**
Age in years, mean (SD)	69 ± 10	68 ± 10
Male, N (%)	29 (66)	15 (48)
Admission type, N (%)		
Surgical	24 (55)	22 (71)
Medical	20 (46)	8 (26)
Trauma	0 (0)	1 (3)
APACHE II score, mean (SD)	22 (6)	20 (7)
Mechanical ventilation, N (%)	23 (52)	9 (29)
E-PRE-DELIRIC score (41), mean (SD)	25 ± 17	20 ± 16
PRE-DELIRIC score (42, 43), mean (SD)	28 ± 14	28 ± 13
RASS score, N (%)		
RASS -2	5 (11)	0 (0)
RASS -1	12 (27)	8 (26)
RASS 0	26 (59)	22 (71)
RASS +1	1 (2)	1 (3)
CAM-ICU positive, N (%)	22 (50)	16 (52)
ICU Length of stay in days at pilot execution, median [IQR]	6 [2-18]	5 [2-9]
ICU-nurses		**N=31**
Age in years, mean (SD)		37 ± 11
Male, N (%)		5 (16)
Experience as ICU certified nurse, N (%)		
None (= student ICU nurse)		5 (16)
Yes < 2 years		7 (23)
Yes < 5 years		4 (13)
Yes < 10 years		5 (16)
Yes > 10 years		10 (32)

Round 1

Execution of cognitive training exercises by researchers

The total time investment for the cognitive training exercises by the researchers was median 1.0 (IQR, 0.5-1.0) minute to explain the exercise to the patient and 2.5 (IQR, 2.0-3.0) minutes to conduct the exercise.

Patients' experiences

The median scores given for practicality and burden were between 2.5 and 5.0. Four exercises did not receive a median score higher than 3.0 (neutral) from the ICU patients, indicating that these exercises posed a burden on them. Therefore, these exercises were excluded (Appendix 4), leaving 7 exercises in the cognitive training exercise set. (Table 3) The vital signs of the patients before, during, and after execution of any of the training exercises did not change significantly; thus they did not influence which of the exercises proceeded to round 2. (Table 4)

Round 2

Execution of the cognitive training exercises by the attending ICU nurse

The time investment for the execution of a cognitive training exercise by the attending ICU nurse during round 2 was measured in time needed for explanation to the patient in a median 2.0 (IQR, 1.0-2.8) minutes and time needed for the execution of the exercise in a median 4.5 (IQR, 3.0-5.0) minutes. The nurses rated the remaining 7 cognitive training exercises as practicable and not burdensome for ICU patients; the median scores were between 3.5 and 4.0. (Table 3)

On the basis of the open-ended questions of pilot round 2, minor textual adjustments were made to the written explanations and examples provided with the exercises to enhance clarity and optimal execution.

Patients' experiences

The patients' median scores for the remaining 7 cognitive training exercises were between 3.3 and 5.0 indicating that these cognitive training exercises were practicable and not burdensome. (Table 3)

Delirious vs. nondelirious patients

A comparison was made between the rates given by delirious and nondelirious patients for the feasibility of the cognitive training exercises. In round 1, the reported feasibility rates differences between the 2 groups. Although scores for clarity, fun factor, and general appreciation were similar, delirious patients experienced more difficulty, burdening, and exhaustion compared with nondelirious patients. After the adjustments were made, these differences disappeared, and the final set of training exercises was rated as feasible in round 2 by both delirious and nondelirious patients. (Table 5)

Table 3 Median scores practicability and burdening per exercise

Training	Round 1		Round 2	
	ICU patient	Researcher	ICU patient	ICU nurse
Digit span	4.0 [3.3-4.8]	4.0 [4.0-4.0]	5.0 [3.0-5.0]	4.0 [2.5-4.0]
Digit game	4.0 [1.0-4.0]	4.0 [2.3-4.8]	4.0 [3.0-4.0]	4.3 [3.6-4.9]
Memory task	4.5 [4.0-5.0]	4.5 [3.6-5.0]	4.5 [4.0-5.0]	4.3 [3.3-4.9]
Symbol searching	3.0 [2.0-4.8]	4.3 [4.0-4.9]	*Excluded after round 1*	
Digit cancelation task	3.0 [2.3-4.5]	4.0 [3.1-5.0]	*Excluded after round 1*	
Blocks task	4.5 [4.0-4.5]	4.5 [3.5-5.0]	4.0 [4.0-4.0]	4.0 [2.3-4.3]
First and second names	3.0 [1.5-3.8]	4.3 [3.6-4.0]	*Excluded after round 1*	
Executive functioning	5.0 [4.0-5.0]	4.0 [3.5-5.0]	4.5 [3.5-5.0]	4.0 [3.0-5.0]
Bells test	4.5 [2.5-5.0]	4.8 [4.1-5.0]	3.3 [2.1-3.8]	3.8 [3.1-4.0]
Picture guess	2.5 [1.3-4.5]	3.5 [2.3-4.8]	*Excluded after round 1*	
Difference searching	3.5 [2.3-4.8]	3.5 [2.5-3.5]	5.0 [4.0-5.0]	3.5 [2.0-4.3]

Practicability and burdening were scored using 5-point Likert scale questions:
1 = very burdensome, 2 = burdensome, 3 = neutral, 4 = not burdensome, and 5 = not at all burdensome

Table 4 Vital signs round 1

	Before training N=44	During training N=44	After training N=44
MAP, median [IQR]	83 [75-98]	88 [74-101]	84 [76-99]
Heart rate, mean (SD)	87 ± 15	88 ± 15	87 ± 16
Respiration rate, mean (SD)	23 ± 6	23 ± 6	22 ± 6
SpO2, mean (SD)	98 ± 2	98 ± 2	97 ± 2

All differences were found to be non- significant (p>0.10)

Table 5 Differences between nondelirious and delirious patients

	Round 1			Round 2		
	Delirious	**Nondelirious**	***p-value***	**Delirious**	**Nondelirious**	***p-value***
Difficulty[1]	3/5 [1-4]	4/5 [3-5]	<0.001	5/5 [4-5]	4/5 [4-5]	0.87
Burdening[1]	2/5 [1-4]	5/5 [3-5]	0.01	4/5 [2-5]	4/5 [4-5]	0.40
Exhaustion[1]	2/5 [1-4]	5/5 [3-5]	<0.001	4/5 [2-5]	4/5 [4-5]	0.29
Clarity[2]	4/5 [4-5]	5/5 [5-5]	0.09	4/5 [4-5]	5/5 [4-5]	0.32
Fun factor[2]	4/5 [4-5]	4/5 [4-4]	0.69	4/5 [3-4]	3/5 [3-4]	0.98
General appreciation[3]	7/10 [7-8]	7/10 [6-8]	0.70	7/10 [7-8]	8/10 [7-9]	0.17

Items were scored using 5 or 10-point Likert scale questions:
[1] 1 = very much, 2 = somewhat, 3 = neutral, 4 = not, and 5 = not at all
[2] 1 = not at all, 2 = not, 3 = neutral, 4 =somewhat, and 5 =very much
[3] 1 =not at all, 10 =Very much
Numbers are expressed as median [IQR]

Discussion

The finding from this study indicate that providing cognitive training exercises to critically ill patients is feasible for ICU patients and for ICU nurses. After 2 pilot rounds, 7 exercises were rated as practicable and not burdensome. In contrast to earlier studies,(21, 32) we included both delirious and nondelirious critically ill patients. Of interest, we show that cognitive training is feasible even in cooperative delirious patients. We believe that it is necessary to execute cognitive training exercises with delirious and with nondelirious patients, because evidence suggests that these exercises not only might prevent delirium but may also shorten delirium duration through cognitive stimulation.(26)

It is generally assumed that preventing delirium and reducing delirium duration in the ICU are relevant for clinical ICU practice to avoid the negative consequences related to delirium.(2) Interestingly, we found that although the execution of the initial set of cognitive training exercises was more difficult for ICU patients with delirium, after the exclusion of 4 burdensome exercises, these differences were no longer present. Moreover, patients with and those without delirium enjoyed doing the cognitive training exercises, which was expressed in similar scores in perceived appreciation and in fun factor. So, the 7 remaining cognitive training exercises not only may be executed despite a positive delirium assessment, ICU patients also enjoy them.

With recent advances in critical care medicine, more patients recover from critical illness;(33) therefore, it is paramount to focus on the stimulating not only the patients' physical function but also their cognitive function.(34) It appears plausible that by providing cognitive training exercises, we may be able to reduce or prevent cognitive decline during and after critical illness.

This study provides a feasible cognitive training protocol to study the effects of cognitive training exercises, as part of an MCI program, on ICU delirium. The complete cognitive training protocol, consisting of 7 exercises, will be included in the MCI program, to enable stimulation of the different cognitive domains affected by delirium: attention, memory, and executive function. In addition, the protocol allows nurses to choose an exercise fitting the capabilities and personal interest of the specific ICU patient. Our recommendation is to execute these exercises twice daily for five minutes each with the ICU patient, and to provide an explanation about the goal to emphasize that the execution of the exercise is far more important than obtaining a high score.(19)

Of interest, when shown effective, cognitive training exercises also can be conducted with ICU patients by their loved ones. This arrangement is valuable not only because the exercises are practicable and easy to execute but especially because of the added value of the involvement of loved ones in ICU patients' care, which is advocated by many societies and committees worldwide.(35-37) This involvement empowers the patients' loved ones and enables the ICU nurses to invest their time in other components of patient care.

Strengths and limitations

This study was designed and conducted as a pilot study and was focused on several important key features of delirium, including disturbed attention, awareness, and cognition.(1) We incorporated a fairly large sample of delirious and nondelirious patients, to whom we randomly assigned the different cognitive training exercises. This study was executed as extension of a earlier performed Delphi study (20) in which the experts did not reach consensus on cognitive training part of the MCI. Therefore, pilot testing the feasibility of cognitive training exercises in ICU patients was a necessary step to prepare for a future randomized, controlled, nonpharmacologic delirium prevention trial in which the effects of the MCI program on delirium will be assessed.(19, 38) Based on the results of this pilot study, we think a proper and well-substantiated decision regarding the feasibility of providing cognitive training exercises in ICU patients can be made, and these selected cognitive training exercises may now be included in the MCI program.(19, 20)

The results of this study should be interpreted in view of some limitations. Patients were recruited following purposive sampling based on a RASS score of -1, 0 or 1 and willingness to cooperate. Although this is a form of nonprobability sampling, which is likely to result in selection bias, purposive sampling, as we used during this study (i.e. inviting a broad sample of patients who are available and meeting the inclusion criteria over fixed time) enabled selection of a balanced sample of critically ill patients, thus reducing the potential bias.(39, 40) Although this study was a single-center study, it was performed in a large academic hospital, with 4 different ICU units equipped to treat adult patients with surgical, trauma, medical, as well as cardiothoracic conditions, which may improve the generalizability of the results. In our view, both the consecutive sampling and the inclusion of patients with different diagnoses provided a representative sample for this pilot study.

Conclusion

We showed that the use of cognitive training aimed at the minimization of cognitive decline and, ultimately, the preventing and reducing delirium in critically ill patients is feasible for delirious patients and nondelirious patients in the ICU, as well as for ICU nurses. As a next step, research is needed to determine the clinical effect on ICU-related delirium of a MCI intervention program including cognitive training.

Acknowledgments

We thank Lisa van Ede for data management and all participants for their contributions and time in taking part in this study. This study was performed in the Department of Intensive Care Medicine, Radboud University Medical Center, Nijmegen, The Netherlands.

Financial disclosures

None declared.

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Online data supplement

e-Appendix 1 Cognitive training exercises

Digit span: exercising attention and short term memory.

Pick a card containing 4 sets of 2 digits, 3 digits or 4 digits. Start with the combinations of 2 digits, increase the number for a higher level of difficulty.

Example:
The attending nurse picks one of the options below (B: 5-2-8), and reads it to the patient. The patient is asked to point to the right combination.

A: 5 - 6 - 2
B: 5 - 2 - 8
C: 8 - 2 - 3
D: 2 - 5 - 9

The patient may point or tilt his head when the nurse points at the right answer. When not mechanically ventilated, the digits may also be vocally repeated.

A: 1 - 9
B: 1 - 7
C: 9 - 1
D: 2 - 3

A: 5 - 6 - 2
B: 5 - 2 - 8
C: 8 - 2 - 3
D: 2 - 5 - 9

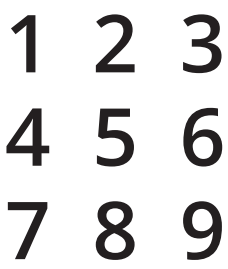
A: 3 - 6 - 1 - 8
B: 6 - 3 - 8 - 4
C: 6 - 3 - 4 - 1
D: 1 - 6 - 8 - 4

Digit game: exercise for enhancement of the selective attention and the (verbal) working memory.

The patient is shown the digits below on a separate card:
1 2 3
4 5 6
7 8 9

The nurse reads three digits out loud, which the patient is asked to repeat (verbally or by pointing at) the right numbers.

This exercise may be shortened or lengthened to decrease or increase difficulty.
Also, the digits may be repeated chronologically or in reverse order.



Memory task: exercise of the attention, working memory and long-term memory

Ask the patient to name the days of the week chronologically (automatism) starting on Sunday. When successful also ask the patient to do it in reverse order (challenge), starting at Sunday

Variation:
Vary the weekdays with months, starting at December, chronologically, and in reverse order.
Challenge: Use the Alphabet.

When the patient is unable to speak: use the cards, and let the patient point out the right order.

oktober	augustus
juli	april
mei	november
januari	juni
maart	september
december	februari

woensdag
zondag
vrijdag
dinsdag
zaterdag
maandag
donderdag

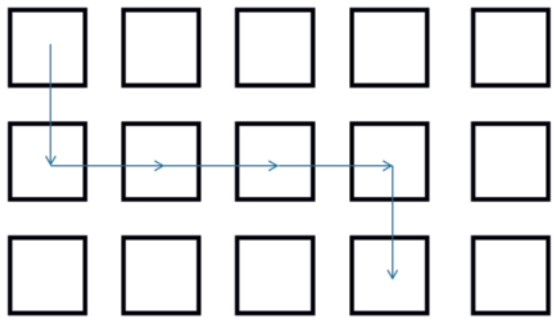
L	G	A	D	W
T	Z	M	J	O
S	C	E	Q	N
Y	P	F	U	X
K	H	B	V	R
I				

Blocks test: exercise for the enhancement of the selective attention and visual working memory.

The patient is shown a card with twenty blocks. The attending nurse points out a route, after which the patient is asked to repeat the route that was shown.

The exercise can be made more challenging by increasing the number of blocks of the route, or by asking the patient to repeat the route in reverse order. Maximum exercise time: 3 minutes.

Easy: 1 to 4 blocks.
Challenge: 5 blocks or more/reverse order.

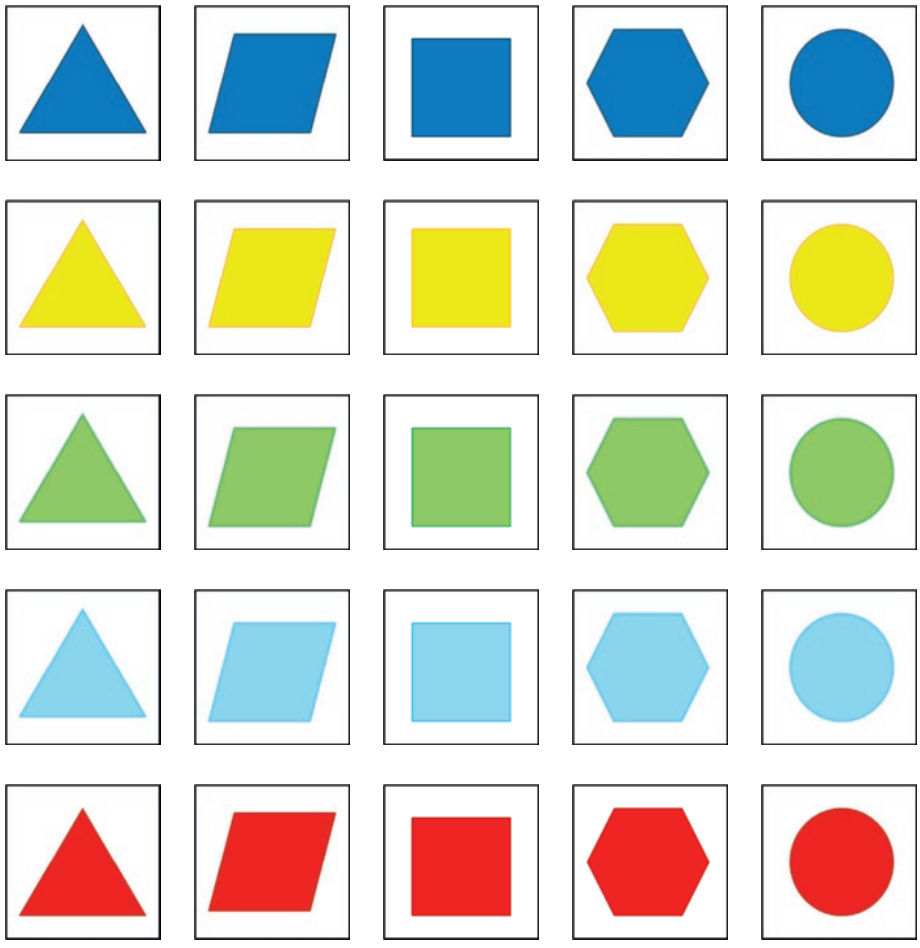


Executive functioning: for exercising the working memory, attention and purposive functioning.
The attending nurse gives the patient different tasks during a maximum of 3 minutes.

Easy task: sorting items based on color, forms or both.

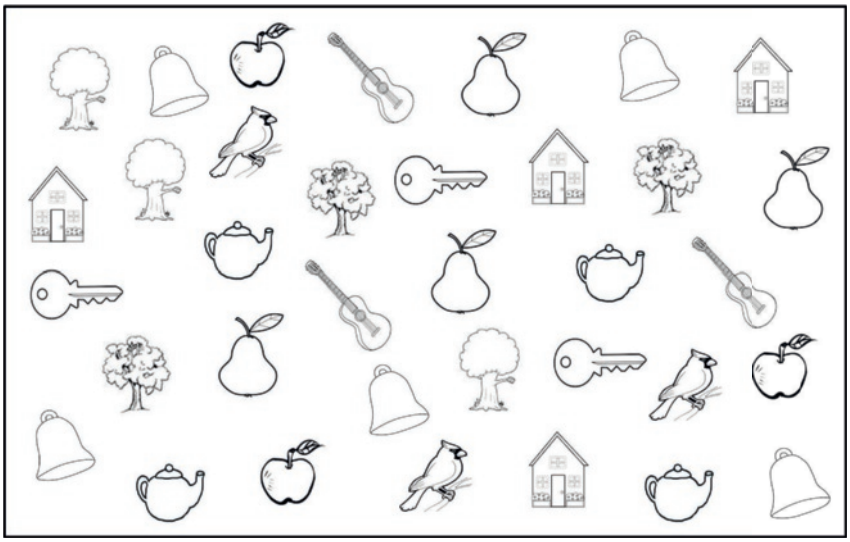
Challenge task: Calculating change.
Examples:
When I buy some fruit, and it's prices €/$ 3,- and I pay 5, what's my change?

When the fruit is discounted 10%, how much change would I get?
(price will be 2.70, so the change will be 2.30)



Bell's test: for exercising the visual selective attention**.**

Use the card below: Ask the patient to point out the bells.
For variation, the other figures may also be used, or the patient may be asked to tell you which figures are on the top (bottom, side) line of the card.



Difference searching

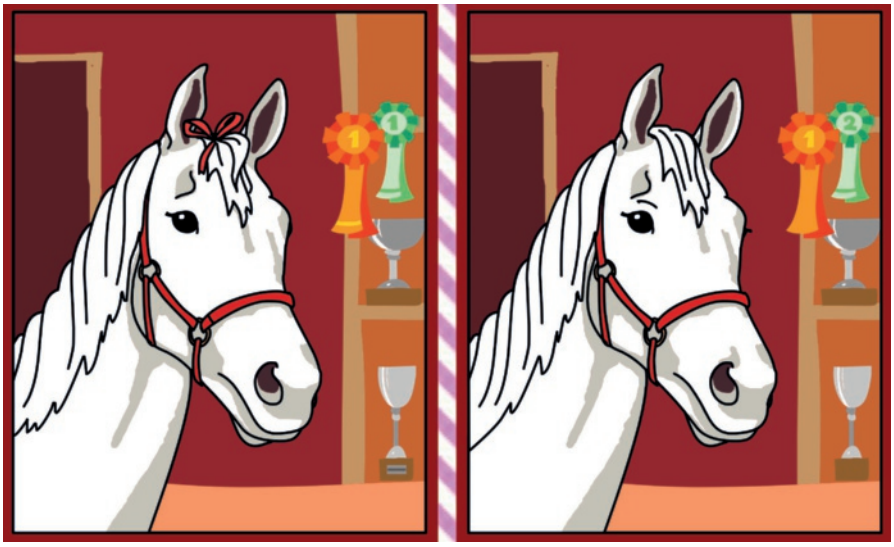
The patient receives a card with one of the pictures below. The pictures contain 5, 6 or 10 differences. Limit the training to maximal 5 minutes.

Answers for the attending nurse

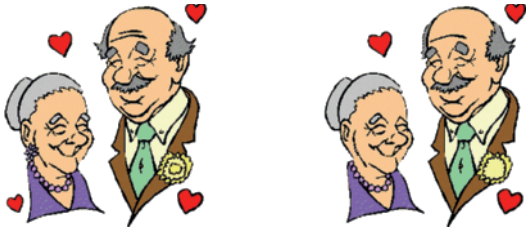
1	Sign U turn misses on the right Orange sign: RELOAD vs DETOUR Yellow sign in the middle Triangle sign: driver vs car Round white/black sign: Right car is upside down
2	Red hair elastic between ears Differences in neck hair Ranks in prizes 1-1 vs 1-2 Grey stripes on the bottom prize Hair lash between the ears
3	Heart left below Jewelry in left ear woman Woman: Eyebrow misses Bunch of hear misses on the left side of the man Wrinkle in forehead man Heart of yellow flower differs
4	Water drops left Nose differs Ear differs Eye differs Hair cap differs Different chest form Black band on swimming gear Stripe through left leg Stripe right above Thumb misses

1. **Find the 5 diffences:**

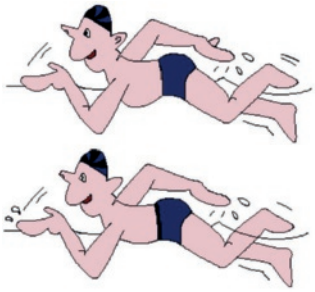
2. **Find the 5 diffences:**



3. **Find the 6 diffences:**



4. **Find the 10 diffences:**



e-Appendix 2 Standard operating procedure for execution of cognitive training exercises

Therapeutic-activities protocol
Aim: targeting the maintenance of cognitive function

The cognitive training exercises are provided to ICU patients with a RASS score of -1, 0 and +1. When the RASS score is lower then -1, only the orientation protocol will be applied. When the RASS score is above 1, actions should first be taken to achieve a RASS of +1 or 0.

The execution of each cognitive training exercise is described in detail in e-Appendix 1. Each cognitive training exercise will be tested for feasibility (practicability and burden) at least four times (2 delirious and 2 nondelirious patients); each time with a different patient. The exercise will be assigned at random to the patients.

RASS -5/-4	RASS -3/-2	RASS -1/0/+1	
No intervention	Orientation protocol	Orientation protocol	Easy
		Digit span	
		Digit game	
		Memory task	
		Symbol searching	
		Digit cancellation task	
		Blocks task	
		First and second names	
		Executive functioning	
		Bells test	
		Picture guess	Difficult
		Difference searching	

Practicability:
Definition: the degree in which the cognitive training exercise is rated as feasible.

- (5-point) Likert scale, for the ICU patient and for the ICU nurse to rate the practicability of the cognitive training exercise.
- Open questions for the ICU patient and for the ICU nurse to assess their opinion about the practicability of the cognitive training exercise.

Burden:

Definition: the degree in which the cognitive training exercise is experienced and rated as burdensome.

- (5-point) Likert scale, for the ICU patient and for the ICU nurse to rate the level of burden of the cognitive training exercise.
- Open questions for the ICU patient and for the ICU nurse to assess their opinion about the burden of the cognitive training exercise.
- Registration of vital signs direct before and after provision of the cognitive training exercise: mean arterial pressure (MAP), heart rate, respiration rate, blood oxygen saturation (SpO2).
- Time investment for ICU nurses (maximum duration of training: 5 minutes, including preparation/registration 10 minutes).

e-Appendix 3 Evaluation form

Important information for the patient: The process and the execution of the cognitive training exercise is important, not the result/score of the exercise! After finishing the exercise, the attending ICU nurse should first finish the questions for the nurse, before evaluating with the patient, to avoid bias.

Exercise							
Data PATIENT							
Date/time	**Age**	**Sex**	**Time admitted to the ICU**	**Ward**	**CAM-ICU score (+ / -)**	**RASS**	**Patient number**
Admission type	**Surgical / Medical / Trauma**						
Respiration	**Ventilator**	**No** **Yes: - Invasive** **- Non-invasive**			**Canulated** **Speachvalve**	**Yes/No** **Yes/No**	
Way of communication					**Open questions possible?**	**Yes/No**	
Other info							

Data ICU Nurse								
Age (years)	**Sex**		**Certified as ICU nurse - since**					
	M	**F**	**No**	**Yes**	**<2 years**	**<5 years**	**<10 years**	**>10 years**
Other info								

Burdening:

Definition: Extent to which the cognitive training exercise is judged as burdensome.

Open questions and 5-point Likert scale: for the nurse to assess the extent of burden.

Questions to the nurse

Time investment (Target: maximal duration of 10 minutes: 5 minutes execution including preparation time, 5 minutes registrations)

Preparation (minutes) Including CAM-ICU?	**.....** Yes/No
Time it took to explain the exercise to the patient (minutes)	
Execution of the exercise (minutes)	

- How burdening was the exercise for the nurse?

Very much	Somewhat	Neutral	Not	Not at all
1	2	3	4	5

Motivation (Time investment, preparation, patient related optimalization, cleaning, registration)

- How burdening is this exercise for the patient?

Very much	Somewhat	Neutral	Not	Not at all
1	2	3	4	5

Motivation

- How exhausting do you think is this exercise for your patient?

Very much	Somewhat	Neutral	Not	Not at all
1	2	3	4	5

Motivation

- Did the patient fall asleep during the exercise?

- Was the patient able to focus and keep attention the whole exercise?

Execution:

Definition: Extent to which the exercise is executable.

Open questions for the attending nurse:

Practicability:

- Please rate the executability of this exercise (1 (bad) -10 (excellent))

Motivation

- How understandable is this exercise for you as the attending nurse?

Not at all	Not	Neutral	Somewhat	Very much
1	2	3	4	5

Motivation

- How understandable does the patient rate the exercise to be?

Not at all	Not	Neutral	Somewhat	Very much
1	2	3	4	5

Motivation

- How difficult was this exercise to execute?

Very much	Somewhat	Neutral	Not	Not at all
1	2	3	4	5

Motivation

General questions for the patient about the cognitive training exercise:

- What are your feelings/opinion about cognitive training exercises? Why?

- General assessment of the exercise: (0 bad -10 excellent)

Burden:

Definition: Extent to which the patient feels burdened by the exercise.

Open questions for the patient:

- How burdensome do you rate this exercise?

Very much	Somewhat	Neutral	Not	Not at all
1	2	3	4	5

Motivation

- How exhausting do you rate this exercise?

Very much	Somewhat	Neutral	Not	Not at all
1	2	3	4	5

Motivation

- How much did you enjoy this exercise?

Not at all	Not	Neutral	Somewhat	Very much
1	2	3	4	5

Motivation

<u>Practicability</u>:
Definition: Extent to which the patient feels the exercise is executable.
Open questions for the patient:

- How do you feel about the executability of this exercise? Rate between 1 (bad) and 10

Motivation

- How understandable is this exercise for you?

Not at all	Not	Neutral	Somewhat	Very much
1	2	3	4	5

Motivation

- How hard was this exercise for you?

Very much	Somewhat	Neutral	Not	Not at all
1	2	3	4	5

Motivation

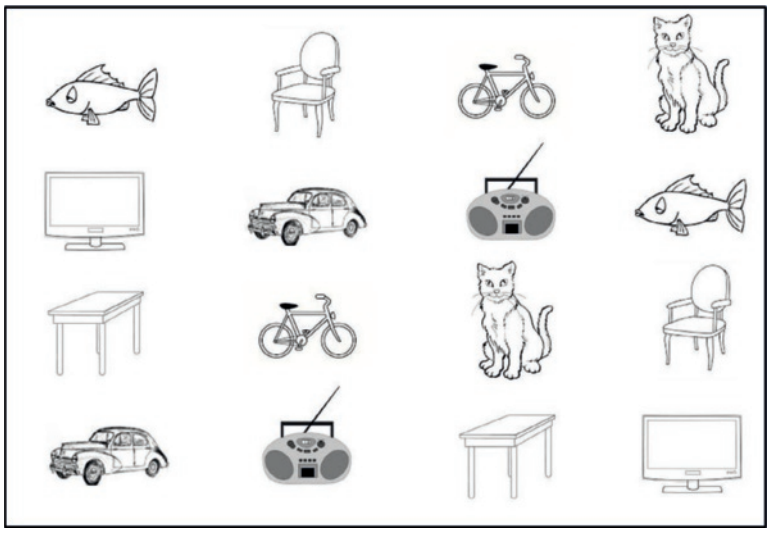
e-Appendix 4 Excluded cognitive training exercises after round 1

Symbol searching: training exercise to handle information using visual perception and selective attention.

The patient receives a card which contains multiple pairs of symbols. The patient should find as many pairs as possible in 2 minutes time.

Variations in difficulty:
Easy: 16 clearly different symbols (8 pairs).
Medium: 24 partly related symbols (12 pairs).
Challenge: 24 partly related symbols (12 pairs): pointing out which pairs are related (table-chair, horse and cow etc.).

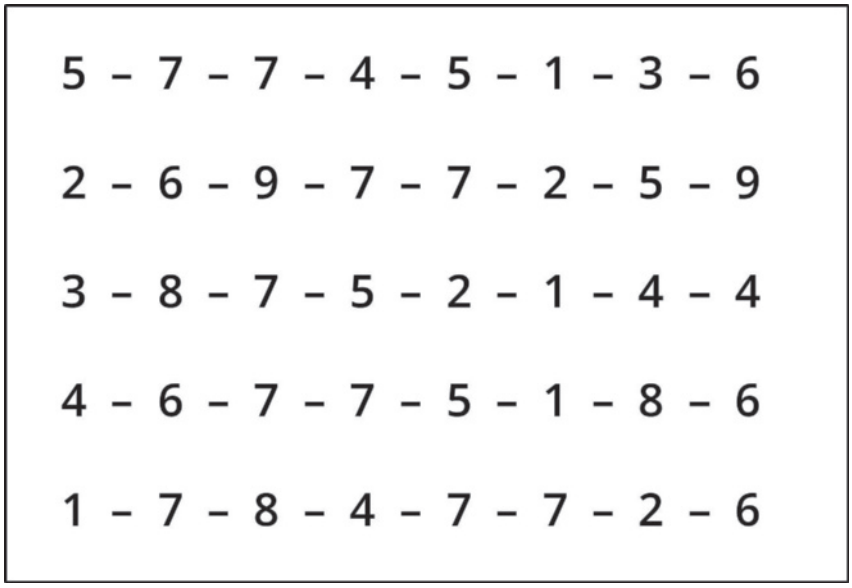
The patient may point out or vocally identify the right combinations. When deemed infeasible, the nurse may point out the symbols, to which the patient may nod.



Digit cancelation task: for exercising selective attention and visual perception.

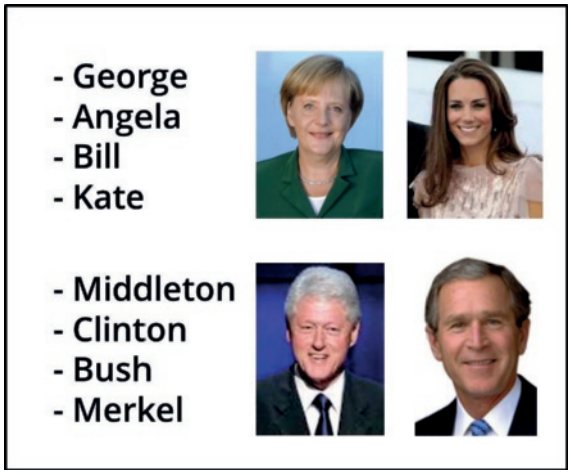
A card containing a matrix consisting of multiple digits is provided to the patient. During 2 minutes the nurse asks the patient to point out combinations of digits (7-7).

Easy combinations of two digits.
Challenge: Increasing the number of digits, making combinations which are displayed in reversed order.



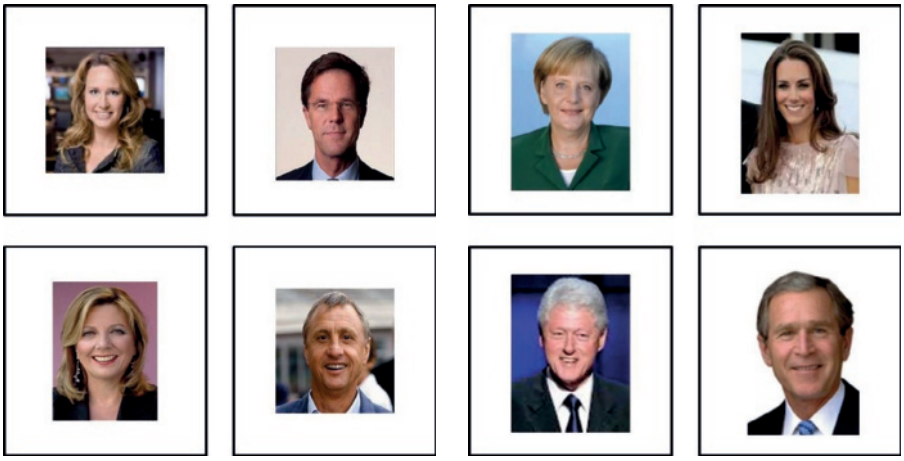
First and second names: for exercising the learning ability in daily life

In this exercise patients are asked to remember First and second names of celebrity's and other well known people. Patients are presented the first and second names, and are asked to remember for several minutes.



Patient chart

- Helga - Loretta - Mark - Johan - Schrijver - Rutte - Cruijff - Van Leur	- George - Angela - Bill - Kate - Middleton - Clinton - Bush - Merkel



Picture guess: for exercising reasoning and working memory

In this exercise the nurse chooses a location or an activity from a card. The patient may only ask questions which can be answered with yes/no, and by eliminating possibilities should be able to find out which location or activity is described.

The exercise should last no longer than 5 minutes. This exercise is only suitable for patients who can speak or have sufficient writing possibilities.

CHAPTER 7

The impact of nUrsiNg DEliRium Preventive INterventions in the Intensive Care Unit (UNDERPIN-ICU): A study protocol for a multicentre, stepped wedge randomized controlled trial

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Int J Nurs Stud. 2016;68:1-8

Abstract

Background: Delirium is a common disorder in Intensive Care Unit (ICU) patients and is associated with serious short- and long-term consequences, including re-intubations, ICU readmissions, prolonged ICU and hospital stay, persistent cognitive problems, and higher mortality rates. Considering the high incidence of delirium and its consequences, prevention of delirium is imperative. This study focuses on a program of standardized nursing and physical therapy interventions to prevent delirium in the ICU, called UNDERPIN-ICU (nUrsiNg DEliRium Preventive INterventions in the ICU).

Objective: To determine the effect of the UNDERPIN-ICU program on the number of delirium-coma-free days in 28 days and several secondary outcomes, such as delirium incidence, the number of days of survival in 28 and 90 days and delirium-related outcomes.

Design and Setting: A multicenter stepped wedge cluster randomized controlled trial.

Methods: Eight to ten Dutch ICUs will implement the UNDERPIN-ICU program in a randomized order. Every two months the UNDERPIN-ICU program will be implemented in an additional ICU following a two months period of staff training. UNDERPIN-ICU consists of standardized protocols focusing on several modifiable risk factors for delirium, including cognitive impairment, sleep deprivation, immobility and visual and hearing impairment.

Participants: ICU patients aged ≥18 years (surgical, medical, or trauma) and at high risk for delirium, E-PRE-DELIRIC ≥35%, will be included, unless delirium was detected prior ICU admission, expected length of ICU stay is less then one day or when delirium assessment is not possible.

Discussion: For every intervention the balance between putative benefit and potential unwanted side effects needs to be considered. In non-ICU patients, it has been shown that a similar program resulted in a significant reduction of delirium incidence and duration. Recent small studies using multicomponent interventions to prevent delirium in ICU patients have also shown beneficial effect, without unwanted side effects. We therefore feel that the proportionality of potential positive effects of the UNDERPIN-ICU program, weighed against potential unwanted side effects is favorable. Since this has not been rigorously proven in ICU patients, we will study the effects of this program in ICU patients using a stepped wedge design.

Trial registration: The study is registered in the clinical trial registry: https://clinicaltrials.gov/.

Introduction

Delirium is defined as an acute disturbance in level of awareness, attention and cognition, with a fluctuating course, caused by a direct physical condition, and occurs over a short period of time.(1) Delirium is a serious disorder in critically ill patients in the Intensive Care Unit (ICU). The overall incidence of delirium in ICU patients is approximately 30%,(2, 3) and even higher in patients admitted to the ICU for two days or longer.(4) It has serious short- and long-term consequences for ICU patients. Delirium is associated with prolonged duration of mechanical ventilation, length of stay in the ICU, and length of stay in the hospital.(2, 4) During their ICU stay patients who suffer from delirium are more likely to involuntarily remove tubes and catheters compared to nondelirious patients, and the incidence of re-intubations and ICU readmissions is significantly higher. In addition, delirium leads to long-term cognitive problems, is associated with higher mortality rates and can influence long-term quality of life.(4-8) Moreover, delirium leads to a higher workload for ICU nurses (9) and a higher financial burden due to increased costs for the ICU as well as the hospital.(10)

Considering the high incidence of delirium and these serious consequences, reducing burdening by delirium is imperative, comprising delirium prevention as well as reducing the duration of delirium. Important in effectively preventing delirium is the early identification of high-risk patients, as optimal use of preventive measures is warranted in these patients because of their vulnerability.(11) A validated prediction model (the Early PREdiction of DELIRium IC (E-PRE-DELIRIC) model) allows a reliable calculation of the chance that a patient will develop delirium and may facilitate early identification of high-risk patients.(12) With use of such a delirium prediction model it has been shown that prophylactic pharmacological treatment with haloperidol may have important beneficial effects in patients at high risk for delirium, including a significant decrease in delirium incidence an increase in the number of delirium free days in 28 days.(13) Despite the beneficial effects of haloperidol, the incidence of delirium remained rather high in high risk patients. Therefore, there is need to investigate alternative (non-pharmacological) interventions aimed at preventing delirium and its deleterious consequences.

Multiple risk factors are associated with delirium.(14, 15) Hence, a multicomponent intervention targeting several risk factors represents a promising strategy for delirium prevention.(16) In non-ICU patients, it has been shown that a program with standardized interventions focusing on several modifiable delirium risk factors, including cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment, resulted in a significant reduction of the delirium incidence and duration.(17, 18) These interventions do not seem to be associated with significant harm for the patients.(16) In ICU patients, data of such a program consisting of standardized interventions are lacking. However, in studies focusing on specific parts of the program beneficial effects have been reported.

(19-22) Recent studies using a non-pharmacological multicomponent intervention program to prevent delirium in the ICU yielded insufficient proof regarding the efficacy of the program, as a consequence of the used study designs, the limited sample size and problems with data collection.(23-25) Therefore, further research using a more rigorous design and a larger sample size in multiple ICUs is needed, also including an estimation of the efficacy and cost-effectiveness of the program.

During this current study we will implement a multicomponent program including non-pharmacological nursing and physical therapy interventions aimed at delirium prevention in the ICU. This program, called UNDERPIN-ICU program (nUrsiNg DEliRium Preventive INterventions in the Intensive Care Unit), consists of standardized multicomponent interventions tailored to ICU patients (26, 27) and focuses on delirium risk factors that can be influenced by nursing and physical therapy interventions: cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment.

Objectives

The primary objective of this study is to determine the effect of the UNDERPIN-ICU program on the number of delirium-coma-free days in 28 days.

The secondary objectives are threefold: to determine the effect of the UNDERPIN-ICU program on: delirium incidence; the number of days of survival in 28 and 90 days; delirium-related outcomes; ICU and hospital length of stay; Quality of Life (QoL) and cognitive function of ICU patients, to determine the effect of the UNDERPIN-ICU program in different subgroups: e.g. admission type, predicted delirium risk, and lastly to assess the cost-effectiveness of the UNDERPIN-ICU program.

Methods

Reporting method

Following the Standard Protocol Items: Recommendations for Interventional Trails (SPIRIT 2013) – checklist.(28)

Study design and setting

This study will be conducted using a multicenter stepped wedge cluster randomized controlled trial.(29, 30) Eight to ten Dutch ICUs from both academic and general hospitals are selected based on their membership of the Dutch ICU Delirium Consortium as well as their commitment to improve their quality of care regarding ICU delirium. At baseline all ICUs will simultaneously start with the control period. The order in which an ICU will move to the intervention period will be randomized. Every two months the UNDERPIN-ICU program will be implemented in an additional ICU. From that point on the UNDERPIN-ICU program will be part of the standard care in that ICU. In each ICU two months of staff training will be provided, after which the ICU moves from control to intervention. (Figure 1) Every ICU will participate for the entire study period. We chose this design since implementation of the program is only feasible at ward level, because randomization at patient level would result in contamination between patients in the intervention group and patients in the control group.(31) This contamination could possibly result in a diluted effect of the program including risk for a false-negative outcome.

Figure 1 Timeline and randomization (C: control, T: training, I: intervention)

Ward	Month 1-2	Month 3-4	Month 5-6	Holiday 7-8	Month 9-10	Month 11-12	Month 13-14	Month 15-16	Month 17-18	Holiday 19-20	Month 21-22	Month 23-24	Month 25-26	Month 27-28
1	C	T	I	I	I	I	I	I	I	I	I	I	I	I
2	C	C	T	I	I	I	I	I	I	I	I	I	I	I
3	C	C	C	C	T	I	I	I	I	I	I	I	I	I
4	C	C	C	C	C	T	I	I	I	I	I	I	I	I
5	C	C	C	C	C	C	T	I	I	I	I	I	I	I
6	C	C	C	C	C	C	C	T	I	I	I	I	I	I
7	C	C	C	C	C	C	C	C	T	I	I	I	I	I
8	C	C	C	C	C	C	C	C	C	C	T	I	I	I
9	C	C	C	C	C	C	C	C	C	C	C	T	I	I
10	C	C	C	C	C	C	C	C	C	C	C	C	T	I

Eligibility criteria for patients

In order to be eligible to participate in this study, patients should be: aged ≥18 years; surgical, medical or trauma patients; admitted to one of the participating ICUs and at high risk for delirium (≥35% determined with the E-PRE-DELIRIC prediction tool).(12) Patients will be not eligible if they: are delirious before ICU admission; have an ICU stay < one day; if reliable assessment for delirium is not possible due to: sustained coma during complete ICU stay defined as Richmond agitation sedation score (RASS)(32) of -3/-4/-5; serious auditory or visual disorders; inability to understand Dutch; severely mentally disabled; serious receptive aphasia.

Interventions

The UNDERPIN-ICU program consists of interventions tailored for ICU patients focusing on the modifiable delirium risk factors: visual and hearing impairment, to prevent or treat sensory deprivation and ultimately the loss of orientation; sleep deprivation, to minimize/avoid sleep deprivation; cognitive impairment to (re)orientate patients with regard to time, place and person to prevent or minimize decline; and immobility, to improve patients' functional mobility in the ICU and to stimulate patients' cognition. These interventions are based on scientific literature as well as a Delphi study and a pilot study.(26, 27) See e-Appendix 1 Delphi study (27) for the UNDERPIN-ICU program (Chapter 5 Thesis).

Outcomes

The primary outcome of the study is the number of delirium-coma-free days in 28 days. Secondary outcomes are: delirium incidence; the number of days of survival in 28 and 90 days; delirium-related outcomes including: duration of mechanical ventilation, incidence of re-intubation, or restart of mechanical ventilation in case of tracheostomy patients, incidence of ICU re-admission, unplanned removal of tubes/catheters, and the use of physical restraints; ICU and hospital length of stay; QoL and cognitive function of ICU patients at ICU admission (baseline), and three and twelve months after ICU discharge; an exploratory subgroup analyses (e.g. based on admission type, predicted delirium risk); a process evaluation to explain the effects based on adherence to the interventions; and a cost-effectiveness analysis which will include an economic evaluation.

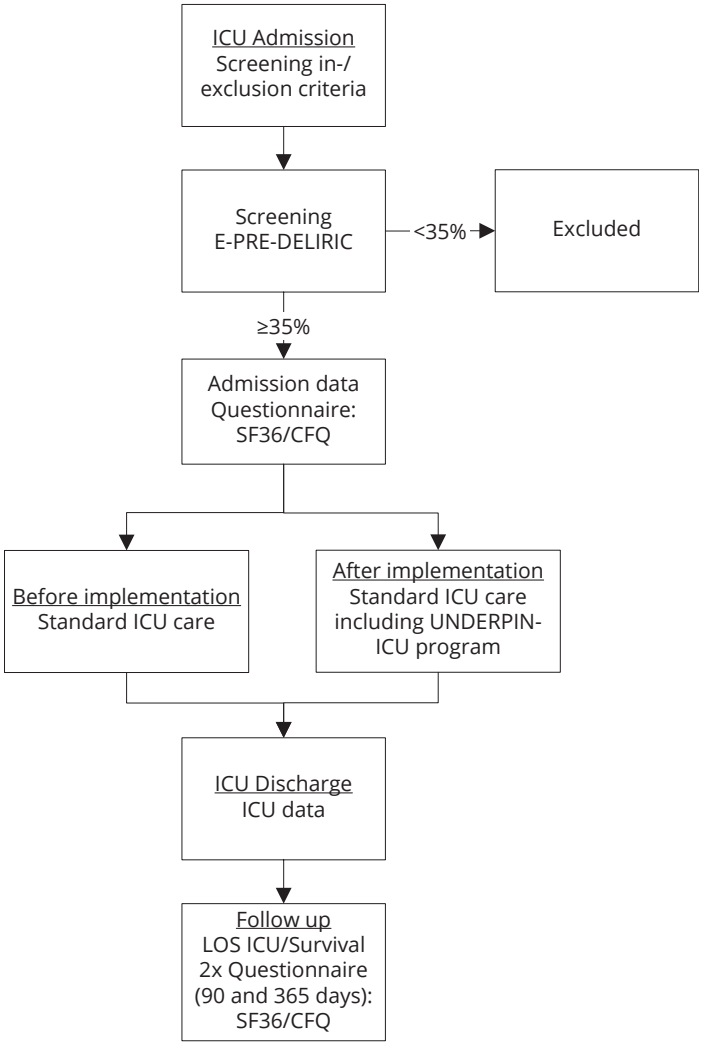
Participant timeline

Baseline characteristics of the patient (e.g. age, gender, predicted delirium risk score, APACHE-II score) will be collected. In order to detect delirium all consecutive patients will be screened by well trained nurses using the validated Dutch translation of the CAM-ICU at least once each shift (more often if indicated, like during periods of fluctuating symptoms or levels of sedation).(33, 34) This screening is part of the daily ICU care. Before the study starts, all ICU nurses will receive a refresher course concerning the CAM-ICU

on top of their in-house CAM-ICU training. This to guarantee a similar level of expertise in every participating centre regarding delirium assessment. (See Figure 2)

All primary and secondary parameters collected during this study are already routinely registered in the participating ICUs. During the two-month training period of the UNDERPIN-ICU program, no data will be collected.

Figure 2 Participant timeline



Sample size

Sample size of the study is calculated to detect a clinically relevant effect on the number of delirium-coma-free days in 28 days (primary outcome). The UNDERPIN-ICU program is considered to be effective if the number of delirium-coma-free days increases from 20 to 22 days in the high-risk group at the end of the study, with a standard deviation of 5. This difference is considered to be clinically relevant. A standard stepped wedge design (i.e., one cluster switches at each step) of 10 clusters with 14 measurement periods having 12-13 patients/period/cluster provides more than 80% power to detect the above difference for an alpha=.05 and ICC=.01 for clustering at ward levels (10x14x12.5=1750 ICU patients).(35) Based on other cohort studies, recruitment of 6–7 high-risk patients/month/ICU (so 12–13 per measurement period of two months) is considered feasible.

Recruitment

All patients admitted to the ICU will be screened for their risk for delirium as part of standard care. Patients at high risk for delirium will be included in the study as soon as possible after ICU admission. Due to the relative early onset of delirium after ICU admission the UNDERPIN-ICU program needs to be started as quickly as possible to optimize the possibilities for the UNDERPIN-ICU program to be effective.

Assignment of interventions

The UNDERPIN-ICU program used in this study will become standard treatment in all participating ICUs. (See Figure 1) These ICUs will be assigned to the intervention based on cluster randomization. This means that the moment of implementation of the UNDERPIN-ICU program per ICU will be determined randomly in this study. During the study, every participating ICU will implement the program.

Randomization will be performed at the start of the study. By nature of the interventions, this study cannot be blinded.

Data collection and management

The start of data collection for this study is planned for January 2017.

Delirium diagnosis

Patients will be diagnosed as delirious when they have at least one positive delirium screening (confusion assessment method (CAM)-ICU)(33, 34) during their complete ICU stay or when they are treated for delirium with haloperidol (without a positive CAM-ICU screening). The duration of delirium is defined as time from the first positive CAM-ICU or treatment with haloperidol, until the beginning of two consecutive days of negative delirium screenings. For ICU patients this is defined as a negative CAM-ICU screening, and when on the ward a Delirium Observation Screening (DOS) scale 3.(36) Reoccurrence of

delirium, defined as a new delirium episode occurring after a minimum of 48 h of negative delirium scores, will be documented.

Delirium-coma-free days in 28 days

This is defined as the number of days a patient is not delirious and not in coma in 28 days starting from the day of inclusion in the study. A delirium-coma-free day is defined as a nondelirious day with a RASS (32) greater than -3/-4 or -5.

Survival days in 28 and 90 days

This is defined as the number of days that patients survive in 28 and in 90 days.

Time to successful extubation

This is the registered time in hours that the patient is on the mechanical ventilator before successful extubation. When the patient is ventilated mechanically several times during one admission, the ventilator times will be added. Both invasive and non-invasive ventilation will be registered.

Incidence of re-intubation

Patients who need to be intubated within 28 days after ICU admission, following a previous extubation, irrespectively the reason for re-intubation, will be counted as incident case for re-intubation.

Incidence of ICU re-admission

Patients who need to be readmitted to the ICU within 28 days, irrespectively the reason for readmission, will be counted as incident cases for ICU readmission.

Incidence of unplanned removal of tubes/catheters

Incidents in which patients remove their tube or catheter themselves will be counted as incident cases for unplanned removal. The period in which this is measured is during patients' ICU stay or during the period when the patient is delirious (in case a patient is discharged to the ward) with a maximum of 28 days.

Incidence of physical restraints

Patients who need physical restraints (fixation of their limbs to prevent them from removing tubes or lines) within 28 days, will be counted as incident cases for physical restraints.

ICU- and hospital length of stay

This is defined as the number of days a patient is admitted to the ICU. Hospital length of stay is defined as number of days a patient is admitted to the hospital.

Quality of Life (QoL) and cognitive function of ICU patients

QoL will be assessed using the Short Form (SF)-36 Health Survey questionnaire. This is a validated quality of life questionnaire existing of physical and mental components distributed over eight items.(37, 38) In addition, cognition will be assessed using the validated self-reporting cognitive failure questionnaire (CFQ).(39) This validated self-evaluating questionnaire consists of 25 items (39) and four dimensions of cognition: memory, distractibility, blunders, and (memory for) names.(40)

Patients will be asked to complete the questionnaires at baseline/ICU admission, three months after admission and one year after admission. When the patient at admission is not able to complete the QoL questionnaires, patient's next of kin will be asked to complete the questionnaires, as they can also reliable assess the quality of life on admission to the ICU.(41)

Exploratory analysis

For exploratory analysis data will be collected about admission type (surgical, medical or trauma) and predicted delirium risk (determined with a delirium prediction model (E-PRE-DELIRIC) for ICU patients).

Process evaluation and cost-effectiveness

A process evaluation will be performed to determine the relation between both the compliance to the interventions and contextual factors of the different ICUs on the effects that will be measured within the UNDERPIN-ICU study. In addition, the quality of the delirium assessments will be measured. Process data on the execution of the different interventions will be collected by performing real time observations of the activities of the ICU nurses and patients to determine the adherence to the interventions. Also, questionnaires will be used to determine both the baseline standard of care per ICU during the control period and the adherence of the ICU nurses to the interventions during the intervention period. In addition, observations of contextual factors like ward characteristics of the different participating ICUs will be performed.

Since costs for patients scoring positive for delirium are higher compared to non-delirium patients,(10) an improvement in delirium outcome as a result of the UNDERPIN-ICU program may result in cost-effectiveness. The cost-effectiveness analysis will include an economic evaluation divided over two parts. First, on patient level volumes of care will be measured prospectively over the in-hospital time path of study. Second, per modality standard cost-prices will be determined using the Dutch guideline completed by real cost prices via activity based costing.(42, 43)

Data management

All data will be collected electronically in an Electronic Clinical Report Form (E-CRF). This is a secured website to which all participating ICUs need to log in with a unique password to add data of their subjects' study parameters. Data handling will comply with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens WBP). Participating ICUs only have access to their own data. The key to the login codes will be safeguarded by the investigator.

Statistical analyses

Descriptive statistics will be presented as mean SD or median and interquartile ranges, depending on distribution. Continuous outcomes (e.g., QoL, cognitive function) will be compared between groups using linear multilevel models (patients nested within ICUs). If necessary, continuous skewed data (e.g., number of delirium-free days, length of stay) will first be log-transformed. Binary outcomes (e.g., delirium) will be compared between groups using logistic multilevel models. For time to event outcomes (e.g., survival time within 28 days), a multilevel Cox proportional hazard model (frailty model with random effect for ICU) will be used.(44) Two problems with the data are foreseen to possibly occur. First, due to the limited number of clusters the multilevel models, especially the frailty model and the logistic multilevel model, may not converge. In that case, clusters (ICUs) will be fitted as fixed effects or a summary measures approach will be employed. Second, data may be too far from normally distributed, so that they are not sufficiently normalized by log transformation (and, due to the limited number of clusters, one cannot rely on the robustness of regression analysis against non-normality that occurs for large samples). In that case, non-parametric tests, dichotomization of data by sensible cut-offs, or permutation tests (based on the parametric tests) will be considered for inference.

Data will be analyzed according to the 'intention to treat' principle, but in secondary analyses we will also carry out per protocol analyses. Missing value analysis will be performed and if necessary, missing data will be imputed using multiple imputations. Statistical significance is defined as a P-Value < 0.05. Data will be analyzed using IBM SPSS Statistics or SAS software.

Primary study parameter

The main analysis is the comparison of delirium-free days without coma between the intervention and control groups.

Secondary study parameters

The data of the secondary study parameters will be presented quantitatively and compared between intervention and control groups.

Exploratory analysis

The influence of potential prognostic covariates, e.g., admission type and predicted delirium, risk will be investigated by including each of these as covariates and their interaction with the intervention in regression analyses. Additionally, the influence of these will be graphically investigated using subgroup analyses (forest plots).

Analysis process evaluation and cost-effectiveness

During the process evaluation analysis the data from the effect and process evaluation will be merged to get insight in the relation between the effectiveness of the UNDERPIN-ICU program and the process consisting of compliance to the interventions and contextual factors. To determine the quality of the delirium assessments, inter rater reliability measurements of the CAM-ICU will be performed, followed by the calculation of the Cohen's kappa coefficient.

Cost-effectiveness will be analyzed by comparison of delirium-free days as well as by compliance to the interventions between the intervention and control group. Also cost-effectiveness ratio will be expressed as cost per delirium-free day gained and cost per Quality Adjusted Life Year (QALY) gained.(45) Furthermore, a budget impact analysis will be conducted to assess how health care budgets are changed when offering the UNDERPIN-ICU program.

Monitoring

During this study, data will be monitored by an independent monitor. The participating ICUs will be monitored before as well as after implementation of the UNDERPIN-ICU program. A random patient sample will be checked regarding the eligibility for inclusion and source data verification of the primary outcome measure and several secondary outcome measures will be performed.

Harms

Adverse events (defined as any undesirable experience occurring to a patient during the study, whether or not considered related to the intervention) reported spontaneously by the patient or observed by the investigator or staff will be recorded.

Auditing

Compliance to the UNDERPIN-ICU program will be measured by performing observations and the use of registration lists for both ICU nurses as well as participating observations and measurements using electronically supportive devices.

Ethics

This study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act (WMO). Handling of the data will comply with the Dutch Personal Data Protection Act. This study has been approved by the Medical research ethics committee (MREC) Arnhem-Nijmegen region (No. NL2013/173). The need for informed consent was waived, because the UNDERPIN-ICU program is a change in health care policy for which no explicit consent of the patient (according to the WMO) is necessary. Nevertheless, all included patients will receive written information about the study.

Access to data

All investigators have access to their local trial data during the study period. After termination of the data collection period only the authors of the final manuscript, monitors and legal representatives will have access to the data, which will be stored in a Trusted Digital Repository. After termination of the study, the anonymized data will be made available for future research.

Ancillary and post trail care

Since the participating ICUs will adjust their standard care to include the UNDERPIN-ICU program, no additional provisions are needed for the participants. Participants will not receive any compensation.

Dissemination policy

Regardless of the results of the study, the results will be shared via presentations on (inter-) national congresses and published in peer reviewed scientific journals, preferably trough open access. Authorship will comply with the recognized ethical standards concerning publications and authorship, established by the International Committee of Medical Journal Editors. Also, the results will be disseminated using social media and integrated in our existing Delirium ICU app which is word widely available. When the program will harm the patients, a de-implementation plan will be developed and executed in the participating centers.

Discussion

Prevention of delirium in the ICU is very important as delirium is a common disorder in ICU patients, resulting in negative consequences.(2) Non-pharmacological multicomponent interventions targeting several modifiable delirium risk factors represent a promising prevention strategy.(16, 46) However, the effectiveness of a program consisting of such interventions is not yet rigorously studied in ICU patients.(23-25) In this study, we will implement the UNDERPIN-ICU (nUrsiNg DEliRium Preventive INterventions in the Intensive Care Unit) program and study its effect on delirium in ICU patients. With this study we aim to decrease the burden of delirium for ICU patients, as well as study the effect of the UNDERPIN-ICU program on cost-effectiveness in the ICU. If our UNDERPIN-ICU study indeed demonstrates positive effects of non-pharmacological interventions on ICU delirium and (cost)-effectiveness, it will change the care for ICU patients on a large scale. This current study has several strong features. The design, a stepped wedge cluster randomized controlled trial, can provide strong evidence of the effectiveness of the UNDERPIN-ICU program and indicates higher quality than results from non-randomized trials.(47) In addition, this design is beneficial due to an increased statistical power as a result of both between and within group comparisons.(48) Also, the design facilitates phased implementation resulting in a decreased risk for contamination between study groups (49) and less risk of bias since all ICUs can be trained in performing the UNDERPIN-ICU program by the same persons (PR, MvdB). The UNDERPIN-ICU program has a strong fundament as it is based on literature as well as expert and patient opinion. The use of a literature review provided a scientific base for the draft intervention program, and during both a Delphi study and a pilot study the UNDERPIN-ICU program was tailored to ICU patients.(26, 27) In addition, currently the implementation of an intervention program is recommended for ICU delirium management including prevention strategies.(50) The use of an intervention program already has been shown effective in improving other ICU outcomes like acute kidney injury and sepsis.(51, 52)

Nowadays an important aspect regarding a newly developed intervention program like the UNDERPIN-ICU program, is its cost-effectiveness.(53) As delirium is associated with an increased length of stay,(2) and a delay in transfer to a general ward is costly,(54) improving ICU efficiency and optimizing cost-effectiveness by delirium prevention is essential. Therefore, the cost-effectiveness of the UNDERPIN-ICU program will be part of the analysis of this study.

There are also some limitations that need to be addressed. As we will implement the UNDERPIN-ICU program as a whole per cluster, the contribution per individual intervention will not be clear from the primary study results. Therefore we will perform a process analysis to assess which intervention or contextual factor inhibited or promoted the effectiveness of the UNDERPIN-ICU program.(55) It should be taken into account that despite

the fact that this study will be conducted in multiple Dutch ICUs from both academic and general hospitals, our results may not be globally generalizable because of possible differences in ICU logistics and resources as well as in cultural aspects.(56) Although local tailoring consisting of minor modifications of the UNDERPIN-ICU program may be needed, we believe that the main conclusions of our study will be generally valid.

Declaration of interests

The authors declare they have no competing interests.

Acknowledgments

Prof. Dr. Theo van Achterberg, Dr. Bart Staal, Dr. Huub Wollersheim, and Prof. Dr. Ria Nijhuis-Van der Sanden are investigators and assisted with the original protocol.

Funding

'Junior research round 2013', Nijmegen Centre for Evidence Based Practice (NCEBP), Radboud university medical center. Role during study design and conducting the study: none.

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CHAPTER 8

Development and validation of an abbreviated questionnaire to easily measure cognitive failure in ICU survivors: A multicenter study

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Crit Care Med. 2018;46(1):79-84

Abstract

Objectives: To develop and validate an abbreviated version of the Cognitive Failure Questionnaire that can be used by patients as part of self assessment to measure functional cognitive outcome in ICU survivors.

Design: A retrospective multicenter observational study.

Setting: The ICUs of two Dutch university hospitals.

Patients: Adult ICU survivors.

Interventions: None.

Measurements and main results: Cognitive functioning was evaluated between 12 and 24 months after ICU discharge using the full 25-item Cognitive Failure Questionnaire (CFQ-25). Incomplete CFQ-25 questionnaires were excluded from analysis. Forward selection in a linear regression model was used in hospital A, to assess which of the CFQ-25 items should be included to prevent a significant loss of correlation between an abbreviated and the full CFQ-25. Subsequently, the performance of an abbreviated Cognitive Failure Questionnaire was determined in hospital B using Pearson's correlation. A Bland Altman plot was used to examine whether the reduced-item outcome scores of an abbreviated Cognitive Failure Questionnaire were a replacement for the full CFQ-25 outcome scores. Among 1,934 ICU survivors, 1,737 were included, 819 in hospital A, 918 in hospital B. The Pearson's correlation between the abbreviated 14-item CFQ and the CFQ-25 was 0.99. The mean of the difference scores was -0.26 and 95% of the difference scores fell within +5 and -5.5 on a 100-point maximum score.

Conclusions: It is feasible to use the abbreviated CFQ-14 to measure self-reported cognitive failure in ICU survivors as this questionnaire has a similar performance as the full CFQ-25.

Introduction

Recent advances in the treatment in the Intensive Care Unit (ICU) have resulted in substantially reduced mortality rates after critical illness.(1, 2) As a consequence, there has been a shift in emphasis from preventing immediate mortality to reducing long-term impact of critical illness in survivors.(3) Indeed, it has been shown that ICU survivors often develop physical, mental, and cognitive impairments following ICU discharge.(4, 5) These impairments are associated with a reduced health related quality of life (HRQOL), functional status and daily functioning of ICU survivors, and together have been coined as the postintensive care syndrome (PICS).(2, 6) PICS has far reaching consequences for both ICU survivors and their families.(2, 7) In particular, long-term cognitive impairment is a growing public health problem,(8) as it occurs in 4 to 62% of the ICU survivors (9) and poses a great burden on the economy.(10) Furthermore, cognitive impairment is associated with depression, increased dependence and poor social functioning.(11) Both the frequent occurrence and deleterious consequences of cognitive impairment following critical illness require further recognition and action of both clinicians and researchers.(11) To date, survivors' perception of their cognitive function, which could help to understand the functional implications of cognitive impairment, received limited study. Improved identification of survivors' perception of cognitive impairment is an essential step toward meeting the needs of ICU survivors and their families.

Post-ICU cognitive impairment affects a person's attention, processing speed, memory, as well as executive function.(11) Consequently, everyday cognitive failure negatively impacts daily routine and HRQOL. Seemingly simple tasks that a person normally should be able to perform without errors, suddenly become complicated.(12, 13) To assess a person's likelihood of committing such errors in everyday life, multiple self-report measures are available.(13) The Cognitive Failures Questionnaire (CFQ) designed by Broadbent et al. (1982) is the most frequently used and most comprehensive measure in terms of covered domains of daily life failures.(13, 14) This self-administered questionnaire consists of 25 items that cover failures of perception, memory, and motor function (14) and therefore is the designated questionnaire to identify ICU survivors' perception of their cognitive function.

Given the multifaceted nature of PICS, several questionnaires are needed to study relevant issues related to physical, cognitive, and mental health impairments to enable a thorough measurement of the presence and consequences of PICS. In earlier studies in ICU survivors non-response was considered a problem with around 70% returned 25-item CFQ (CFQ-25) despite sending reminders and/or follow-up phone calls.(15, 16) We hypothesize that introducing an optimal short form of the full 25-item CFQ (CFQ-25) for ICU survivors will possibly less burden the survivors as well as increase the response rates and efficiency. With that the aim of our study was to develop and validate an abbreviated version of the CFQ-25 that can be used by patients as part of self assessment to measure functional cognitive outcome in ICU survivors.

Materials and methods

Design and Study population

This study was a retrospective study using the data of two prospective cohort studies aimed at examining the impact of delirium during ICU stay on long-term outcome and self-reported cognitive problems in survivors of critical illness carried out in two university hospitals in the Netherlands.(15, 16)

In the original studies,(15, 16) all consecutive adults admitted to the mixed medical-surgical ICUs were included between January 2008 and February 2009 in Hospital A, and January 2011 and July 2014 in hospital B. In the original study,(15) patients from hospital A were excluded if they had been admitted to the ICU for <1 day; were unable to be reliably assessed for delirium due to: sustained coma in the ICU, inability to understand Dutch, severe preexisting mental disability such as retarded metal development or Alzheimer's disease, serious receptive aphasia, or serious auditory or visual disorders; and if the delirium screening was not complete during their ICU stay. In the original study,(16) patients from hospital B were excluded if they had been admitted to the ICU for less than 2 days, were transferred from an ICU of another hospital, or if they were suffering from an acute neurologic illness such as stroke or subarachnoid hemorrhage or another condition that could hamper delirium assessment. In this current study, patients were excluded from analysis when they had an incomplete CFQ-25.

This study was conducted in accordance with the applicable rules as described in the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and the Medical Research Involving Human Subjects Act (WMO).

The Medical ethical research committee (MREC) Arnhem-Nijmegen region, the Netherlands (CMO Region Arnhem-Nijmegen number 2010-008) and the local MREC from the University Medical Center Utrecht, the Netherlands (Institutional Review Board numbers 10-006, 10-056, 12-421) reviewed this study and waived the need for approval.

Data collection

After 12 to 24 months after ICU discharge, ICU survivors' perceived cognitive functioning was evaluated using the validated Dutch translation of the CFQ-25.(17) This translated questionnaire has shown satisfactory psychometric qualities based on both a high test-retest stability and internal consistency.(17) We used the CFQ dimension structure of Wallace et al. (2002), comprising the four dimensions memory, distractibility, social blunders, and names.(15, 18, 19) On each of the 25 items, the ICU survivors scored the frequency with which that type of cognitive failure occurred to them during the last 6 months, on a 5-point Likert scale ranging from "never" (0) to "very often" (4).(12) The most applied way to measure persons' cognitive functioning based on their proneness to everyday cognitive mistakes, is to sum up the ratings of the 25 individual items of the CFQ, yielding a score

from 0-100, with a higher score indicating more self-reported cognitive failure.(20)

Demographic variables were age, gender, admission type, and acute admission, and Acute Chronic Health Evaluation II and IV (APACHE II and APACHE IV) were collected as measures for illness severity in the first 24 hours after ICU admission.(21, 22) Also data on ICU and hospital length of stay and delirium based on the Confusion Assessment Method for the ICU (CAM-ICU) were collected.(23, 24)

Statistical analysis

We first developed the abbreviated CFQ and subsequently we validated the abbreviated CFQ.

Development of the abbreviated CFQ

In the development phase, using data from hospital A, we used forward selection in a linear regression model to assess which of the 25 CFQ items should be included to prevent a significant loss of correlation between the abbreviated CFQ and the CFQ-25. Criteria to determine the optimal model for the abbreviated CFQ were: a minimal number of CFQ items with the maximum R Square possible and a proportional coverage of the items on the dimensions memory, distractibility, social blunders, and names.(18) This was operationalized as follows: we performed linear regression on the data with forward selection in SPSS. This resulted in 25 models, starting with 1 CFQ item up to 25 CFQ items which showed an increase in R Square as we added CFQ items to the model. We determined the point at which the R square was maximal with a minimal number of CFQ items possible, in other words, the point when the increase of R Square stabilized after including an extra CFQ item to the model. At this point, we studied the number of included items and their coverage of the dimension structure. This analysis ultimately resulted in an abbreviated version of the CFQ for ICU survivors with the minimal number of items, that can replace the CFQ-25.

Validation of the abbreviated CFQ

Subsequently, in the validation phase the data of hospital B were used. First the performance of the abbreviated CFQ was assessed using Pearson's correlation. Second, to examine whether the reduced-item outcome scores, i.e. the predicted scores, of the abbreviated CFQ were replaceable for the CFQ-25 outcome scores, and thus whether there was agreement between the abbreviated CFQ and the CFQ-25, we used a Bland Altman plot.

Differences between hospital A and B in demographic variables, illness severity, ICU and hospital length of stay, and delirium were calculated using t-test, dhi-square or Mann-Whitney U test depending on distribution and measurement level.

Data were analyzed using IBM SPSS Statistics version 22 for windows (IBM Corp,

Armonk, NY). Statistical significance was defined as a p value of less than 0.05, and the null hypotheses were tested against two-sided alternatives.

Results

Two cohorts were used. In hospital A, 819 of the 914 ICU survivors (90%) had a complete CFQ-25. Their mean (SD) age was 63 (14) years, and 608 (67%) were men. The median length of ICU stay (LOS ICU) was 1 day [interquartile range (IQR), 1-2]. 171 (19%) were delirious during ICU admission. In hospital B, 918 of the 1020 ICU survivors (90%) had a complete CFQ-25. These survivors had significantly different characteristics, including age, sex, and APACHE scores. (Table 1) ICU survivors with incomplete CFQ-25 questionnaires also had comparable characteristics. In total, among 1,934 ICU survivors, 1,737 (90%) had a complete CFQ-25 available for analysis.

Table 1 Characteristics of the study population

Variables	Hospital A N=819	Hospital B N=918	P
Age in years, mean (SD)	62 (14)	58 (16)	<0.001
Male, N (%)	563 (69)	571 (62)	<0.05
Admission type, N (%)			<0.001
Surgical	597 (73)	470 (51)	
Medical	115 (14)	310 (34)	
Trauma	38 (5)	0	
Neurological/-surgical	69 (8)	138 (15)	
Acute admission, N (%)	341 (42)	619 (67)	<0.001
APACHE II score, mean (SD)	14 (5)	18 (7)	<0.001
APACHE IV score, mean (SD)	52 (20)	62 (26)	<0.001
CAM-ICU positive, N (%)	143 (18)	380 (49)	<0.001
ICU Length of stay in days, median [IQR]	1 [1-2]	5 [3-9]	<0.001
Hospital Length of stay in days, median [IQR]	7 [5-13]	21 [13-36]	<0.001

Development of the abbreviated CFQ

Following forward selection in a linear regression model, the predefined criteria that we used to determine the optimal model for the abbreviated CFQ comprising a minimal number of CFQ items, a maximum R Square, and proportional coverage of the items on the dimensions memory, distractibility, social blunders, and names (18) were most optimal in the model with 14 CFQ items. The R Square of this model was 0.973, and the included questionnaire items were in order of forward selection 17, 21, 3, 9, 14, 6, 22, 10, 16, 12, 15, 7, 24, and 2. (Table 2, Table 3 and e-Appendix 1) The next step in forward selection would have resulted in a 15-item model with the identical CFQ items as the 14-item model plus questionnaire item 18 which belonged to dimension memory. Inclusion of item 18 would have resulted in an overrepresentation of the dimension memory compared with the other dimensions, especially blunders.(18) In addition, the increase of R square to 0.978 was not considered to be clinically relevant.

Table 2 Correlations with 25-item CFQ and formula 14-item CFQ model

Model	R	R square
1	0.748	0.560
5	0.942	0.886
10	0.974	0.949
11	0.978	0.957
12	0.981	0.963
13	0.984	0.969
14	0.987	0.973
15	0.989	0.978
16	0.990	0.980

Formula 14-item CFQ model# = (0.483 + (1.488 * CFQ_17) + (2.184 * CFQ_21) + (1.779 * CFQ_3) + (1.647 * CFQ_9) + (1.790 * CFQ_14) + (1.484 * CFQ_6) + (1.701 * CFQ_22) + (1.670 * CFQ_10) + (2.001 * CFQ_16) + (1.971 * CFQ_12) + (1.541 * CFQ_15) + (1.367 * CFQ_7) + (1.362 * CFQ_24) + (1.485 * CFQ_2)).

Items in order of forward selection

Validation of the abbreviated CFQ

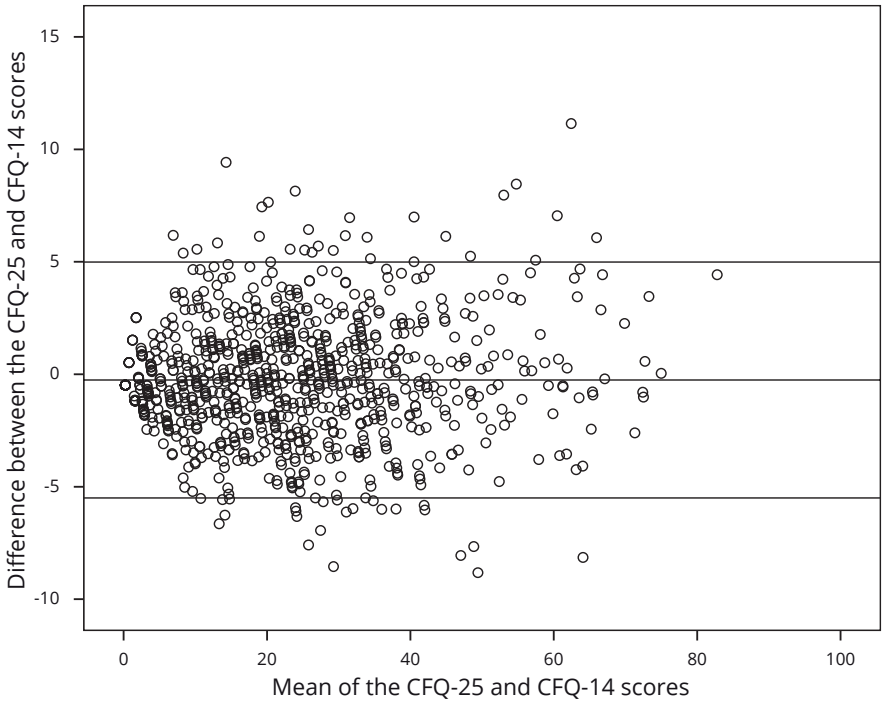
14-item CFQ (CFQ-14) and the CFQ-25 were significantly correlated, R equals to 0.986 ($p<0.0001$). The mean (SD) score of the ICU survivors on the CFQ-25 was 22.8 (16.1) and the mean (SD) on the CFQ-14 was 23.0 (15.9).The mean (SD) of the difference scores between the CFQ-25 and the CFQ-14 was -0.257 (2.67) which is surrounding zero. Of the difference scores 95% were falling within + 5 and - 5.5 on a 100-point maximum score. Meaning the CFQ-25 outcome scores are replaceable by the CFQ-14 outcome scores and as such the CFQ-14 can be used to assess self-reported cognitive failures in an ICU population. (Figure 1)

Table 3 CFQ item distribution of both the CFQ-25 and CFQ-14 on the dimension structure of Wallace et al. 2002 (18)

CFQ dimension structure of Wallace et al. 2002	Distribution of the CFQ-25 items~	Proportion*	Distribution of the CFQ-14 items~	Proportion
(1) Memory	3, ***6***, ***12***, 13, ***16***, ***17***, 18, 23	8/26=31	***6, 12, 16, 17***	4/14=29
(2) Distractibility	1, ***2***, ***3***, 4, ***15***, 19, ***21***, ***22***, 25	9/26=35	***2, 3, 15, 21, 22***	5/14=36
(3) Blunders	5, 8, ***9***, ***10***, 11, ***14***, ***24***	7/26=27	***9, 10, 14, 24***	4/14=29
(4) Names	***7*** en 20	2/26=8	***7***	1/14=7

~The items of the 14-item model are displayed in fat italic
*The number of CFQ items is 26, because item 3 is distributed over dimension 1 and 2 (18)
The 15-item model would include the items of the 14-item model plus item 18

Figure 1 Bland Altman plot of the CFQ-25 and the CFQ-14



Validation phase: derived from hospital B data only

Discussion

We describe the development and validation of an abbreviated self-reporting CFQ (CFQ-14) to assess cognitive failure in ICU survivors. This abbreviated version reproduces more than 98% of the variance of the original 25-item CFQ (CFQ-25), and the outcome scores are highly correlated with the original CFQ-25 outcome scores. Furthermore, the CFQ-25 outcome scores are replaceable by the CFQ-14 outcome scores. This means the abbreviated CFQ-14 is comparable to the CFQ-25 and can be used to examine ICU survivors' perception of their cognitive functioning more efficiently than the full CFQ-25.

Given the major negative consequences of cognitive impairment following ICU admission,(2, 7) further recognition is warranted.(11) Routine screening for cognitive failure in ICU survivors could help to understand the functional implications of cognitive impairment and ultimately to early recognize PICS. Identification of cognitive failure is essential and clinically relevant as it provides clinicians with important functional information necessary for the support of the ICU survivors during their recovery. It also could provide valuable information regarding the ICU survivors' HRQOL, which may be used by both clinicians and researchers to improve ICU patients' outcome by the development and/or use of preventive measures.(25, 26) In line with the DSM-V, the ultimate strategy to detect cognitive impairment is a combination of self-reported cognitive failure and objective neuropsychological tests.(27) The performance of neuropsychological tests, however, is very laborious and expensive. The CFQ-25 (14) is a realistic and already used strategy to screen large numbers of ICU survivors for self-reported cognitive failure,(15, 16, 28); however, the number of questions to answer and response rates are regarded a limitation. A shorter version likely improves the compliance of survivors to fill out the complete questionnaire and might result in a higher response rate.

As we consider the length of the CFQ-25 a weakness, we selected out a subset of CFQ items to develop an optimal short version and validated it in another sample of ICU survivors. Similar to multiple studies that were also aimed at the reduction of the number of questionnaire items in various questionnaire subjects and patient populations,(29-31) we used a linear regression model to select out the optimal subset of CFQ items. Another conventional approach for data reduction of questionnaires is principal component analysis.(32) However, we wanted to develop a measure that results in a total score comparable to the total score of original CFQ-25 because it allows for a direct comparison of the results between studies using the CFQ-14 for measuring cognitive failure, and studies using the CFQ-25. Since principal component analysis is less appropriate for this purpose we did not choose for this method.

The patient's cognitive status before ICU admission is important in the identification of post-ICU cognitive failure. Due to critical illness and its consequences, a part of the ICU patients are unable to fill out a questionnaire at ICU admission; for these patients their

next of kin are asked to complete the questionnaire. Earlier research showed that the ratings of respondents on the full 25-item CFQ significantly correlate to the ratings of their spouses.(14) This might be similar for our abbreviated version of the CFQ for ICU survivors; however, before using the CFQ-14 at ICU admission, by ICU patients or their next of kin, it should be validated for that purpose first.

Several risk factors for cognitive impairment in ICU survivors are known, including acute stress and acute disease, older age, and delirium.(11) Multiple studies reported an association between delirium duration and worse long-term cognitive outcomes.(8, 15, 16) Delirium frequently occurs in ICU patients.(33) In addition, the age of the world population is increasing. As age is an important risk factor for delirium,(34) the number of people with cognitive impairment is expected to grow, warranting low-threshold monitoring of cognitive function in ICU survivors. Due to its length and low burden, the short 14-item CFQ can easily be used in daily practice to measure self-reported cognitive failure following ICU admission providing valuable information about ICU survivors cognitive function for example in outpatient clinics that are focused on intensive care follow-up. However, the specific test-performance of the CFQ-14, including perceived burden, response rate, and completion time, still needs to be determined and compared with the original CFQ-25.

An important strength of this study is its large sample size. Our sample consisted of mixed (neuro) surgical, medical, trauma, and neurologic patients, from two different ICUs with different characteristics of study population which contributes to the generalizability of the results. However, as in both cohorts trauma and neurocritical care patients are underrepresented, one should be cautious regarding generalization of our results towards this specific population. Future research should include a subgroup analysis to further study the applicability of the CFQ-14 in these specific patients.

However, several limitations of this study need to be addressed as well. First, although the short 14-item CFQ is a valid questionnaire to examine the experience of cognitive failures of ICU survivors, it is unclear whether or not self-evaluated subjective cognitive failure is related to objectively measured cognitive function. Previous studies, in various patient categories, on this subject have shown inconsistent results.(35, 36) Therefore it is important to study this relation in future research. Despite this knowledge gap, the self-evaluated CFQ-14 provides valuable information about ICU survivors' perceived cognitive functioning which can be used to better recognize PICS and as an alert for the necessity of preventive measures or for further cognitive examination. Second, the CFQ is a self-reporting questionnaire and therefore one should take into account that under- or overestimation of cognitive failure may be an issue. Involvement of the ICU survivor's next of kin in the survivors' cognitive evaluation may be a solution to prevent this under- or over estimation.(28)

In conclusion, we developed and validated an abbreviated 14-item version of the CFQ which showed similar performance as the full 25-item questionnaire. It is feasible to use this CFQ-14 to measure self-reported cognitive failure in ICU survivors, possibly yielding increased response rates and efficiency.

Acknowledgments

The authors would like to thank the research nurses and the intensive care teams of each of the participating sites for their help in collecting the data.

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Online data supplement

e-Appendix 1 Cognitive Failures Questionnaire[#]

1. Do you read something and find you haven't been thinking about it and must read it again?
2. *Do you find you forget why you went from one part of the house to the other?*
3. *Do you fail to notice signposts on the road?*
4. Do you find you confuse right and left when giving directions?
5. Do you bump into people?
6. *Do you find you forget whether you've turned off a light or a fire or locked the door?*
7. *Do you fail to listen to people's names when you are meeting them?*
8. Do you say something and realize afterwards that it might be taken as insulting?
9. *Do you fail to hear people speaking to you when you are doing something else?*
10. *Do you lose your temper and regret it?*
11. Do you leave important letters unanswered for days?
12. *Do you find you forget which way to turn on a road you know well but rarely use?*
13. Do you fail to see what you want in a supermarket (although it's there)?
14. *Do you find yourself suddenly wondering whether you've used a word correctly?*
15. *Do you have trouble making up your mind?*
16. *Do you find you forget appointments?*
17. *Do you forget where you put something like a newspaper or a book?*
18. Do you find you accidentally throw away the thing you want and keep what you meant to throw away -- as in the example of throwing away the matchbox and putting the used match in your pocket?
19. Do you daydream when you ought to be listening to something?
20. Do you find you forget people's names?
21. *Do you start doing one thing at home and get distracted into doing something else (unintentionally)?*
22. *Do you find you can't quite remember something although it's "on the tip of your tongue"?*
23. Do you find you forget what you came to the shops to buy?
24. *Do you drop things?*
25. Do you find you can't think of anything to say?

[#]Items included in the 14-item CFQ are displayed in italic

CHAPTER 9

General discussion and conclusions

General discussion

This thesis focuses on early prediction of ICU-acquired delirium and the development of a multicomponent non-pharmacological intervention program targeting delirium prevention in critically ill patients. In this final chapter we present the main results described in this thesis in a broader theoretical and practical context at different levels of the ICU healthcare system, i.e. organization, ICU nurse, patient and family, and reflect on the implications of our findings for ICU practice. This is followed by a discussion of methodological considerations, aims for future research, and the general conclusions.

Organization

Worldwide, rising costs are a major challenge to healthcare.(1-3) Patient care in the Intensive Care Unit (ICU) has a big share in the hospital costs. These costs will further increase due to the use of more advanced medical technology and the aging population, resulting in an increased number of patients who need treatment in the ICU.(4, 5) Delirium is a common problem in the ICU, associated with worse patient outcomes.(6) Importantly, a significant number of ICU survivors develop long-term cognitive impairment, related to the occurrence of delirium during their ICU stay.(7) Post-ICU cognitive impairment is associated with depression, increased dependence and poor social functioning.(8) Furthermore, ICU survivors are often physically and mentally impaired following ICU discharge.(9, 10) These impairments are associated with a reduced health related quality of life (HRQOL), functional status and daily functioning of ICU survivors. Together with cognitive impairment these are described as the post-intensive care syndrome (PICS).(11, 12) PICS has extensive consequences for both ICU survivors and their families,(11, 13) demanding adequate follow-up and focus on optimal rehabilitation of ICU survivors.(5, 11) As a consequence, not only the ICU patients, their families, and the healthcare professionals are paying a high price for delirium, but it is also expensive for our healthcare system.(14) To keep ICU care feasible and sustainable, the organizational model of ICUs should be reconsidered in order to meet current and future care demand within available resources. Recently, a framework for value-based healthcare in intensive care organizations was proposed.(5)

Value-based healthcare is based on three important principles. First, the goal of healthcare should be the value of care for patients. This means that instead of thinking in terms of delivering their specialty well and cheap, healthcare professionals should improve the value for patients who want good health outcomes. Second, the organization of healthcare should be organized around medical conditions and care cycles, since value arises when the care for patients is delivered in a system covering the total package needed to treat a patient's medical condition, including common co-morbidities. Engagement of patients within their healthcare is recommended. Third, patient outcomes and costs

should be measured and reported to indicate efficient or effective care. In summary, value-based healthcare aims to improve patients' outcome without increasing costs, or decreasing costs without impairing patient outcome.(1-3)

Although we did not specifically focus on the implementation of value-based healthcare in the ICU, the studies on delirium prediction and prevention that we described in this thesis facilitate the proposed framework (5) and cover different parts that are needed to become a value-based intensive care organization. For the implementation of value-based healthcare in the ICU, two phases of care integration are proposed, phase one consisting of horizontal integration and phase two consisting of vertical integration. In phase one, a value-based intensive care organization should be build; that is a free-standing intensive care department with an intensivist as clinical leader of the ICUs and care following a value-based healthcare model in all involved ICUs.(5, 15) In phase two, the care for ICU patients should focus on their whole care cycle, including the episode of critical illness, as well as critical illness survivorship. This can be achieved by managing the care for ICU patients not only in the ICU, but also during their recovery in departments and institutions that provide post-ICU and post-acute care to ICU survivors.(5) Interventions during ICU follow-up should be personalized and targeting impairments of physical, psychosocial, functional, as well as cognitive origins, and include risk-based preventive strategies.(5)

To build a value-based intensive care organization in phase one, first patient value, meaning benefit for the patients' health outcome, should be created.(5) Because of the negative consequences of delirium on both the short-and long-term, prevention of delirium is important to create value for ICU patients. Our studies on delirium prediction (**chapter 2, 3, 4**) may well contribute to the process of becoming a value-based ICU, since delirium prediction enables the use of preventive measures in high risk patients only, resulting in efficient delirium care by a reduction of both resources and healthcare professionals' time, and thus costs. Furthermore, the use of both available delirium prediction models following a two-stage calculation,(16, 17) by using the E-PRE-DELIRIC model at ICU admission and the PRE-DELIRIC model in low-risk patients after 24 hours of ICU admission to calculate a patients' risk for delirium, allows for patient selection in clinical trials based on their risk for delirium. (**chapter 4**) This fits in with another important element in phase one, namely reducing waste, in this case waste of money, recourses, and healthcare professional - and patient time in research projects. So that the invested work adds to patient value.(5) Risk stratification in studies on ICU delirium is not only efficient in terms of reducing waste, it may also increase the chance of finding an effect, which ultimately might improve ICU patients' outcome and with that ICU patients' value. To smartly use current information technology, the predictors of both delirium prediction models can be built into readily available electronic healthcare software programs, making real-time data collection easy and cheap, and also allowing for alerts in case of

high-risk patients as a reminder for health care professionals to start delirium preventive measures.(18) A key element in the implementation of value-based healthcare in the ICU is to create value for patients by knowing the true costs of care and measurement and improvement of long-term patient outcome.(2, 3, 5) The proposed UNDERPIN-ICU study, **chapter 7**, might provide insight in both the clinical effectiveness and cost-effectiveness of a quality improvement strategy for ICU delirium care following the implementation of the multicomponent non-pharmacological intervention (MCI) program aimed at delirium prevention during a stepped wedge cluster randomized controlled trial in multiple Dutch ICUs. Since delirium is common in the ICU and associated with an increased ICU length of stay,(6) and a delay in transfer to a general ward is costly,(19) improving ICU efficiency and optimizing cost-effectiveness through delirium prevention is needed. In addition, data on quality of life and cognitive function of ICU patients at ICU admission as well as three and twelve months after ICU discharge will be collected providing insight in the ICU survivors' long-term outcome.(20) However, new studies on long-term outcome might consider to follow patients for an even longer period of time;(21) for example, a period of five years is already usual in other patient groups who also suffer from long-term complications of their illness.(22) Other important elements in phase one, assessment of the current state of the ICU and desired goals by health system leaders and a clinical and financial transformation, were not covered by our studies.(3, 5)

Key element in phase two of implementing value-based healthcare in the ICU is focusing on the total health of ICU patients including survival of their critical illness.(5) Up to 62% of the ICU survivors suffer from long-term cognitive impairment making it a growing public health problem.(7, 23) Studies reported an association between ICU delirium and impaired long-term cognitive outcomes.(23-25) Age is an important risk factor for delirium.(26) Since the world population is aging, the number of ICU survivors with cognitive impairment is expected to grow, warranting low-threshold monitoring of cognitive function in ICU survivors. In **chapter 8** we described the development of the abbreviated version of the cognitive failure questionnaire (CFQ-25). This short 14-item questionnaire (CFQ-14) will be helpful in phase two, since it can more easily be used in daily clinical practice to measure self-reported cognitive failure following ICU admission providing valuable information about ICU survivors cognitive function. For example, in outpatient clinics that are focused on follow-up of ICU patients. This information may provide insight in the functional implications of cognitive impairment and may be a starting point for the development of interventions towards creating value for ICU survivors by meeting their needs related to cognitive failure. However, prior to its use, the specific test-performance of the CFQ-14, including perceived burden, response rate and completion time, needs to be determined and compared to the original CFQ-25. Furthermore, the abbreviated 14-item CFQ should be validated with objectively measured cognitive function using neuropsychological tests. In addition, it is important to study whether the 14-item CFQ can be used at ICU admission

by ICU patients or their family members, as due to their critical illness ICU patients are often unable to fill out questionnaires at ICU admission themselves.

Other important impairments that ICU survivors suffer from were not part of this thesis.

Patient and family

Patients in the ICU are critically ill, meaning they have an impaired function of one or more vital organ systems with a high risk of life-threatening deterioration of their condition.(27) Therefore, ICU patients need monitoring and support of their vital functions by using complex technical equipment, for example mechanical ventilation in case of respiratory failure.(28) The ICU patients' acute critical illness and corresponding treatments are important risk factors to develop delirium in the ICU.(26) As a result, many ICU patients suffer from delirium, which is associated with multiple negative consequences, including prolonged mechanical ventilation, increased length of stay in the ICU and hospital, and an increased mortality rate in the short-term and cognitive impairment in the long-term.(6, 23) Due to these negative consequences ICU survivors often have problems returning to the life they lived before their ICU admission. Therefore, delirium management should be an important part of ICU care to improve ICU patients' outcome in both the short- and long term.

The currently recommended ICU guidelines and care bundles focus on the prevention of these negative consequences of their critical illness,(29) by monitoring pain, agitation and delirium (PAD guidelines)(30) and providing ICU care using the assessment, prevention, and management of pain; both spontaneous awakening and breathing trials; choice of analgesia and sedation; delirium assessment; early mobility and exercise; and family engagement and empowerment (ABCDEF) bundle.(29) Although it is shown that their use positively affects delirium outcome,(31) implementation of these guidelines in the daily clinical ICU practice is going slow and varies across individual components.(29, 31) Especially family engagement and empowerment needs further implementation towards a full realization of patient- and family-centered ICU care.(31) In patient-centered-care the patient's beliefs, values and preferences are directive in treatment recommendations and decision making.(32, 33) Patient- and family-centered-care (PFCC) is an extension of patient-centered care and defined as 'an approach to the planning, delivery, and evaluation of healthcare that is grounded in mutually beneficial partnerships amongst healthcare providers, patients, and families'.(34) This approach, that is necessary for a holistic and value based healthcare delivery,(1, 35) recognizes the importance of the contribution of family to care for ICU patients.(28, 36) For example, since patients in the ICU often are intubated and cannot speak for themselves, the family of ICU patients can facilitate a better communication and understanding of the patient.(37) Still, the main priority is to meet the patient's needs and thus family involvement should be in tune with the patient's wishes.(28)

Family and patient involvement has been divided in different components that range from relatively passive to active forms, including involvement as: presence; having needs met/being supported; communication; decision making; and contributing to care.(36) Regardless of the form, to facilitate family involvement an open ICU visiting policy is a prerequisite, meaning unrestricted visiting hours in the ICU. Access to a patient should depend on the patient's preference, unless the presence of family violates the patient's medical condition.(31) In Europe over 80% of the ICUs do not have unrestricted visiting hours and even over 60% allow visitation for less than 5 hours per day.(31) Of interest, an open ICU visiting policy is a promising strategy for delirium prevention, since absence of visitors has been indicated a risk factor for delirium,(38) and a recent single-center before-after study showed that an extended ICU visiting policy of 12 hours per day was associated with a decreased delirium incidence and duration.(39) This might be explained by the fact that extended visiting hours allow family to visit ICU patients longer, more often, and in a flexible schedule and thus for more active forms of family involvement in ICU care.(39) It is shown that when family is actively involved in patient care, there is a higher prevalence of interventions for delirium prevention and treatment in the ICU.(31) This is important knowledge to take into account when implementing delirium preventive strategies.

Important for patient and family involvement in ICU care is having their needs met, and support and inform them about the ICU patient's condition.(36) The studies on delirium prediction in the ICU that we described in **chapter 2, 3 and 4** facilitate adequate communication with ICU patients and their families about the patient's risk to develop delirium during his or her complete ICU length of stay. If it is known that a patient is at high risk to develop delirium, family members can be educated about delirium and engaged to help provide strategies to reduce the incidence or duration of delirium.(40)

The proposed multicomponent non-pharmacological intervention (MCI) program, aimed at ICU delirium prevention, (**chapter 5 and 6**) , consists of standardized protocols focusing on five modifiable delirium risk factors: cognitive impairment, sleep deprivation, immobility and visual and hearing impairment. The effect of this MCI program on delirium outcomes will be studied during the nUrsiNg DEliRium Preventive INterventions in the Intensive Care Unit (UNDERPIN-ICU) study, of which we described the study protocol in **chapter 7**. During the UNDERPIN-ICU study ICU patients' families not only will be an important link to enable the ICU nurses to properly perform the interventions of the different protocols of the MCI program, family members will also be involved in ICU care during many interventions. Within the different protocols family involvement is needed in levels ranging from more passive to active forms including presence, communication and contributing to care.(36) For example, in the orientation protocol facilitation of regular visits from family by providing wide visiting hours is asked. To get to know an ICU patient, the family and nurse should compile a poster containing information about

the patient, including preferred calling name, favorite music, books and hobbies. In the sleep deprivation protocol the patient's family should be asked what the patient does at home to promote sleep and if necessary to bring any devices. In the immobility protocol the presence of family is stimulated. Whenever feasible, instructed family should initiate, encourage and remind the patient to mobilize early or do exercises multiple times a day. (20, 41) Due to its aim and the high degree of family involvement, this MCI program might be a valuable addition to the currently promoted guidelines that focus on the prevention of negative consequences of the patient's critical illness (29, 30) and it will contribute to further implementation of patient- and family-centered care. Moreover, the degree of family involvement in the interventions of the MCI program might improve its implementation during the UNDERPIN-ICU study.(31) In the process evaluation that will be part of the UNDERPIN-ICU study it is essential to monitor the visiting policy and degree of family involvement in ICU care in each participating ICU before as well as after the implementation of the MCI program.

Of interest, when shown effective, the cognitive training exercises (**chapter 6**) that are part of the cognitive impairment protocol can be executed with ICU patients by their family instead of by nurses as proposed during the UNDERPIN-ICU study period. Not only because of the fact that the pilot study showed that the exercises are practicable and easy to execute, but especially because of the added value of the involvement of family in ICU patients' care which is also stimulated by many ICU societies and committees worldwide.(42, 43) Furthermore, we involved ICU patients in the development of the cognitive training exercise protocol during a pilot study which we described in **chapter 6**. Following purposive sampling cooperative ICU patients that were willing to participate were asked for their opinion about the feasibility, operationalized as practicability and burdening, of the cognitive training exercises that were initially based on available literature and expert opinion. This pilot study was an important step in view of family- and patient-centered-care in the ICU. However, due to the degree of illness of this patient group it was not feasible to incorporate ICU patients in the development of the other standardized protocols of the MCI-program during the Delphi study. For future research on the development of interventions for ICU patients, one might consider consulting ICU survivors and/or their family members as part of an expert panel to take their values and preference into account.

Role of ICU nurses

ICU nurses are at the frontline of the care for ICU patients, they are at the bedside around the clock, continuously monitoring the patients' health status, coordinating and providing patient care and supporting the patients and their family during the ICU stay.(28, 44) Therefore, ICU nurses are often the first to notice a change in the patients' condition and play a critical role in responding to these changes and preventing adverse events.(45) As a result, ICU nurses are essential for successful delirium management in the ICU, consist-

ing of delirium monitoring, as well as prevention and treatment. Managing ICU-acquired delirium is important, since ICU delirium not only leads to impaired short- and long-term patient outcome, it also increases ICU nurses workload.(46)

Currently, based on the PAD-guidelines (30) ICU nurses' role in delirium management is mainly focused on delirium monitoring by using one of the recommended delirium assessment tools, the Confusion Assessment Method for the ICU (CAM-ICU) (47, 48) and the Intensive Care Delirium Screening Checklist (ICDSC).(49) Delirium prevention is a small part of this guideline due to the lack of compelling data demonstrating a positive effect on delirium outcome. No positive recommendations are provided for delirium treatment or pharmacological delirium prevention, and for non-pharmacological measures to prevent delirium, only early mobilization of ICU patients is recommended. For pain, agitation and delirium management several strategies are recommended, including daily sedation interruption, promoting sleep, and an inter-disciplinary team approach.(30) Recently, the ABCDEF bundle added family engagement and empowerment to these strategies. These strategies focus on the commitment of all members of the inter-professional ICU team, including ICU nurses, physical therapists, social workers, nurse practitioner or physician assistant, and physicians.(29) Given the central role of ICU nurses in the care for ICU patients, we feel their position within ICU care should be exploited in new delirium preventive strategies.

Since delirium is associated with multiple risk factors,(26, 50) an MCI program targeting multiple modifiable delirium risk factors for delirium and that is carried out by nurses, seems a promising strategy for delirium prevention or mitigation of delirium consequences. In non-ICU patients it is already shown that a program including non-pharmacological interventions that was focused on cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment significantly reduced both delirium incidence and duration. (51, 52) To date, insufficient proof is available for the use of such a program in ICU patients. In **chapter 5 and 6** we described the development of an MCI program. This MCI program consists of standardized multicomponent interventions tailored to ICU patients and is based on scientific literature as well as expert and patient opinion. The use of a literature review provided a scientific base for the draft intervention program, and during both a Delphi study and a pilot study the MCI program was tailored to ICU patients. Given that ICU nurses will have a central role in carrying out the MCI program, they were extensively involved in the development of the program. A third of the experts who participated in the Delphi study were ICU nurses. This was not only important for the sense of ownership to stimulate the response rate during the Delphi study (**chapter 5**), it also might improve the implementation of the MCI program during the future UNDERPIN-ICU study (study protocol described in **chapter 7**).(53-55) Also, in the pilot study (**chapter 6**) ICU nurses participated in the rating of the feasibility of cognitive training exercises in ICU patients, which further improved the chance for a successful implementation of the MCI program

during the future UNDERPIN-ICU study.

The central role of ICU nurses in the MCI program might stimulate nurse empowerment and clinical leadership within the participating ICUs during the future UNDERPIN-ICU study, and fits perfectly within the current and future perspectives on the nurse profile.(56) In the Dutch nurse 2020 profile, an important role of the nurse is to provide both personalized and standardized care, in a holistic manner by taking into account the patients' wishes and context.(56) The MCI program will ask for both clinical expertise and taking into account the ICU patients' values by using the standardized protocols of the program as appropriate for each specific ICU patient. After the two-months training period, nurses will be asked to adopt a proactive attitude and to carry out the MCI program from their own expertise in collaboration with the patients, their families and other disciplines. Due to the implementation of the MCI program during the future UNDERPIN-ICU study the ICU nurses not only may increase their knowledge on delirium management and their potential influence on delirium prevention, they might also contribute to a quality improvement of delirium care within their ICU, since it is known that currently available guidelines and care bundles on delirium care are implemented incompletely and further improvement is necessary.(29, 31) Ultimately, the ICU nurses might positively influence delirium outcome and as a consequence decrease their own workload.(46)

However, to efficiently use nurses' time for delirium prevention, it is recommended to only carry out preventive measures in those patients at high-risk to develop delirium, especially since these patients may benefit the most from early prevention.(57) It is well known that healthcare professionals' delirium predictions are less accurate than those of a delirium prediction model,(58) therefore routine prognostic delirium evaluation in daily ICU practice might be a solution. In **chapter 4** we suggested to use the E-PRE-DELIRIC model to predict patients' delirium risk immediately after ICU admission and to update the risk scores of the low risk patients after 24 hours in the ICU with the PRE-DELIRIC model, to achieve the most optimal prediction of ICU delirium. To calculate patients' risk using both the E-PRE-DELIRIC and PRE-DELIRIC models, it is necessary to collect all data of the models' predictors and to process this data in the patient's file. ICU nurses have an important role in the data collection and - processing. For example by asking the patient, the patient's family or general practitioner about the patient's history on cognitive impairment or alcohol abuse, or to collect blood samples of the patient. When the patient's risk for delirium is calculated, ICU nurses are the most designated health care professionals to take action in case of a high risk for delirium and adopt a leadership attitude in providing delirium preventive measures and informing both the patient and family about the calculated delirium risk together with the ICU physicians.

Methodological considerations

Methodological considerations for each separate study were described in the corresponding chapter in this thesis. In this paragraph, we will discuss general methodological considerations. The studies described in this thesis were conducted using various designs. For the studies on early prediction of delirium in ICU patients we used a multinational prospective cohort design in ICUs from Australia, Europe, and North America. This is the recommended design to answer prognostic questions, as cohort studies are not restricted by strict eligibility criteria that might limit generalizability.(59) In addition, it is preferable to conduct a prospective study to optimally measure and document the predictors and outcome of the study,(59, 60) as it is important to standardize and clearly define the predictors and methods of measurement to enable reproducibility by others and to enhance the applicability of the results into practice.(60, 61). The multinational character of the studies further improved the generalizability of the results to other ICUs in the world. One might argue that adjusting the ICU delirium prediction models to a specific center to account for differences in ICUs may improve both models' performance. It is plausible that this is correct, however, this would obviously limit the generalizability. Therefore, we prefer a general prediction model that can be widely used rather than an ICU specific model.

It is important to take the assessment of our main outcome delirium into consideration. This was assessed using one of the recommended delirium assessment tools the CAM-ICU (30, 47) or the ICDSC in all our studies.(49) Naturally, the performance of both models in daily practice differs and is not optimal.(62, 63) However, in our studies ICU patients were screened for delirium at least twice daily, during the complete ICU length of stay. This increased the chance of correct delirium scores, in light of the fluctuating course of delirium. In addition, we also defined delirium to be present when haloperidol and other anti-psychotics were administered for delirium treatment to prevent false negative delirium assessments, since it is shown that the sensitivity of the delirium assessment tools in daily clinical practice can be low.(58, 63, 64)

The multicomponent non-pharmacological intervention (MCI) program that we developed and tailored to ICU patients during both a Delphi and a pilot study has a strong foundation, as it is based on scientific literature as well as expert and patient opinion. However, one might consider the literature review that was performed as part of the Delphi study a weakness, as it was not a systematic review. Consequently, reproducing the literature search is more difficult. However, the draft MCI program was based on the available literature at time of the search and therefore a representative draft program was proposed to the experts to judge the feasibility and completeness for ICU patients during the subsequent stages of the Delphi study. In addition, recent pilot studies (65, 66) aimed at reducing ICU delirium by the implementation of a non-pharmacological protocol

targeted mostly the same risk factors with comparable interventions as our MCI program. We will study the effect of the MCI program on delirium outcome during a large stepped wedge cluster randomized controlled trial. In contrast to recent pilot studies,(65, 66) this design allows for sufficient proof regarding the efficacy of an MCI program on delirium in ICU patients.

Directions for future research

Delirium prediction in ICU patients

For future research we recommend to check for the necessity of an update of both available delirium prediction models, the E-PRE-DELIRIC and PRE-DELIRIC models, as important new risk factors for delirium in the ICU may emerge due to changes in daily clinical practice in the ICU. For an update, called model revision, it is necessary to have insight in new risk factors for delirium, both available at ICU admission or within 24 hours of ICU admission. Subsequently, a new prediction study is needed to determine which of the new risk factors improve the models' performance and should be used for model revision.

Furthermore, the development study of the E-PRE-DELIRIC model showed that while the delirium incidence remained stable over time in the four groups in this study, the predictive value of the model increased over time. In future research, it would be interesting to study the influence of differences between early and late delirium on delirium prediction. In addition, the influence of the method of delirium assessment on the performance of both delirium prediction models could be explored, as new promising techniques like EEG monitoring, or a combination of different available delirium assessment tools will become available soon. Of interest, future research also could focus on the development of a prediction model that can be used daily to calculate a patient's risk for delirium the next day. Such a model might provide more precise predictions, since patients' illness severity and thus delirium risk may fluctuate during their ICU stay due to for example infections, complications, surgery or other factors that influence patients' risk for delirium.

Non-pharmacological delirium prevention

The effectiveness of the MCI program that we developed will be studied in ICU patients during the future UNDERPIN-ICU study. Essential in the process evaluation as part of the study is to monitor the visiting policy and degree of family involvement in ICU care in each participating ICU before as well as after the implementation of the MCI program.

Furthermore, the effect of passive cognitive training in ICU patients could be explored. In patients who are not responsive and unable to carry out cognitive training exercises, it might be effective to passively provide cognitive stimulation using for example audio or visual stimulation. Possible strategies may be based on techniques that are used in the rehabilitation process of patients suffering from coma (i.e. early intensive neuro rehabilitation in Dutch referring to VIN (vroege intensieve neurorevalidatie)).

General conclusions

Delirium prediction in ICU patients

Our studies showed that both the E-PRE-DELIRIC and PRE-DELIRIC models statistically perform moderate-to-good. Although the predictive accuracy of the PRE-DELIRIC is somewhat better, the E-PRE-DELIRIC model scores significantly better on user convenience. Moreover, the PRE-DELIRIC model needs data obtained during 24 hours, while the E-PRE-DELIRIC can be obtained at ICU admission, allowing direct preventive measures in patients at high risk for delirium, as well as stratified randomization in studies at the point of ICU admission. In patients who appear to be at low risk for delirium at ICU admission, it is of additional value to update their predicted risk scores using the PRE-DELIRIC model after 24 hours in the ICU.

Non-pharmacological delirium prevention

We developed a feasible multicomponent non-pharmacological intervention program aimed at preventing and mitigating delirium in the ICU based on expert consensus. This MCI program has a strong foundation as it is based on literature as well as expert and patient opinion. As a next step, further research is carried out by means of the UNDER-PIN-ICU study to determine the clinical effect of the MCI program including cognitive training on ICU delirium.

We developed and validated an abbreviated 14-item version of the CFQ which showed similar performance as the original full 25-item questionnaire. It is feasible to use this CFQ-14 to measure self-reported cognitive failure in ICU survivors, possibly yielding increased response rates and efficiency.

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CHAPTER 10

Summary

Summary

Delirium is defined as acute brain dysfunction, characterized by a disturbance in attention, awareness, and cognition. It fluctuates during the course of the day and is caused by an underlying medical condition. Delirium is a common problem in the Intensive Care Unit (ICU), burdening around a third of the patients and is associated with worse patient outcome warranting the use of strategies to prevent ICU delirium.

Current delirium management guidelines emphasize the need for prevention of delirium by performing non-pharmacological interventions, in which ICU nurses play a central role. Identification of patients' risk for delirium is essential to facilitate efficient use of these promising delirium preventive strategies in the ICU.

Main aims of the thesis

- To develop and validate an early ICU delirium prediction model, to determine if delirium can be reliably predicted immediately after ICU admission;
- To gain insight in the statistical performance and user convenience of different available ICU delirium prediction models;
- To develop a multicomponent non-pharmacological intervention program aimed at preventing delirium in ICU patients targeting the modifiable delirium risk factors cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment;
- To develop and validate an abbreviated self-reported questionnaire to easily measure cognitive failure in ICU survivors.

Delirium prediction in ICU patients

The first part of this thesis focused on early **prediction of delirium** in critically ill patients.

After a general introduction (**chapter one**) we described a large multinational prospective cohort study in thirteen ICUs from seven countries in **chapter two**. Multiple logistic regression analysis was used to develop and validate the Early PREdiction model for DELIRium in ICu patients (E-PRE-DELIRIC model). Over 2,900 ICU patients were included. The E-PRE-DELIRIC model consists of only nine predictors that are available at ICU admission: age, history of cognitive impairment, history of alcohol abuse, blood urea nitrogen, admission category, urgent admission, mean arterial blood pressure, use of corticosteroids, and respiratory failure. The model showed a moderate-to-good statistical performance, which remained similar after temporal validation. Of interest, the predictive accuracy of the model was higher for delirium that developed later compared to delirium that developed early following ICU admission. The E-PRE-DELIRIC model enables the identification of patients' delirium risk for the complete ICU length of stay immediately at admission using only nine predictors, allowing the use of early preventive strategies aimed at the reduction of incidence and severity of ICU delirium in high-risk patients.

As a general rule, before any (ICU) prediction model can be used outside the developmental settings, it is essential to confirm its predictive performance in a new cohort of patients, independent from the dataset used during development and initial validation, and to determine its generalizability. As no external validation was performed for both available ICU delirium prediction models, the E-PRE-DELIRIC and recalibrated PRE-DELIRIC model, we externally validated both models as described in **chapter three**. We performed a multinational cohort study including approximately 2,200 patients from 11 ICUs from Australia, Canada, Europe, and the United States. Using a large, heterogeneous cohort of critically ill adults both the E-PRE-DELIRIC and PRE-DELIRIC models showed a moderate-to-good statistical performance in a new and independent sample allowing for generalization to other ICUs in the world. Consistent with the results from other primary external validation studies, the discrimination of both the E-PRE-DELIRIC and (recalibrated) PRE-DELIRIC model was lower in the validation study than in the original studies. However, despite this somewhat lower predictive value, the models still provide a more accurate risk score compared to prediction by clinicians.

To enable clinicians to choose between both available delirium prediction models, we compared the predictive performance and user convenience of the E-PRE-DELIRIC and PRE-DELIRIC models and determined the value of the use of both models in a two-stage calculation in **chapter four**. In this study we showed that while both ICU delirium prediction models statistically performed moderate-to-good, the PRE-DELIRIC model predicted delirium somewhat better. However, ICU physicians rated the user convenience of E-PRE-DELIRIC superior to PRE-DELIRIC. Moreover, the PRE-DELIRIC model needs data obtained during the first 24 hours of ICU admission, while the E-PRE-DELIRIC can be obtained at ICU admission, allowing direct preventive measures in patients at high risk for delirium, as well as stratified randomization in studies at the moment of ICU admission. Importantly, our analyses indicate that when the E-PRE-DELIRIC model predicts a low risk for delirium, an additional calculation using the PRE-DELIRIC model after 24 hours in the ICU increases the model's sensitivity to detect patients that will develop delirium. In other words, with this two-step approach, patients who are incorrectly identified as low-risk patients at ICU admission, can still be identified 24 hours later. Based on these results we suggest to primarily use the E-PRE-DELIRIC model and in patients who appear to be at low risk for delirium at ICU admission, to update their predicted risk scores using the PRE-DELIRIC model after 24 hours in ICU.

Non-pharmacological delirium prevention

The second part of this thesis focused on **non-pharmacological prevention of delirium** in critically ill patients. In **chapter five and six** we described the development of a multicomponent non-pharmacological intervention (MCI) program aimed at delirium prevention in the ICU consisting of nursing and physical therapy interventions, focusing

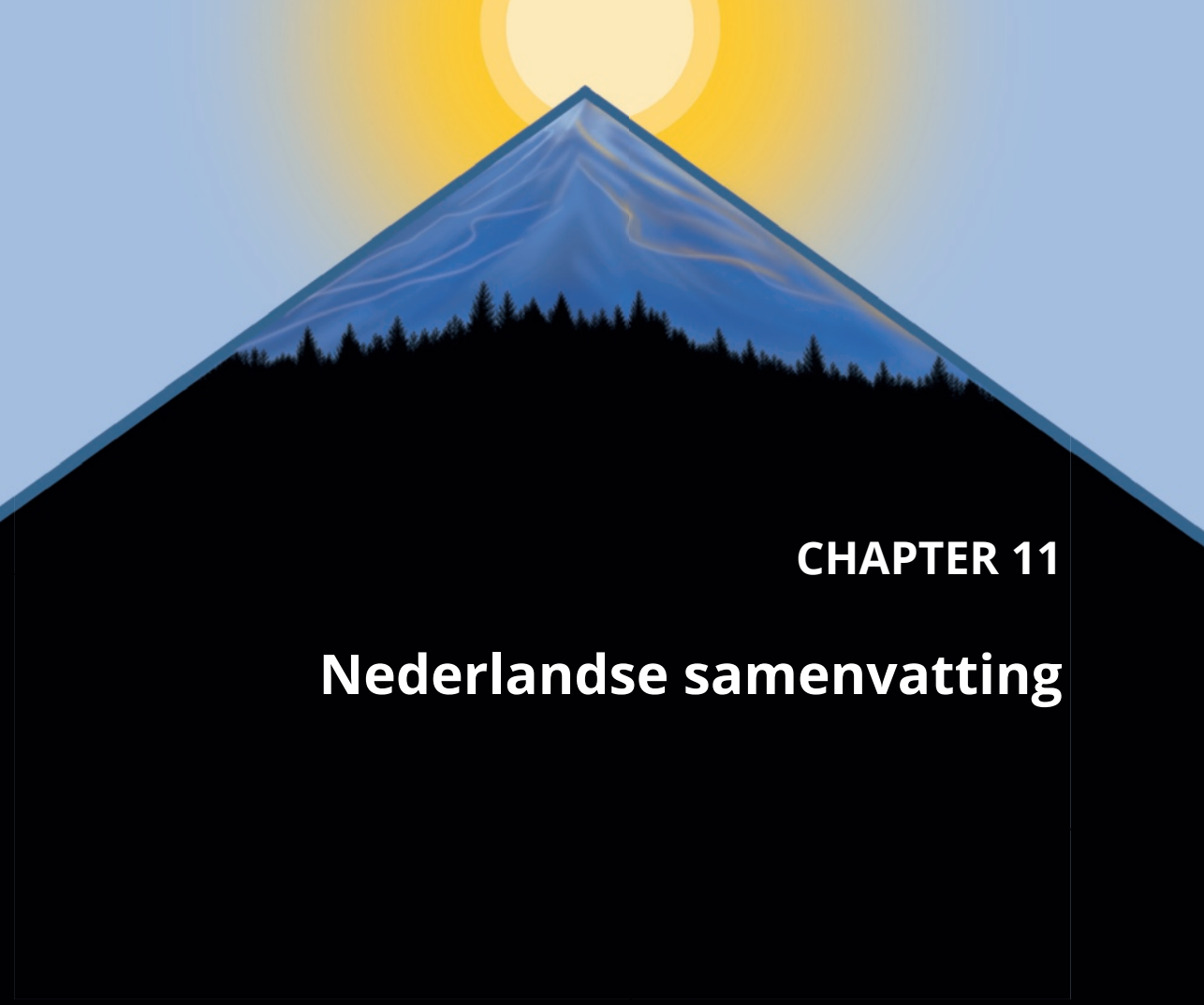
on cognitive impairment, sleep deprivation, immobility, and visual and hearing impairment. In **chapter five** we described a modified RAND Delphi study during which we used experts' opinion to achieve group consensus on the feasibility and completeness of an MCI program for ICU patients. A total of 38 experts were selected following purposive sampling, consisting of critical care nurses, intensivists, physical therapists, and senior nurse scientists. Multiple stages from the modified RAND/UCLA Appropriateness Method (RAM) were used, including a literature review to develop a concept MCI program, and individual feasibility rating and ranking of the interventions. After two rounds the experts agreed on the feasibility of the interventions targeting sleep deprivation, immobility, visual and hearing impairment, and cognitive impairment. However, no consensus was reached on cognitive training, which consists of daily cognitive training exercises to maintain cognitive function by targeting skills in the area of attention, different forms of memory, and executive functioning. Because of the necessity of consensus before adding an intervention to the final MCI program, an additional prospective cohort pilot study was conducted to examine the feasibility of the use of cognitive training exercises in ICU patients for both the patients and nurses (**chapter six)**. A set of cognitive training exercises was composed based on available literature and expert opinion and tested during multiple rounds for feasibility in ICU patients as well as in nurses. Feasibility of the exercises, defined as the degree to which the exercises were rated as practicable and burdening, was evaluated using Likert scales and open-ended questions, vital signs and time investment. In total, 75 ICU patients were included. During the first round eleven exercises were separately tested by nursing researchers in 44 cooperative patients (of whom 22 were delirious). While vital signs did not alter during execution, four exercises were evaluated as burdensome and therefore excluded. In a second round the remaining exercises were tested in 31 patients (of whom 16 were delirious) by their attending ICU nurse. All exercises were rated as practicable and not burdening by both delirious and nondelirious ICU patients, and by the nurses. Total time investment per exercise was median 4.5 minutes [Interquartile range; 3.0-5.0 minutes]. Thus, this pilot study showed that the use of cognitive training exercises is feasible for ICU patients, as well as for ICU nurses, even in delirious ICU patients that are cooperative. Future research is needed to determine the clinical effect of the MCI program including cognitive training on ICU delirium. This means we developed a feasible multicomponent non-pharmacological intervention (MCI) program to prevent ICU delirium based on expert consensus. These results represent an essential step towards a future stepped wedge cluster randomized controlled trial to determine the effect of an MCI program on delirium in ICU patients.

In **chapter seven** we described the study protocol for the multicenter stepped wedge cluster randomised controlled trial (nUrsiNg DEliRium Preventive INterventions in the ICU; the UNDERPIN-ICU study) in which the effect of the MCI program on the number of delirium-coma-free days in 28 days in the ICU will be studied. The MCI program focuses on

delirium risk factors that can be influenced by nursing and physical therapy interventions, aimed to counteract sleep deprivation, immobility, visual and hearing impairment, and cognitive impairment. Within a study period of 28 months ten Dutch ICUs will implement the MCI program in a randomized order. Every two months the program will be implemented in an additional ICU following a two months period of staff training. ICU patients aged ≥18 years (surgical, medical, or trauma) and at high risk to develop delirium, determined using the E-PRE-DELIRIC model, will be included. Secondary outcome measures are ICU length of stay, number of days of survival and delirium incidence, as well as patient-reported outcome measures, such as quality of life and cognitive functioning.

Identification of cognitive failure following ICU delirium is essential and clinically relevant as it provides clinicians with important functional information necessary for the support of the ICU survivors during their recovery. Since ICU survivors often develop physical, mental, and cognitive impairments following ICU discharge, several questionnaires are needed to study the relevant issues related to these impairments resulting in an overload of questions for ICU survivors. In **chapter eight** we described the development and validation of an abbreviated version of the Cognitive Failure Questionnaire (CFQ) that can be used by patients as part of self evaluation to measure functional cognitive outcome in ICU survivors. We conducted a retrospective observational cohort study in two Dutch university hospitals. Cognitive functioning was evaluated between 12 and 24 months after ICU discharge using the full 25 item CFQ (CFQ-25). Over 1,700 adult ICU survivors were included for analysis, around half in each hospital. Following forward selection in a linear regression model the most optimal model included 14 CFQ items. This abbreviated version reproduced over 98% of the variance of the original 25 item CFQ and the outcome scores were highly correlated with the original CFQ-25 outcome scores. Furthermore, the CFQ-25 outcome scores were replaceable by the CFQ-14 outcome scores. So, the abbreviated CFQ-14 was comparable to the CFQ-25 and therefore can be used to examine ICU survivors' perception of their cognitive functioning more efficiently than the full CFQ-25, possibly yielding both an improved compliance of survivors to fill out the complete questionnaire and an increased response rate.

In **chapter nine,** the general discussion, we presented the main results described in this thesis in a broader theoretical and practical context at different levels of the ICU healthcare system: organization, ICU nurse, patient and family and reflected on the implications of our findings for ICU practice. Followed by a discussion of methodological considerations, aims for future research, and the general conclusions.



CHAPTER 11

Nederlandse samenvatting

Samenvatting

Delirium, ook wel delier of acute verwardheid genoemd, is gedefinieerd als een acute stoornis van het brein. Het wordt gekenmerkt door bewustzijnstoornissen, aandachtsstoornis en een gestoorde cognitie, waarbij de symptomen fluctueren gedurende de dag. Er is altijd een onderliggende medische conditie die ten grondslag ligt aan het ontstaan van een delirium. Delirium is een veelvoorkomend probleem op de Intensive Care (IC) en geassocieerd met een slechtere prognose voor de patiënt. Ligduur in het ziekenhuis, zelfs sterfte wordt negatief beïnvloed door de aanwezigheid van delirium. Omdat ongeveer een derde van de IC patiënten belast is met de negatieve gevolgen van delirium, is het gebruik van preventieve strategieën ter preventie van delirium op de IC noodzakelijk.

De huidige delirium management richtlijnen benadrukken het belang van delirium preventie middels het gebruik van non-farmacologische interventies waarin verpleegkundigen een centrale rol spelen. Vroegtijdige identificatie van het risico op delirium van IC-patiënten is essentieel voor een efficiënt gebruik van deze veelbelovende strategieën ter preventie van delirium op de IC.

Doelstellingen van dit proefschrift

- Het ontwikkelen en valideren van een vroeg IC delirium predictiemodel om te bepalen of delirium meteen na opname op de IC betrouwbaar voorspeld kan worden;
- Het verkrijgen van inzicht in de voorspellende waarde en het gebruikersgemak van verschillende beschikbare IC delirium predictiemodellen;
- Het ontwikkelen van een non-farmacologisch interventieprogramma ter preventie van delirium bij IC-patiënten, bestaande uit meerdere componenten, gericht op de beïnvloedbare delirium risicofactoren: slaapgebrek, immobiliteit, visuele en auditieve beperkingen, en cognitieve stoornissen;
- Het ontwikkelen en valideren van een verkorte vragenlijst om gemakkelijk zelfgerapporteerde cognitief falen in IC-overlevenden te meten.

Delirium predictie bij IC-patiënten

Het eerste deel van dit proefschrift is gericht op het **vroeg voorspellen van delirium** bij kritiek zieke patiënten.

Na een algemene inleiding in **hoofdstuk 1** beschrijven we in **hoofdstuk 2** een grote multinationale prospectieve cohort studie die is uitgevoerd in dertien IC's uit zeven landen. Multiple logistische regressie is gebruikt voor het ontwikkelen en valideren van het vroeg IC delirium predictie (E-PRE-DELIRIC) model. Meer dan 2900 patiënten werden geïncludeerd in deze studie. Het E-PRE-DELIRIC model bestaat uit negen voorspellende factoren ('pre-

dictoren') die meteen bij opname beschikbaar zijn: leeftijd, een geschiedenis van cognitief falen of van alcoholgebruik, ureum, opname categorie, acute opname, gemiddelde arteriele bloeddruk, gebruik van corticosteroïden, en respiratoir falen. Bij de ontwikkeling liet het E-PRE-DELIRIC model een matige tot goede voorspellende waarde zien die gelijk bleef na validatie. Relevant is dat de voorspellende waarde van het model beter was voor delirium dat later tijdens de IC-opname ontstond in vergelijking met delirium dat al vroeg na de IC-opname ontstaan was. Het E-PRE-DELIRIC model maakt het mogelijk om met slechts negen predictoren het risico van patiënten op delirium tijdens de IC-opname te identificeren. Hierdoor kunnen al vroeg preventieve strategieën ingezet worden bij IC-patiënten met een verhoogd risico op delirium ter vermindering van de delirium incidentie en -ernst.

Als algemene regel geldt dat het bepalen van de generaliseerbaarheid van een predictiemodel noodzakelijk is voorafgaand aan het gebruik van een predictiemodel buiten de setting waarin het ontwikkeld is. Hierbij wordt de voorspellende waarde van het model onderzocht in een cohort van patiënten dat onafhankelijk is van het cohort dat gebruikt werd tijdens de ontwikkeling en initiële validatie van het model. Omdat er voor beide beschikbare IC delirium predictiemodellen, het E-PRE-DELIRIC model en het PRE-DELIRIC model, eerder geen externe validatie uitgevoerd was, beschrijven we in **hoofdstuk 3** de externe validatie van beide modellen. We hebben een multinationale cohort studie uitgevoerd met bijna 2200 patiënten vanuit 11 IC's gelegen in Australië, Canada, Europa en de Verenigde Staten. In dit grote, heterogene en onafhankelijke cohort van ernstig zieke volwassenen lieten zowel het E-PRE-DELIRIC als het PRE-DELIRIC model een matige tot goede voorspellende waarde zien. Hierdoor is generalisatie van de resultaten naar andere IC's over de wereld nu toegestaan. Net als in andere studies die primair gericht waren op de externe validatie van predictiemodellen, was de discriminatie van zowel het E-PRE-DELIRIC als het (gerekalibreerde) PRE-DELIRIC model lager in de validatiestudie dan in de originele studies. Echter, ondanks de wat lagere voorspellende waarde geven de predictiemodellen nog steeds een betere voorspelling van het risico op delirium dan de voorspelling door zorgverleners.

Om het zorgverleners mogelijk te maken te kiezen tussen beide beschikbare IC delirium predictiemodellen, hebben we in **hoofdstuk 4** de voorspellende waarde en het gebruikersgemak van het E-PRE-DELIRIC en PRE-DELIRIC model vergeleken en bepaald wat de waarde was van het gebruik van beide modellen in een tweetrapsberekening. In deze studie hebben we laten zien dat, terwijl beide modellen een matige tot goede voorspellende waarde hadden, het PRE-DELIRIC model delirium iets beter voorspelde. Echter, de IC-artsen scoorden het gebruikersgemak van het E-PRE-DELIRIC model juist hoger dan dat van het PRE-DELIRIC model. Bovendien heeft het PRE-DELIRIC model data nodig verkregen gedurende de eerste 24 uur van IC-opname, terwijl het E-PRE-DELIRIC model meteen bij

IC-opname kan worden ingevuld. Hierdoor kunnen preventieve maatregelen tot 24 uur eerder worden ingezet bij patiënten met een verhoogd risico op delirium en kan randomisatie plaatsvinden in toekomstige studies op basis van delirium risico.

Van belang is dat de analyses aangeven dat wanneer het E-PRE-DELIRIC model een laag risico op delirium voorspelt, een aanvullende berekening met het PRE-DELIRIC model na 24 uur IC-opname de sensitiviteit van het model verhoogt om de patiënten die delirium ontwikkelen te detecteren. Met andere woorden, met de tweetrapsberekening kunnen patiënten die incorrect geïdentificeerd zijn als laagrisico patiënten bij opname, 24 uur later alsnog geïdentificeerd worden. Gebaseerd op deze resultaten stellen we voor om primair het E-PRE-DELIRIC model te gebruiken en bij de patiënten die een laag risico op delirium blijken te hebben, hun voorspelde risico scores te updaten met het PRE-DELIRIC model na 24 uur IC opname.

Non-farmacologische delirium preventie

Het tweede deel van dit proefschrift is gericht op **non-farmacologische preventie van delirium** in IC-patiënten. In **hoofdstuk 5 en 6** beschrijven we de ontwikkeling van een multi-componenten non-farmacologisch interventie (MCI) programma, gericht op delirium preventie op de IC middels verpleegkundige en fysiotherapeutische interventies met als focus het beperken van slaapgebrek, immobiliteit, visuele en auditieve beperkingen, en cognitieve stoornissen. In **hoofdstuk 5** hebben we een aangepaste RAND Delphi studie beschreven waarbij we gebruik hebben gemaakt van de mening van experts om groepsconsensus te bereiken over de haalbaarheid en compleetheid van een MCI programma voor IC-patiënten. In totaal werden 38 experts, bestaande uit IC-verpleegkundigen, intensivisten, fysiotherapeuten en senior verplegingswetenschappers, geselecteerd met behulp van doelgerichte steekproeftrekking. Meerdere stadia van de aangepaste 'RAND/UCLA Appropriateness Method (RAM)' werden gebruikt, waaronder een literatuurstudie voor het ontwerp van een concept MCI programma, een individuele haalbaarheidsscore en rangschikking van de interventies. Na twee ronden waren de experts het eens over de haalbaarheid van de interventies gericht op slaapgebrek, immobiliteit, visuele en auditieve beperkingen en cognitieve stoornissen. Echter, er werd geen consensus bereikt over cognitieve training bestaande uit dagelijkse cognitieve oefeningen ter behoud en verbetering van de cognitieve functie door het richten op vaardigheden op het gebied van aandacht, verschillende vormen van geheugen en uitvoerende functies. Omdat het bereiken van consensus over een interventie noodzakelijk was voorafgaand aan het toevoegen van een interventie aan het definitieve MCI programma, werd een aanvullende prospectieve pilotstudie uitgevoerd om de haalbaarheid van cognitieve training oefeningen voor zowel IC-patiënten als verpleegkundigen te onderzoeken (**hoofdstuk 6**). Op

basis van literatuur en de mening van experts werd een set van cognitieve training oefeningen samengesteld en tijdens meerdere ronden getest op haalbaarheid voor zowel de IC-patiënten als verpleegkundigen. De haalbaarheid van de oefeningen, gedefinieerd als de mate waarin de oefeningen als uitvoerbaar en belastend werden gescoord, werden geëvalueerd met behulp van Likertschaal- en open vragen, vitale functies en tijdsinvestering. In totaal werden er 75 patiënten geïncludeerd. Tijdens de eerste ronde werden elf oefeningen apart van elkaar getest door verpleegkundige onderzoekers bij 44 coöperatieve patiënten van wie 22 delirant waren. Terwijl de vitale functies van de patiënten niet veranderden tijdens de uitvoering van de oefeningen, werden vier oefeningen beoordeeld als te belastend en daarom geëxcludeerd. Tijdens de tweede ronde werden de overgebleven oefeningen getest door de IC-verpleegkundigen van dienst bij 31 patiënten van wie er 16 delirant waren. Alle oefeningen werden beoordeeld als uitvoerbaar en niet belastend door zowel delirante als niet-delirante IC-patiënten en door de verpleegkundigen. De totale tijdsinvestering per oefening was mediaan 4,5 minuten [1^{e} en 3^{e} kwartiel; 3,0-5,0 minuten]. Concluderend, deze pilotstudie liet zien dat het gebruik van cognitieve training oefeningen haalbaar is voor zowel IC-patiënten als verpleegkundigen en zelfs voor coöperatieve delirante patiënten. Toekomstig onderzoek is nodig om het klinische effect van het MCI programma inclusief cognitieve training op IC delirium te bepalen. Dit betekent dat we op basis van overeenstemming van experts een haalbaar multi-componenten non-farmacologisch interventie (MCI) programma ter preventie van IC delirium ontwikkeld hebben. Deze resultaten vertegenwoordigen een belangrijke stap als voorbereiding op een toekomstige verpleegkundige interventie trial om het effect van een MCI programma op delirium bij IC-patiënten te bepalen.

In **hoofdstuk 7** hebben een studieprotocol beschreven voor een verpleegkundige interventie studie (nUrsiNg DEliRium Preventive INterventions in the ICU; de UNDERPIN-ICU studie). Tijdens deze studie wordt het effect van het MCI programma op het aantal delirium- en comavrije dagen gedurende 28 dagen op de IC onderzocht. Het MCI programma richt zich op meerdere risicofactoren die kunnen worden beïnvloed door verpleegkundige en fysiotherapeutische interventies die gericht zijn op slaapgebrek, immobiliteit, visuele en auditieve beperkingen en cognitieve stoornissen. Binnen een studieperiode van 28 maanden gaan 10 Nederlandse IC's het MCI programma in gerandomiseerde volgorde implementeren. Elke twee maanden zal het programma geïmplementeerd worden in een nieuwe IC, waarbij gedurende een periode van twee maanden de staf getraind wordt. Patiënten van 18 jaar en ouder (opgenomen op de IC vanwege een chirurgische, medische of trauma reden) met een hoog risico op delirium, bepaald met het E-PRE-DELIRIC model, worden geïncludeerd. Secundaire uitkomsten zijn IC-opnameduur, het aantal overlevingsdagen in 28 dagen en delirium incidentie. Daarnaast worden zelfgerapporteerde patiëntuitkomsten bepaald, zoals kwaliteit van leven en cognitieve functie.

Identificatie van cognitief falen als gevolg van IC delirium is essentieel en klinisch relevant omdat het voor zorgverleners belangrijke informatie geeft wat van belang is voor het ondersteunen van IC-patiënten tijdens hun herstel. Aangezien IC-overlevenden vaak fysieke, mentale en/of cognitieve beperkingen ontwikkelen volgend op de IC-opname, zijn meerdere vragenlijsten nodig om alle relevantie kwesties gerelateerd aan deze beperkingen te bestuderen. De omvang van de vragenlijsten kan resulteren in een overbelasting voor IC-overlevenden. In **hoofdstuk 8** hebben we de ontwikkeling en validatie van een verkorte versie van de cognitief falen vragenlijst (CFQ) beschreven. De CFQ kan worden gebruik als onderdeel van zelfrapportage om de functionele cognitieve uitkomst van IC-overlevenden te meten. We hebben hiervoor een retrospectieve cohort studie uitgevoerd in twee Nederlandse universitaire ziekenhuizen. De cognitieve functie is tussen 12 en 24 maanden na IC-opname geëvalueerd middels de volledige 25 item CFQ (CFQ-25). Meer dan 1700 volwassen IC-overlevenden werden geïncludeerd in de analyse, ongeveer de helft in elk ziekenhuis. Het meest optimale model volgens 'voorwaartse selectie' van items in een lineair regressiemodel bevatte 14 CFQ items. Deze verkorte vragenlijst reproduceerde meer dan 98% van de variatie van de originele 25 item CFQ en de uitkomstscores waren sterk gecorreleerd met de originele CFQ-25 uitkomst scores. Ook waren de CFQ-25 uitkomstscores vervangbaar door de CFQ-14 uitkomstscores. Dus de verkorte CFQ-14 was vergelijkbaar met de CFQ-25 en kan daarom worden gebruikt om de perceptie van IC-overlevenden van hun cognitieve functie efficiënter te onderzoeken dan met de CFQ-25. Dit zal waarschijnlijk resulteren in een verbeterde naleving van IC-overlevenden om de complete vragenlijst in te vullen en een hoger responspercentage.

In **hoofdstuk 9**, de algemene discussie, hebben we de belangrijkste resultaten van dit proefschrift beschreven in het licht van een bredere theoretische en praktische context op verschillende niveaus van het IC-gezondheidssysteem: organisatie, IC-verpleegkundige, en patiënt en familie. Daarnaast reflecteren we op de klinische implicaties van ons onderzoek, gevolgd door een discussie van methodologische overwegingen, doelen voor toekomstig onderzoek en de algemene conclusies van dit proefschrift.

APPENDIX

List of abbreviations
Dankwoord
Curriculum Vitae
Portfolio
Publicatielijst

List of abbreviations

- ABCDEF-bundle: the assessment, prevention, and management of pain; both spontaneous awakening and breathing trials; choice of analgesia and sedation; delirium assessment; early mobility and exercise; and family engagement and empowerment bundle
- APACHE II and APACHE IV: Acute Chronic Health Evaluation II and IV
- AUROC: Area under the Receiver Operating Characteristic curve
- BUN: blood urea nitrogen
- CAM-ICU: the Confusion Assessment Method for the ICU
- CFQ: Cognitive Failures Questionnaire
- CFQ-25: 25-item Cognitive Failure Questionnaire
- CI: confidence interval
- DECISION study: *DE*lirium predi*CT*/on in the inten*SI*ve care unit: comparis*ON* of two delirium prediction models study
- DI: disagreement index
- DOS scale: Delirium Observation Screening scale
- DSM-5: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition
- E-CRF: Electronic Clinical Report Form
- E-PRE-DELIRIC model: Early PREdiction model for DELIRium in ICu patients
- ESICM: European Society of Intensive Care Medicine
- GCS-score: Glasgow Coma Scale-score
- HRQOL: health related quality of life
- ICDSC: the Intensive Care Delirium Screening Checklist
- ICU: intensive care unit
- IPR: interpercentile range
- IPRAS: interpercentile range adjusted for symmetry
- IRBs: Institutional Review Boards
- IRR: inter-rater reliability
- IQR: Interquartile range
- LOS: length of stay
- MAP: mean arterial blood pressure
- MCI program: multicomponent non-pharmacological intervention program
- MREC: Medical Research Ethics Committee
- PRE-DELIRIC model: PREdiction model for DELIRium in ICu patients
- PoDeCoD: Postoperative Delirium and Cognitive Dysfunction
- PICS: postintensive care syndrome
- RAM: RAND/UCLA appropriateness Method Delphi study
- RASS: Richmond Agitation-Sedation Scale

- RC: reverence category
- REBs: Research Ethics Boards
- Riker SAS: Riker Sedation-Agitation Scale
- SD: standard deviation
- SF-36: Short Form-36 Health Survey questionnaire
- SOFA: the Sequential Organ Failure Assessment score
- SpO2: blood oxygen saturation
- SPIRIT: Standard Protocol Items: Recommendations for Interventional Trails– checklist
- TRIPOD: Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis
- QALY: Quality Adjusted Life Year
- QOL: Quality of Life

Dankwoord

Tijdens de totstandkoming van proefschrift heb ik van veel mensen steun en vertrouwen ontvangen waarvoor ik erg dankbaar ben.

Mijn speciale dank gaat uit naar:

Mijn promotor **Peter Pickkers**
voor je slimme, originele en vernieuwende ideeën, enthousiasme en positieve instelling, kritische blik, voorkeur voor informatieve figuren, (foute) humor en het creëren van een hecht en fanatiek onderzoeksteam op de afdeling Intensive Care

Mijn promotor **Lisette Schoonhoven**
voor het inspireren en je vertrouwen in mijn overstap naar verpleegkundig onderzoek, je oog voor detail en het menselijke aspect, constructieve en directe feedback, het bewaken van de balans, kritisch luisteren, methodologische kennis en tips m.b.t. de Engelse taal

Mijn copromotor **Mark van den Boogaard**
voor je onuitputtelijke enthousiasme, collegialiteit en beschikbaarheid voor al mijn 'dagelijkse' vragen, vakinhoudelijke kennis, het vertrouwen dat je me gegeven hebt, pragmatische aanpak in het vinden van oplossingen, doorzettingsvermogen en streven naar het beste resultaat

Theo van Achterberg
voor de begeleiding tijdens de opstart van mijn promotietraject als promotor bij IQ healthcare

Mijn manuscriptcommissie
Hester Vermeulen, Marieke Schuurmans, Monica Pop-Purceleanu

Leidinggevenden van de afdeling Intensive Care
Hans van der Hoeven en Anne-Miek Broods
voor het faciliteren van een hele fijne en stimulerende werkplek

Collega (ex-)promovendi en postdoc onderzoekers van de afdeling Intensive Care
Remi Beunders, Jonne Doorduin, Lucas van Eijk, Quirine Habes, Christopher Geven, Roger van Groenendael, Linda Hamers, Stan Hartman, Pleun Hemelaar, Ruud van Kaam, Dorien Kiers, Rebecca Koch, Matthijs Kox, Benno Lansdorp, Jenneke Leentjens, Guus Leijte, Lex van Loon, Eline Oppersma, Esther Peters, Nienke Peters van Ton, Lisanne Roesthuis, Roeland Stolk, Kim Timmermans, Jeanette Vreman, Marieke Zegers, Jelle Zwaag
met in het bijzonder mijn kamergenoten
Mirrin Dorresteijn, Jelle Gerretsen
Wytske Geense, Paul Rood (paranimf) **en Marloes Witjes**
voor jullie collegialiteit, belangstelling, kritische blik, positieve feedback, tips, sportiviteit en gezelligheid

Alle stafleden, fellows, arts-assistenten en verpleegkundigen van de afdeling Intensive Care

De researchverpleegkundigen van de afdeling Intensive Care
met in het bijzonder
Marieke van der A, Hetty van der Eng, Margreet Klop-Riehl, Chantal Luijten-Arts, Noortje Roovers en Hellen van Wezel

Secretariële ondersteuning van de afdeling Intensive Care
Nelly Gerrits-Gommans, Rachel Quibell-Melssen, Sjoukje van Wanroij, Jennie Wegh-Holtland
met in het bijzonder
Yvonne Kaspers

ICT ondersteuning van de afdeling Intensive Care
Sjef van der Velde, Maikel Couwenberg en Marcel Houwer

Datamanagers van de afdeling Intensive Care
Hidde Heesakkers, Lisa van Ede en Myriam Löffler

Mijn mentor
Marcel Olde Rikkert

Student
Ibrahim Arslan

Mijn collega's bij IQ healthcare
met in het bijzonder
Annick Bakker-Jacobs voor de secretariële ondersteuning
de senior onderzoekers, postdocs en promovendi van Sectie 3 Verplegingswetenschappen voor de leerzame PhD bijeenkomsten en gezelligheid
Dennis Pasveer voor zijn ICT ondersteuning

Het Lectoraat Acute Intensieve Zorg van de Hogeschool van Arnhem en Nijmegen
met in het bijzonder
Lilian Vloet, Sivera Berben en Remco Ebben
voor de mogelijkheid om als extern lid te leren over praktijkgericht onderzoek en de verbinding tussen onderzoek, praktijk en onderwijs

Radboud Institute for Health Sciences van het Radboudumc (voormalig NCEBP)
voor de subsidie Junioronderzoekerronde 2013

Alle proefpersonen
voor hun deelname aan de onderzoeken beschreven in dit proefschrift

Alle artsen en (research)verpleegkundigen van de deelnemende ziekenhuizen

All collaborating investigators and co-authors
for their valuable contribution to the studies and publications in this thesis

Rogier Donders en Steven Teerenstra
voor hun statistische ondersteuning

Arjen Slooter
en de (ex-)promovendi van de 'Brain at risk group' van het UMC Utrecht
met in het bijzonder
Ilse Kant, Simone van Montfort, Tianne Numan, Annemiek Wolters

Evelien Jagtman
voor het ontwerp van de kaft en het binnenwerk van dit proefschrift

Mijn studiegenoten en vrienden
met in het bijzonder
Loes Bijl, Marja van der Bijl, Maria Broeren, Janny de Jong, Joke Lemans, Marleen Lovink (paranimf)**, Ariene Morren, Diana Meijer, Eldert de With, Mariska Wijma**

Mijn lieve schoonfamilie
met in het bijzonder
Cees & Ria, Erwin, Tiemen en Silvan, Wilmar & Chantal

Mijn lieve familie
met in het bijzonder
Heit & mem, Arjen & Gerralt, Jan & Jildou en Sterre, Dirk & Marijke, Jelte en Jorrit

Mijn lieve man en zoons
Mark, Abe en Sido
voor alle onvergetelijke, fijne, grappige en bijzondere momenten die we samen als gezin beleven, ik hou van jullie! Samen kunnen we de wereld aan en gaan we nog veel hoge bergen beklimmen :)

Curriculum Vitae

Annelies Wassenaar werd geboren op 19 oktober 1982 in Menaldum. Na het behalen van haar HAVO-diploma aan de AMS te Franeker, volgde zij de duale variant van de studie HBO-Verpleegkunde aan de NHL Hogeschool Leeuwarden en in het Medisch Centrum Leeuwarden. Na haar diplomering werkte ze als verpleegkundige op verschillende afdelingen waaronder afdeling longziekten en poli cardiologie. Als verpleegkundige op afdeling longziekten was zij lid van het Project Innovatie Team longziekten/reumatologie tijdens het Kroonwiel project in het Medisch Centrum Leeuwarden. Dit was een team ter verbetering van kwaliteit en efficiëntie van zorg. Vervolgens startte zij als leerling op de afdeling Intensive Care (IC) van het Medisch Centrum Leeuwarden en rondde zij succesvol de opleiding tot IC-verpleegkundige af aan het Wenckebach Instituut van het Universitair Medisch Centrum Groningen. Vanuit Leeuwarden maakte ze de overstap naar Nijmegen en werkte daar op de afdeling Intensive Care van het Canisius-Wilhelmina Ziekenhuis. Gedurende haar werk als IC-verpleegkundige in het Canisius-Wilhelmina Ziekenhuis volgde zij een wiskunde opleiding en deed zij staatsexamen VWO, om vervolgens te starten met de Premaster en daarna de Master van de opleiding Klinische Gezondheidswetenschappen aan de Universiteit Utrecht. In het kader van haar afstuderen deed zij een kwalitatief onderzoek naar hoe IC-verpleegkundigen hun rol zien in de ervaren veiligheid van IC-patiënten. Met dit onderzoek won zij de Talma Eykman Award. Nog voor haar afstuderen werd zij aangenomen als junior onderzoeker/promovenda bij IQ healthcare en de afdeling Intensive Care van het Radboudumc te Nijmegen. Op deze afdelingen deed zij onder begeleiding van haar promotoren Prof. dr. Peter Pickkers, Prof. dr. Lisette Schoonhoven en copromotor dr. Mark van den Boogaard onderzoek naar de predictie en non-farmacologische preventie van delirium bij IC-patiënten wat resulteerde in dit proefschrift. Tijdens haar promotietraject werd een van haar artikelen genomineerd voor de Anna-Reynvaan Wetenschapsprijs en was zij Abstract Award Winner bij het ESICM Lives congres in Wenen.

Naast haar werk als promovenda was zij extern lid van de kenniskring van het Lectoraat Acute en Intensieve Zorg van de Hogeschool van Arnhem en Nijmegen.

Annelies is getrouwd met Mark Noordenbos. Samen hebben zij twee zoons, Abe (2014) en Sido (2016).

PHD PORTFOLIO

Name PhD candidate: A. Wassenaar, MSc *Department: Intensive Care Medicine* *Graduate School: Radboud Institute for Health Sciences*	*PhD period: 01-03-2013 – 01-11-2017* *Promotors: Prof. P. Pickkers, Prof. L. Schoonhoven* *Co-promotor: Dr M. van den Boogaard*	
	Year(s)	ECTS
TRAINING ACTIVITIES		
a) Courses & Workshops		
- *Statistical course at the research department of the ICU*	2013	0.5
- *NCEBP Introduction Course*	2013	1.0
- *BROK*	2013	1.5
- *Academic writing*	2014	3.0
- *Management voor promovendi*	2014	3.0
- *Scientific integrity*	2015	1.0
- *Presentation skills*	2015	1.5
- *Presenteren van eigen onderzoek*	2015	1.5
- *Research Data Management for PhD's*	2015	0.1
- *Klinische predictiemodellen K80 (EpidM)*	2015	2.0
- *Advanced conversation*	2016	1.5
- *Loopbaan management*	2016	0.7
- *BROK herregistratie*	2017	0.1
b) Symposia & congresses		
- *Nederlandse vereniging voor Intensive Care (NVIC) congres (poster)*	2013 & 2016	3 days & 2 days
- *Annual Meeting of the European Delirium Association (EDA) (poster and oral)*	2015 & 2017	2 days & 2 days
- *European Society of Intensive Care Medicine (ESICM) (poster and oral)*	2015 & 2017	3 days& 3 days
c) Other		
- *Refereerbijeenkomsten IQ healthcare, Radboudumc*	2013-2015	
- *PhD meetings Verplegingswetenschap IQ healthcare, Radboudumc*	2013-2017	
- *Research meetings Intensive Care unit, Radboudumc*	2013-2017	
- *Kenniskring Lectoraat Acute en Intensieve Zorg, Hogeschool van Arnhem en Nijmegen*	2013-2017	
- *Refereerbijeenkomsten delirium onderzoek, UMCU/Radboudumc*	2013-2017	
TEACHING ACTIVITIES		
d) Supervision of internships / other		
- *Medical student*	2015	
- *Research assistants / data managers*	2013-2016	
TOTAL (of part a)		**17.4**

A

Publicaties

Numan T, Van den Boogaard M, Kamper AM, Rood P, **Wassenaar A**, Abawi M, Claassen JA, Coesmans M, Dautzenberg PL, Dhondt TA, Diraoui SB, Eikelenboom P, Emmelot-Vonk MH, Faaij RA, van Gool WA, Groot ER, Hagestein-de Bruijn C,Hovens JG, van der Jagt M, de Jonghe A, Koek HL, van der Kooi AW, Kromkamp M, Lagro J, Leentjens AF, Lefeber GJ, Leijten FS, Leue C, de Man T, van Marum RJ, van der Mast R, van Munster BC, Osse RJ, Portier CB, Rius Ottenheim N, Röder CH, Schoon Y, Tromp A, van der Vlugt JJ, Vondeling AM, Weinstein H, Witlox J, van Zanten JS, Zeman PM, Peelen LM, Slooter AJ, et al. 'Delirium detection with a brief, single-channel electroencephalography recording'. Submitted.

Wassenaar A, Schoonhoven L, Devlin J, van Haren FMP, Slooter AJC, Jorens PG, van der Jagt M, Simons KS, Egerod I, Burry LD, Beishuizen A, Matos J, Donders ART, Pickkers P, van den Boogaard M.. 'Delirium prediction in the intensive care unit: comparison of two delirium prediction models'. Submitted.

Wassenaar A, Schoonhoven L, Devlin J, van Haren FMP, Slooter AJC, Jorens PG, van der Jagt M, Simons KS, Egerod I, Burry LD, Beishuizen A, Matos J, Donders ART, Pickkers P, van den Boogaard M. 'External validation of two delirium prediction models for intensive care unit patients'. Submitted.

Wassenaar A, Van den Boogaard M. 'Integration of an Abbreviated ICU Cognitive Failure Questionnaire. The authors reply'. Crit Care Med. Accepted for publication.

Wassenaar A, Rood P, Boelen D, Schoonhoven L, Pickkers P, van den Boogaard M. 'Feasibility of cognitive training in critically ill patients: A pilot study'. Am J Crit Care. 2018 Mar;27(2):124-135.

Wassenaar A, De Reus J, Donders ART, Schoonhoven L, Cremer OL, de Lange DW, van Dijk D, Slooter AJC, Pickkers P, van den Boogaard M. 'Development and validation of an abbreviated questionnaire to easily measure cognitive failure in Intensive Care Unit survivors: a multicenter study'. Crit Care Med. 2018 Jan;46(1):79-84.

Wassenaar A, van den Boogaard M, UNDERPIN-ICU study group, Schoonhoven L, Pickkers P. 'Determination of the feasibility of a multicomponent intervention program to prevent delirium in the Intensive Care Unit: A modified RAND Delphi study'. Aust Crit Care. 2017 Nov;30(6):321-7.

Wassenaar A, Rood P, Schoonhoven L, Teerenstra S, Zegers M, Pickkers P, van den Boogaard M. 'The impact of nUrsiNg DEliRium Preventive INnterventions in the Intensive Care Unit (UNDERPIN-ICU): A study protocol for a multi-centre, stepped wedge randomized controlled trial'. Int J Nurs Stud. 2017 Mar;68:1-8.

Wassenaar A, van den Boogaard M, van der Hooft T, Pickkers P, Schoonhoven L. 'Providing good and comfortable care by building a bond of trust': nurses views regarding their role in patients' perception of safety in the intensive care unit. J Clin Nurs. 2015 Nov;24(21-22):3233-44.

Wassenaar A, van den Boogaard M, van Achterberg T, Slooter AJC, Kuiper MA, Hoogendoorn ME, Simons KS, Maseda E, Pinto N, Jones C, Luetz A, Schandl A, Verbrugghe W, Aitken LM, van Haren FMP, Donders ART, Schoonhoven L, Pickkers P. 'Multinational development and validation of an early prediction model for delirium in ICU patients'. Intensive Care Med. 2015 Jun;41(6):1048-1056.

Wassenaar A, Schouten J, Schoonhoven L. 'Factors promoting intensive care patients' perception of feeling safe: A systematic review'. Int J Nurs Stud. 2014 Feb;51(2):261-73.

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