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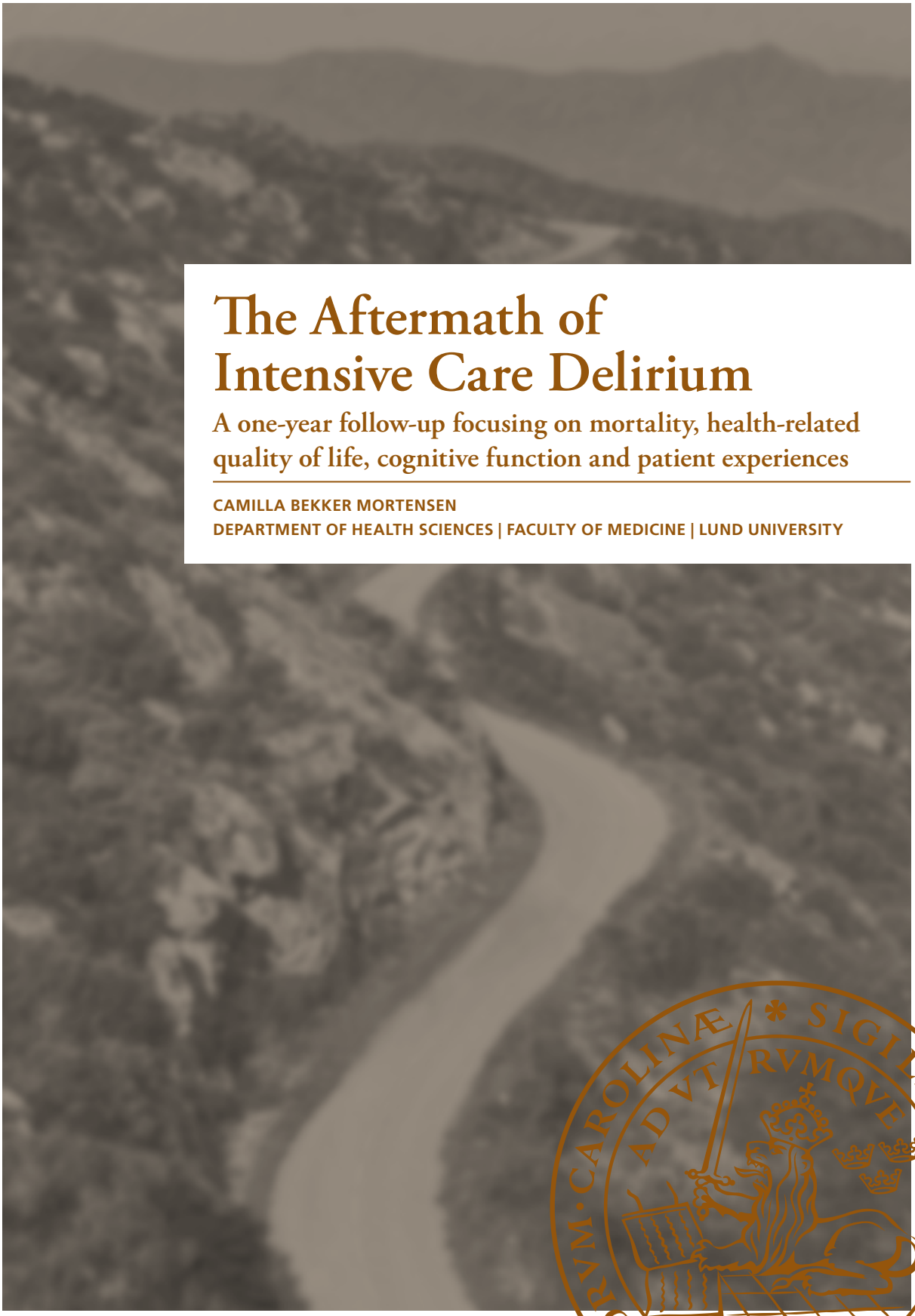

The Aftermath of Intensive Care Delirium

A one-year follow-up focusing on mortality, health-related quality of life, cognitive function and patient experiences

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Title and subtitle: The Aftermath of Intensive Care Delirium: One year follow-up focusing on mortality, health-related quality of life, cognitive function and patient experiences.

Abstract:

Delirium is a serious and common condition in the intensive care unit (ICU), which affects 30-50 % of the patients and is associated with increased mortality and morbidity in the context of long-term outcomes. No evidence-based treatment for delirium exists, and currently, delirium is mainly treated pharmacologically with haloperidol, a typical antipsychotic agent. The "Agents Intervening against Delirium in the Intensive Care Unit (AID-ICU)"is a multicentre, randomised, placebo-controlled trial that explored the benefits and harms of haloperidol in treating ICU patients with delirium. As limited evidence exists on the long-term outcomes of haloperidol for treating patients with delirium, this thesis is part of a pre-planned follow-up of AID-ICU trial that focuses on investigating the long-term outcomes, such as mortality, health-related quality of life (HRQoL), cognitive function, and patient perspective, which are outlined in three studies with a protocol article to enhance the transparency and validity of study I.

Study I assessed the long-term outcomes of mortality and HRQoL in acutely admitted adult patients with delirium treated in ICU with haloperidol versus placebo. All analyses were pre-planned and obtained at 1-year after randomisation to the AID-ICU, where 1000 patients participated. We assessed HRQoL using Euroqol's questionnaire: EQ-5D-5L and vital status was obtained through national registers. The results showed that treatment with haloperidol in patients with delirium, reduced mortality at 1-year follow-up, but did not statistically significantly improve their HRQoL.

Study II investigated the cognitive function of Danish patients from three participating sites one year after randomisation to the AID-ICU. Cognitive functions were assessed using two neuropsychological tests, the Repeatable Battery for Assessing Neuropsychological Status (RBANS) and Trail Making Tests A&B. These were performed either in the hospital or at a home visit. The results showed no statistical difference between the two groups but it was found that 42% of the patients had severe cognitive impairments one year later.

Study III explored everyday life experiences of critically ill patients with delirium during the ICU stay, from ICU discharge until 1-year follow-up, focusing on their HRQoL and cognitive function using a qualitative research design with interviews for data collection and the use of the Framework Analysis Method and inductive content analysis. Nine women and eight men participated, all recruited from the AID-ICU. They reported that returning to everyday life after critical illness was a struggle that no one had been aware of or were informed about.

In summary, the results showed that treatment with haloperidol in patients with delirium in the ICU had an impact on long-term survival. In contrast, it did not influence the patients' HRQoL or cognitive function one year later. At the same time the patients reported that recovering from critical illness was a struggle from discharge until one year later filled with many uncertainties and not knowing which actions to take.

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To Alfred, Oskar and Nikolaj

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List of Studies

This thesis is based on the following studies, referred to in the text by their Roman numerals I–III. Please note that the first paper here relates to the RCT protocol article.

RCT-protocol

Mortensen CB, Poulsen L, Andersen-Ranberg NC, Perner A, Lange T, Estrup S, Ebdrup BH, Egerod I, Rasmussen BS, Hästbacka J, Caballero J, Citerio G, Morgan MPG, Samuelson K, Mathiesen O. (2020). Mortality and HRQoL in ICU patients with delirium: Protocol for 1-year follow-up of AID-ICU trial. Acta Anaesthesiologica Scandinavica, 64, 1519-1525. doi: 10.1111/aas.13679

Study I

Mortensen CB, Andersen-Ranberg NC, Poulsen LM, Granholm A, Rasmussen BS, Nørregaard MK, Lange T, Ebdrup BH, Oxenbøll MC, Andreasen AS, Heiberg MB, Bulent U, Scharling HP, Gramstrup LN, Hästbacka J, Bek TJ. Damgaard K. Sommer T, Morgen M, Dey N, Citerio G, Estrup S, Egerod I, Samuelson K, Perner A, Mathiesen O. (2023). Long-term outcomes with haloperidol versus placebo in acutely admitted adult ICU patients with delirium. *Intensive Care Medicine* 2024-01-03 10.1007/s00134-023-07282-7

Study II

Mortensen CB, Poulsen LM, Andersen-Ranberg NC, Samuelson K, Mathiesen O. Long-term cognitive function after haloperidol versus placebo treatment in ICU patients with delirium. In manuscript

Study III

Mortensen CB, Oxenböll Collet M, Samuelson K. (2023). Struggling to return to everyday life—The experiences of quality of life 1 year after delirium in the intensive care unit. Nursing in Critical Care, 28, 670–678. doi: 10.1111/nicc.12939

The RCT-protocol article, Study I and Study III, are available in open access and reprinted with the publishers' permission.

Abbreviations

A2F	ABCDEF-bundle
AID-ICU	The Agents Intervening against Delirium in the Intensive Care Unit.
CAM-ICU	Confusion Assessment Method of the Intensive Care Unit
CCRN	Critical Care registered nurse
CI	Confidence Interval
ICU	Intensive Care Unit
ICDSC	Intensive Care Delirium Screening Checklist
ITT	Intention to treat
IQCODE	Informant Questionnaire on Cognitive Decline in Elderly
FAM	Framework Analysis Method
HRQoL	Health-related quality of life
MD	Mean differences
PADIS	Pain, Agitation/Sedation, Delirium, Immobility and Sleep Disruption in Adult Patients in the ICU (PADIS- guideline 2018)
PICS	Post-Intensive Care Syndrome
PTSD	Post-Traumatic Stress Disorder
QoL	Quality of life
RAM	Roy Adaption Model
RBANS	Repeatable Battery for the Assessment of Neuropsychological Status
RCT	Randomised clinical trail
RD	Risk differences
RoM	Relative ratios of means
RR	Risk ratios
SD	Standard deviation
SOP	Standard Operating Procedure
TMT A & B	Trail Making Test A & B

Introduction

Surviving critical illness often generates a challenging aftermath. Regardless of admission type to the intensive care unit (ICU), ICU survivors may experience an array of long-term impairments related to the critical illness, the ICU environment, the treatment or the organ support received (1).

Long-term outcomes after intensive care treatment refer to the enduring changes in health and functional status patients experience after discharge from the ICU and the hospital. The term encompasses a wide range of declines or impairments, often including physical, cognitive, and mental health impairments. These problems persist for an extended period, affecting the patient's quality of life (QoL) in the months and even years following critical illness and may not be wholly reversible (2). These impairments can manifest as a decline in physical function, such as muscle weakness and weight loss, as well as impairment in cognitive abilities, e.g. memory loss and mental health issues, such as depression and anxiety (3).

A major risk factor for long-term outcomes in the ICU is delirium (4,5). Delirium is an acute brain dysfunction which frequently occurs among critically ill patients in the ICUs, not only leading to a range of unfavourable short-term outcomes but also adding a considerable risk of developing an increased number of different long-term outcomes (6). Currently, delirium in the ICU is mainly treated pharmacologically with various medications, including antipsychotics, where haloperidol, a typical antipsychotic agent, is the most frequently used (7).

Despite increasing awareness of the long-term outcomes after delirium in the ICU, current evidence lacks clear insights into whether the use of antipsychotic treatment effectively can reduce long-term impairments, including cognitive function, and influence factors such as Health-Related Quality of Life (HRQoL) and survival. Furthermore, there is a lack of knowledge concerning these patients' recovery process from critical illness until one year later (8,9). Increased knowledge and understanding of delirium's long-term impact can improve the patient's health and well-being.

Background

Intensive Care

Approximately 26.000 patients are admitted annually to an ICU in Denmark, and internationally, 75-90% of patients survive their critical illness (10,11).

Admission to the ICU typically occurs when a patient's medical condition is critical and requires close monitoring and specialized care. Critical illness is a serious and often life-threatening medical condition that significantly impacts a person's health and requires intensive medical intervention and prolonged treatment.

Patients admitted to the ICU generally suffer from severe illnesses or significant injuries or require life support to sustain organ function, and the primary admission diagnoses are respiratory insufficiency or failure, sepsis, or acute myocardial infarction (12,13). The patient population in a general ICU is heterogeneous in terms of age, disease, severity of illness, or medical speciality and can potentially be anybody; the patients thus have different needs for specialised care and treatment. A patient's length of stay in the ICU varies from 1 day to several months, depending on the severity of the illness.

The patients require constant monitoring due to the complexity of critical illness, and the nurse ratio is frequently one nurse to 1 to 2 patients (14). The patient may be intubated, have respiratory difficulties, unstable hemodynamics with low blood pressure and can have an altered level of consciousness (15). Specialised treatment and care with the proper knowledge, skills, and competencies that a critical care nurse (CCRN) possesses are required to fulfil the needs and complexity of a critically ill patient (16).

Delirium in the ICU

The term delirium is derived from the Latin "delirare" and means of track, referring to the confusion that often characterises the condition (17).

Delirium is a clinical condition that patients in the ICU frequently experience and two recent systematic reviews found a pooled prevalence of delirium in the ICU, ranging from 31 % to 38 % (18,19).

Delirium, an acute organ dysfunction

Delirium is an acute brain dysfunction and, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) of the American Psychiatric Association (DSM-5), is a disturbance in attention and awareness that develops acutely, has a tendency to fluctuate and is related to a medical condition (Table 1) (20,21).

Table 1. Diagnostic and Manual of Mental Disorders, fifth edition(DSM-5) criteria for delirium (21)

A.	A disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
B.	The disturbance develops over a short period (usually hours to a few days), represents a change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
C.	An additional disturbance in cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception).
D.	The disturbances in Criteria A and C are not explained by another pre-existing, established, or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal, such as a coma.
E.	There is evidence from the history, physical examination, or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e., due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple etiologies.

Delirium symptoms usually begin over a few hours or days, come and go during the daytime and deteriorate during the night (crit. B). Delirium occurs as a consequence of a medical condition (crit. E). The symptoms are disturbances in consciousness, e.g., being agitated or apathetic with inattention and reduced awareness of the surroundings (crit. A) and perceptual disturbances (crit. C) (21).

Delirium in the ICU has significant adverse implications, ranging from agitation, pulling out lines and tubes, and prolonged time on mechanical ventilation to increased mortality (18,22–24). Patients with delirium may experience discomfort but may also be in danger to themselves, with an increased risk of self-harm (e.g. accidental extubation) depending on the motor subtype of delirium. The CCRN

must thus be more careful and observant of the patient's clinical condition due to the discomfort and insecurity of the patient (25).

Motor Subtypes of Delirium

Based on the patient's psychomotor activity, delirium is typically divided into one of three motor subtypes: hypoactive, hyperactive and mixed delirium. The clinical presentation of the hypoactive patient is commonly one that appears to resemble apathy and may display symptoms such as depression, stupor and withdrawal. This patient will not present much himself in a nursing context and, due to a withdrawn state of mind, will not interact with the surroundings and will be dominated by symptoms of drowsiness and inactivity (22,26).

The hyperactive patient exhibits signs of agitation and may display symptoms of aggression and restlessness. The hyperactive patient will be more easily recognised due to increased psychomotor activity, may experience loss of control, may be combative and will demand close surveillance from the nurses to avoid self-harm (22,26).

Mixed delirium is where the patient fluctuates between the characteristics of hypoactive and hyperactive delirium (19,22). Mutual for all three motor subtypes is the hallmark symptom in delirium: inattention and confusion with different cognitive deficits as perceptual disturbances as hallucinations or delusions (19). The prevalence of the various motor subtypes is 50-55% for the hypoactive subtype, 13-23% for the hyperactive subtype, and 28-32% for the mixed delirium (18,19).

Pathophysiology of delirium

The pathophysiology of delirium is complex and not fully understood, but unravelling it is crucial for improving care and treatment. Various etiological factors may contribute to the development of delirium, suggesting that multiple neurobiological mechanisms likely interact within the pathogenesis of delirium (27–29). However, in 2017, Maldonado proposed *the system integration failure hypothesis,* a theory that integrates existing approaches to delirium pathophysiology. The hypothesis suggests that physiological factors such as neuronal ageing, inflammation, oxidative stress, neuroendocrine dysfunction, and circadian rhythm dysregulation interact. However, each has a different effect depending on the patient-specific physiological characteristics. Factors contributing to a failure of system integration, and potentially those influencing the observable characteristics of delirium, involve changes in the synthesis, function, and/or availability of neurotransmitters during the onset of delirium. The most commonly described neurotransmitter imbalance in delirium is a reduced level of acetylcholine, which is a neurotransmitter involved in attention and memory, and excess release of dopamine, where dysregulation of dopamine is implicated in altered attention and perception (27).

Risk factors for delirium in the ICU

Several risk factors for delirium in the ICU have been identified, including predisposing factors, e.g. advanced age, pre-existing cognitive impairment, frailty and precipitating factors, e.g., sedatives, opiates, medicinal ventilation, and severity of illness and within these two areas, some risk factors are modifiable, while others are not (see Figure1)(30).

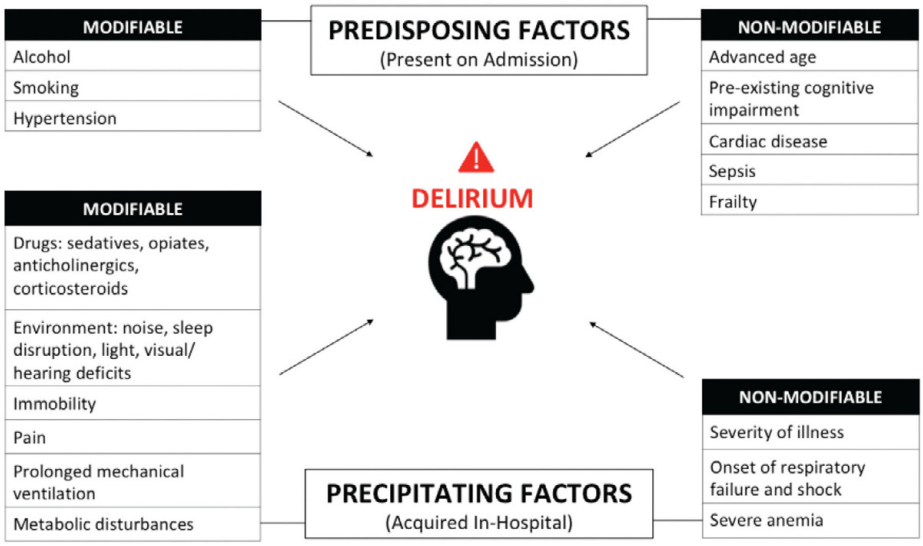

Figure 1. Predisposing and precipitating factors influencing delirium in the ICU. *With copyright from Thieme Publishing; Seminars in Respiratory and Critical Care Medicine*

Managing Delirium in the ICU

Delirium screening is pivotal for effectively managing delirium, and early detection of delirium is essential for improving patient outcomes (31).

Two primary screening instruments in the ICU are the Confusion Assessment Method of the Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC). Both instruments have good psychometric properties and robust evidence supporting their reliability and validity as valuable tools to identify and manage delirium in critically ill patients (32–34).

The differences between CAM-ICU and ICDSC lie within the assessment method and interpretation of the results. CAM-ICU is a simple and quick tool evaluating four features of delirium: acute or fluctuating thinking, inattention, disorganised thinking and altered level of consciousness (32). CAM-ICU can also be used in

mechanically ventilated patients who cannot express themselves verbally. ICDSD is a checklist where eight items are evaluated over a specific timeframe(e.g. a shift of 6-8 hours). ICDSD evaluates an altered level of consciousness, inattention, disorientation, hallucinations/delusions, psychomotor agitation or retardation, inappropriate speech or mood and sleep-wake cycle disturbances (35). CAM-ICU provide a dichotomous response: is delirium present or not, whereas ICDSD can identify patients with subsyndromal delirium characterised by the presence of one or more symptoms of delirium (36).

A prevailing approach for preventing and managing delirium in the ICU is implementing the ABCDEF bundle (A2F). This has been associated with improved patient outcomes, such as survival and a decrease in the prevalence of delirium in the ICU (37,38). A2F bundle is a set of evidence-based, non-pharmacology interventions aiming to improve the outcome of critically ill patients in the ICU, focusing on managing delirium causes, reducing sedation/ventilation/immobility, and incorporating family and rehumanise critical care (39). Each acronym represents a specific element of treatment and care: **A**ssess, prevent and manage pain; **B**oth spontaneous awakening and spontaneous breathing trials; **C**hoice of sedation and analgesia; **D**elirium: assess, prevent and manage; **E**arly mobility and exercise; **F**amily engagement and empowerment. It can be applied to every patient, every day, regardless of admission diagnosis or mechanical ventilation and is designed to address critically ill patients' complex needs and enhance their overall well-being (38).

In 2018, the Society of Critical Care published *the Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility and Sleep Disruption in Adult Patients in the ICU* (referred to as PADIS-guidelines 2018) and is the most comprehensive clinical guideline describing delirium management (40). PADIS guidelines recommend using multicomponent non-pharmacological interventions as described in the A2F bundle and do not recommend any routine use of pharmacological interventions to prevent or treat delirium but should be used to treat agitation and anxiety (40).

However, the findings of Collet et al., which were published in the same year as the guidelines above, demonstrated that haloperidol was the main pharmacological agent used for treating delirium in the ICU (41). This result was supported by a recent scoping review that found that 66% of patients received pharmacological treatment for their delirium, with antipsychotic medication and especially haloperidol being the most commonly used agents (19). Haloperidol is an antipsychotic agent which blocks the dopamine D_2 receptors in the brain. Dopamine is a neurotransmitter associated with mood and behaviour regulation. Haloperidol has beneficial effects on managing agitation and treating the positive symptoms of psychosis, such as delusions and hallucinations. It acts as an antipsychotic medication with sedative properties, achieved by inhibiting dopamine activity through its action as a dopamine receptor antagonist (42).

Delirium is still prevalent in the ICU despite different approaches and comprehensive guidelines, and the impact of haloperidol on long-term mortality and other highly relevant patient outcomes is a particular need for further investigation (8).

Despite the focus on managing and treating delirium in the ICU, delirium may cause numerous complications in the short and long term. There is an increased risk of prolonged mechanical ventilation, extended length of stay in the ICU and hospital, and in-hospital mortality (30).

Delirium has been associated with functional impairment and disabilities after hospital discharge, where activities of daily living (ADL) have been affected, resulting in an increased likelihood of being discharged to long-term care facilities. Furthermore, cognitive impairments with memory deficits, poor concentration and the risk of developing anxiety and post-traumatic stress disorder have been reported (6,30,42). Finally, delirium is associated with increased mortality, and primarily the duration of delirium in the ICU has been linked to a higher mortality (23,24).

Delirium experienced by the patient

Delirium has been described as both distressing and scary. The patients can experience vivid perceptual disturbances, behavioural problems, agitation, temporal confusion, intrusive and delusional memories and emotions such as fear, anxiety, and shame. It is described as frightening because fact and fiction are mixed with hallucinations (43–46).

"Coming out of the elevator, I suddenly realized that I was being forced into a trap. We were in an ANTI-HOSPITAL under the real hospital. The Anti-hospital was built after the Government passed a new law. The law gave the relatives of patients who had died when I was in charge, the right to ask that I was to be executed in the cruellest way, and that as part of their grief, they could watch the process from the auditorium" (46)[1].

These delusional experiences can persist years later for some patients and are still noticeably present and distressing for them (47,48). They may be the reason for long-term psychological challenges such as anxiety, depression, and PTSD (48). On the other hand, not all have any recollection of their delirium experiences or their ICU admission, and the reasons hereof are unknown. Patients are often not aware of the link between these experiences, ICU admission and delirium (47).

[1] With copyright from John Wiley and Sons.

The Aftermath of Intensive Care

The outcomes of delirium in the ICU remain a challenge and cause different implications in the short and long term. The long-term outcomes are mainly closely related to and intertwined with Post-intensive care syndrome (PICS) (6,30,42).

ICU survivors may encounter long-term health challenges associated with their critical illness, irrespective of the initial cause for admission to the ICU. Consequently, it is believed that the challenges in range of morbidity experienced is more extensive following an ICU admission compared to a hospital stay not requiring intensive care and is associated with both increased morbidity and new/or aggravated physical and psychological disabilities that persist long after hospital discharge and impact the patient's quality of life for years (1,49–51). These enduring long-term impairments are known as PICS and, in a recent review by Schwitzer et al. is estimated to affect up to 80% of ICU survivors who will have PICS symptoms at hospital discharge, and more than one-half of these patients will continue to experience symptoms one year later (1,42,50,52).

Post-intensive care syndrome

PICS, in general terms, refers to new and worsened impairments that arise after critical illness and persist beyond acute care hospitalisation. PICS does not only encompass various physical, psychological, and cognitive impairments and domains but may also have social and financial consequences for patients, families, and society. This is a complex relationship where deficits in one area affect and coexist with deficits in another (42). Needham et al. recommended in 2012 using the term PICS to create awareness and improve knowledge about these challenges by using a single term to describe the presence of one or more impairments (50,53,54).

PICS is often unrecognised, and the reasons for this may be due to a lack of systematic screening, a knowledge gap between primary and secondary care, and the ICU survivors' lack of knowledge concerning PICS and the aftermath of critical illness (42,50,55–57). Furthermore, PICS is not a static set of problems but is more similar to a chronic disease, making recovery among patients challenging (55,58).

Several risk factors for developing PICS have been identified and can broadly be divided into two arms: non-modifiable and potentially modifiable/ modifiable:

- Non-modifiable factors are pre-existing factors, e.g., advanced age, frailty, cognitive impairments, and comorbidity (4,42,50,59,60)
- Potentially modifiable /modifiable factors are ICU-specific factors including mechanical ventilation, sedation, sepsis, and delirium (5,42,50).

The physical domain

Up to 80% of the ICU survivors will experience a new physical dysfunction at discharge. The types of physical impairment may be muscle weakness, weight loss, impaired mobility and impaired pulmonary function. These issues can result in a diminished ability to fulfil basic needs and perform instrumental ADL tasks and end up with a lower HRQoL (42,59–62).

The psychological domain

Mood disorders such as depression, anxiety and post-traumatic stress disorder (PTSD) are frequently encountered by ICU survivors, affecting their quality of life negatively and with increased risk of self-harm behaviours (42,63–65). PTSD is primarily closely related to the lack of recollection of the ICU admission and the lack of factual memories or the presence of delusional frightening memories (1). Furthermore, over 50% of the patients will experience sleep disturbances after an ICU admission occurring up to six months after discharge (42).

The cognitive domain

One-third of patients who survive ICU exhibit cognitive deficits one year later (42). Clinical manifestations include a decline in memory (having difficulty in remembering or memory loss), keeping attention (e.g. poor concentration) and executive functions (e.g., problems with planning or problem-solving)(4,66–68). Cognitive impairments affect the ability to perform everyday ADL activities (e.g. bathing, dressing, toileting) and IADL activities (e.g. adherence to medication, housekeeping, cooking), influencing independence, return to work, and HRQoL (4,42,50,66–69).

Delirium has been extensively studied, primarily showing long-term cognitive impairments that persist from the initial recovery phase and continue for years (59,66). Delirium in the ICU and PICS in the long-term are highly intertwined, and among potentially modifiable risk factors is the presence and duration of delirium in the ICU for long-term cognitive impairments (4,5,70,71).

Although there is increased knowledge about delirium's impact on long-term cognitive impairment, knowledge concerning the effect of medical treatment (e.g. haloperidol) on delirium in the ICU influences long-term cognitive impairment is lacking.

Quality of life and health-related quality of life

There is no uniform definition of the concept of "quality of life”, although many attempts have been made to define it. However, there is a consensus that QoL is a subjective and multidimensional concept encompassing various aspects of an individual’s well-being and satisfaction in life. QoL generally includes physical,

emotional, mental and social components and reflects the individual's overall perception of their life and their satisfaction with different aspects of it (72). WHO defines QoL as *"an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad-ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs and their relationship to salient features of their environment"* (73).

In the context of illness, QoL is referred to as "health-related quality of life (HRQoL). While QoL covers all aspects of life, HRQoL is a multidimensional concept that encompasses various aspects of an individual's well-being and health status. HRQoL takes into account the impact of health conditions, treatments and overall health on an individual's QoL (72,73).

However, measuring the HRQoL of ICU survivors is complex and challenging because of the heterogeneity of the patient population and the different trajectories of illness prior to and after critical illness. Nonetheless, ICU survivors report a decrease in HRQoL up to years after critical illness compared to the general population(49,74–77).

Several observational studies have explored long-term HRQoL in former ICU patients who experienced delirium during ICU admission and have reported contradicting results, challenging the interpretation of delirium's impact on long-term HRQoL (67,78–81). However, we lack an understanding of the long-term impact of medical treatments for delirium in the ICU on HRQoL.

Recovery after critical illness- conceptual framework

The main concepts that will be used are Endurance, Resilience and Adaptation.

Despite the increased awareness and knowledge of ICU survivorship, information about this trajectory and interventions to impact the health trajectory of a critical illness are rarely addressed to the ICU survivors; therefore, healthcare professionals can thus play a vital role in helping ICU survivors endure, be resilient and adapt to changes (2,53).

Surviving critical illness is a challenge due to changes in a person's health and, consequently, life circumstances. When a sudden life change occurs when a person encounters a life-altering adversity such as a critical illness, they will enter a phase of shock, pre-resilience, and endurance. Intertwined with critical illness is recovery, another challenge from/after critical illness, from the immediate health shock experienced during the ICU admission, progressing through discharge to the ward/hospital and finally transitioning back home. The patient will be confronted

with a decline in many functions during the critical illness, usually abilities such as talking, waking, and eating. Moreover, the transition from ICU to a hospital ward and further to their home may be challenging due to the lack of comprehensive care ICU survivors need, especially in primary care settings (55). Patients will experience significant changes in their lives after critical illness. Since recovery is not identical for all patients, some will develop problem-solving strategies, while others will experience a lack of resources for recovery (55,82).

Janice Morse has developed a practical theory about suffering applying a nursing and caring science perspective, where one of the two main components is enduring and a framework for resilience in Nursing and healthcare (82,83).

Endurance in this context means getting through an extraordinary physical or psychological situation after a critical illness. The person may feel there is no alternative but to endure their situation when discharged, using all their energy to focus on getting through (84). Protective coping strategies, both internal and external, are essential in this phase. The choice of coping strategies provided by healthcare professionals may empower the person to manage the distress they experience and lead them to a state of resilience (82). Resilience is the capacity to withstand and navigate through difficult situations, learn from them, and emerge from them more robustly. Resilience is not about avoiding stress or difficulties but rather about developing effective coping strategies to manage these difficulties and overcome them (82).

On the other hand, adaptation refers to adjusting to new conditions, changes, or situations. Adaptation is a fundamental concept for adjusting and thriving in response to changes in conditions such as critical illness and recovery. These two concepts are closely related as they both involve responding to challenges; however, where resilience emphasises the ability to recover and maintain well-being after adversity, adaptation focuses on adjusting to new conditions.

The healthcare professional's role during recovery is essential and may contribute with coping strategies such as adaptation, acceptance, hope, and social support to enable resilience (82). Further, to enhance quality of life and promote the recovery process for ICU survivors, targeting interventions within rehabilitation focusing on adaptation may help adjust and promote coping and improve recovery after critical illness. There is no consensus concerning who is responsible for the subsequent recovery phase after a critical illness. In Denmark, the patients are discharged from hospital to primary care settings to manage the further rehabilitation currently is insight into the aftermath of critical illness. However, Mikkelsen et al. stated at a consensus conference in 2020 that ICU professionals should be involved in the aftermath of critical illness by predicting post-ICU problems and providing anticipatory guidance for managing these challenges (57).

The Roy Adaptation Model (RAM) aims to promote a person's adjustment to health and illness (85). The approach focuses on a bio-psycho-social person constantly

interacting with a changing environment and using innate and acquired mechanisms to adapt (86). Nurses/healthcare professionals are, therefore, according to RAM, responsible for enhancing and ensuring adaptation. Using the RAM may guide developing and evaluating interventions designed to support the person's needs during recovery and rehabilitation (86).

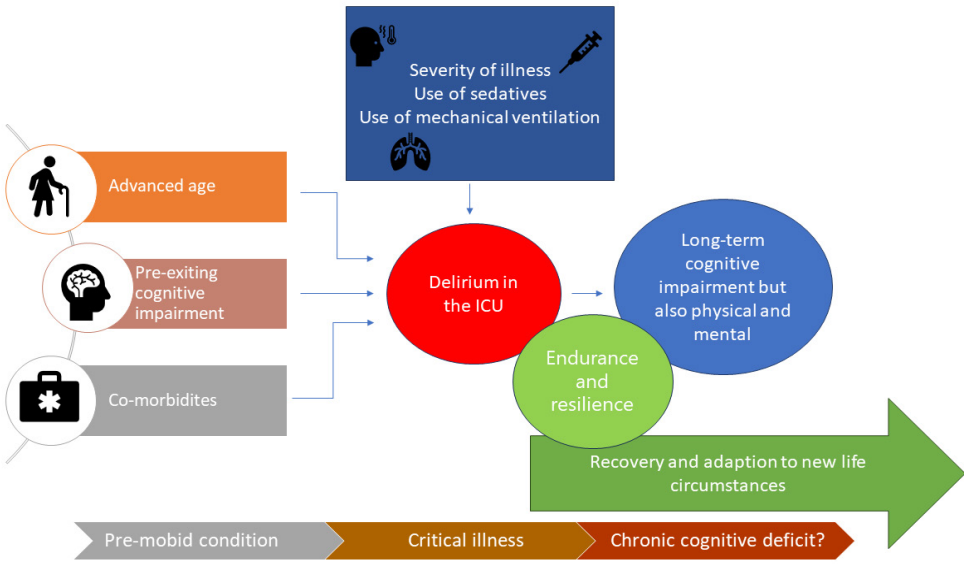

Figure 2. A visual description of the health trajectory during critical illness and delirium Comprehensive picture of the Aftermath of Intensive Care Delirium

Rationale

As ICU mortality declines and the focus on critical care survivors' long-term health outcomes increases, the goal of research in critical care has shifted from survival to return to everyday life (53). These changes highlight the importance of evaluating and understanding long-term outcomes such as, HRQoL in ICU survivors. ICU survivors aim to find themselves again, attempt to understand their situation, and eventually learn to live with an altered understanding of themselves during recovery (55). However, ICU survivors suffering from delirium during ICU may face different challenges in their recovery after hospital discharge compared to the general ICU survivor. Nevertheless, despite the growing awareness and focus on survivorship after ICU, there remains a gap in understanding long-term outcomes that are significant to patients. These include outcomes such as one-year mortality, HRQoL, cognitive function, and the patient's experiences, especially in the context of delirium(8).

The thesis is part of a randomised clinical trial exploring the benefits and harms of medical treatment with haloperidol on delirium in the ICU. The medical approach to managing delirium conventionally involves the administration of antipsychotic medications, with haloperidol being the prevalent choice. However, existing evidence does not provide clarity on whether antipsychotic treatment can effectively reduce long-term impairments such as cognitive function and have an impact on HRQoL and survival, and thus, this thesis aims to investigate this (87–89).

Furthermore, it is imperative to understand how ICU survivors who suffered from delirium manage their recovery from hospital discharge to one year later, as evidence seems limited (55). Increased knowledge and understanding of delirium's long-term impact on ICU survivors will address highly relevant patient-important outcomes and important knowledge gaps may facilitate the development of health-promoting interventions for ICU survivors, such as POST-ICU recovery programs, follow-up clinics or outpatient clinics and but also contribute with important knowledge about the transition they experience from critical illness to hospital discharge to one year later(90,91).

Aim

The overall aim of this thesis is to determine the long-term effects of haloperidol treatment in acutely admitted adult patients with delirium in the ICU on mortality, HRQoL and cognitive functions and to describe these patients' experiences of their quality of life.

The hypothesis for studies I and II is that haloperidol will decrease mortality and increase HRQoL and cognitive function.

The specific aims for each study, including the RCT-protocol were:

RCT-protocol article:

To provide a detailed protocol for study I to enhance transparency and commitment to rigorous research practices, contribute to the study's credibility and minimise various biases (e.g., publication bias).

Stydy I:

To assess long-term outcomes, HRQoL and mortality in acutely admitted adult patients with delirium treated in the ICU with haloperidol versus placebo.

Study II:

To explore the long-term effects of haloperidol versus placebo on cognitive functioning in former acutely ill patients suffering from delirium in the ICU one year later.

Stydy III:

To explore the everyday life experiences of patients who experienced delirium during an ICU stay from discharge until one year later, focusing on the patient’s health-related quality of life and cognitive function.

Methods

Design and study description

An experimental and non-experimental design have been used in this thesis. The experimental design had a deductive reasoning as a starting point. A randomised clinical design (RCT) was used in studies I and II to assess the long-term outcomes of haloperidol for treatment of delirium in the ICU in terms of mortality, HRQoL and cognitive function and a protocol article for study I published before the begin of study I. Study III had a non-experimental design with an inductive approach in order to explore the patients' experience of everyday life after critical illness one year after discharge.

Table 2. Overview of design, participants data collection and data analysis.

	RCT Protocol	Study I	Study II	Study III
Study design	A protocol article to provide a clear description of the methodology used in Study I	Quantitative design A multicentre, randomised, blinded, parallel-group, placebo-controlled trial with a pre-planned one-year follow-up	Quantitative design A multicentre, randomised, blinded, parallel-group, placebo-controlled trial with a pre-planned one-year follow-up	A descriptive-qualitative design with an inductive explorative design
Participants		Participants from the AID-ICU trial	Participants from three major selected sites from the AID-ICU trial	Participants from two selected sites of the AID-ICU trial using purposeful sampling
Data collection		Questionnaire and national registers	Neuropsychological instruments	Interviews
Data analysis		Logistic and linear regression	Linear regression	Framework Analysis Method and content analysis.

Context

The thesis is a part of the AID-ICU research programme. This programme originates from the Collaboration for Research in Intensive Care (www.cric.nu). The multicentre inception cohort study of 99 ICUs worldwide explored the clinical practice for the management of delirium in the ICU in 2016. The results of this study showed that medical treatment with haloperidol was most frequently used, which led to the development of the Agents Intervening against Delirium in the Intensive Care Unit (AID-ICU) trial (41). The AID-ICU trial was a multicentre, randomised, blinded, parallel-group, placebo-controlled trial where eligible patients were randomly assigned in a 1:1 ratio to receive either haloperidol or placebo (isotonic saline). The AID-ICU trial aimed to explore the benefits and harms of haloperidol for treating delirium in the ICU.

For the primary study of AID-ICU trial, a power calculation was performed and assuming that haloperidol would increase or decrease mortality (by 15%) and a shorter hospital admission time than placebo (by 8% greater mean number of days alive and out of the hospital), an estimation of 1000 patients would be required for the trial to have 90% power at the 5% significance level to show such a difference (88,92).

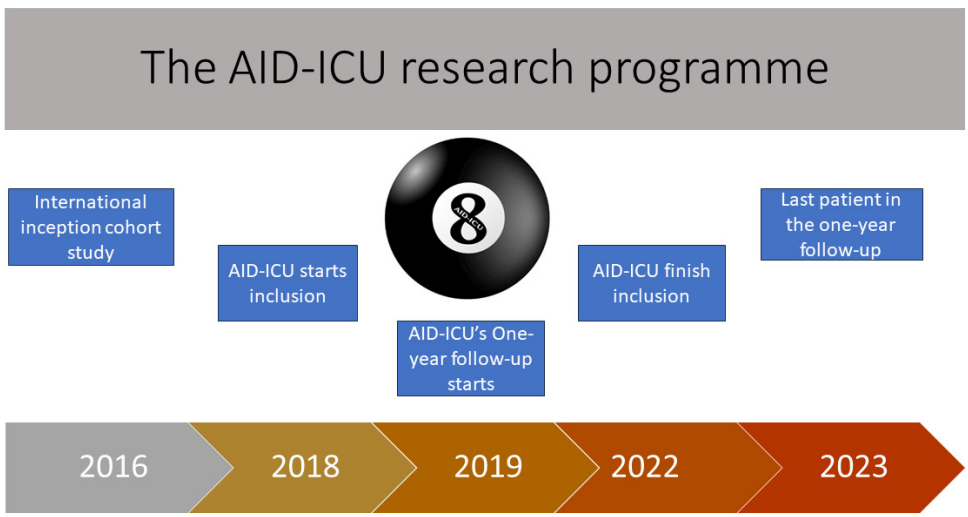

Figure 3. The AID-ICU research programme. Please note that the eight pinball is the AID-ICU research programme logo.

One thousand patients were enrolled in the AID-ICU trial at 16 ICUs in Denmark, Finland, the United Kingdom, and Italy from June 2018 to April 2022.

Instruments used in the AID-ICU trial and in study I & II

Delirium screening assessment tools

The patients had to be screened with a validated delirium screening tool to be eligible for the AID-ICU trial with either the Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC) (32,33).

Both instruments have been developed for use in ICU settings to provide a systematic approach for assessing and screening for delirium, validated in multiple languages, and have excellent psychometric properties and moderate to high interrater reliability (32–34). The CAM-ICU and ICDSC are designed to align with the core features of delirium, and their criteria share similarities with the DSM-5 criteria (21,32,33).

The Confusion Assessment Method (CAM) was created in 1990 by Dr. S Inouye and was the first standardized screening for delirium in hospitalised patients. It was developed as a bedside assessment tool for healthcare professionals with no psychiatric experience and showed good psychometric properties (93). The CAM-ICU was later adapted and designed to detect delirium in ICU settings and with the capability of also being used with non-verbally speaking patients (32).

The CAM-ICU assesses four features of delirium: the acute or fluctuating course of delirium, tests for inattention and disorganized thinking, and altered level of consciousness. It is a brief test that takes less than five minutes to administer and involves a short interview and observation by healthcare professionals. Two tests for attention and organised thinking are performed during the interview. The CAM-ICU provides a current picture of the present state of delirium.

The ICDSC was developed almost simultaneously with the CAM-ICU to detect delirium in a general ICU population, providing a comprehensive checklist for systematic delirium screening and allowing for a more detailed assessment of delirium-related symptoms. ICDSC is a checklist that includes various signs and symptoms associated with delirium, and healthcare professionals score each item based on their observations. ICDSC evaluates the presence of eight symptoms of delirium. ICDSC is usually completed based on observation and information obtained during routine care collected through an entire shift (6-8 hours) (33).

Table 3. Brief oversight of the key elements of CAM-ICU and ICDSC screening tools (32,33).

Tool	CAM-ICU	ICSDC
Purpose	To assess delirium in critically ill patients	To assess delirium in critically ill patients
Evaluation criteria	Evaluates four features of delirium: • Acute onset or fluctuating course • Inattention • Altered level of consciousness • Disorganized thinking	Evaluates eight signs or symptoms of delirium: • Altered level of consciousness • Inattention • Disorientation • Hallucinations, delusions, psychosis • Psychomotor agaitation or retardation • Inappropriate speech or mood • Sleep/wake-cycle disturbance • Symptom fluctuation
Result	If three or four features are present, the patient is positive for delirium.	An obvious manifestation of item =1 point, no manifestation = 0. The score of each item is either 1 or 0 A score≥ 4 suggests delirium.

Both instruments are widely used in ICU, and the choice of which of the two delirium screening tool to use was thus given to the staff at the participating site at the start of the AID-ICU (34,92).

Assessing health-related quality of life

We chose a brief instrument to obtain HRQoL. ICU survivors may be/are a fragile population; a brief instrument is thus less burdensome for the respondents, which can be advantageous in situations where brevity is important (76).

We used the EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L) and the EuroQol Visual Analogue Scale (EQ VAS) to assess HRQoL (94). EQ-5D-5L has been recommended for use in intensive care settings (76,95–97).

EQ-5D-5L is a descriptive system evaluating five dimensions of health. The patients assess their mobility, self-care, usual activity, pain/discomfort, and anxiety/depression and choose the most applicable of five levels ranging from no problems, slight problems, moderate problems, severe problems, and unable to/extreme problems (using a Likert scale 0 to 5) (98).

The result of the questionnaire represents an individual health state profile, called EQ-5D-5L profile, which can be converted into a single summary score, an EQ-5D-5L index value set. The index value set reflects how people think they are according to the preferences of the general population of a country/region (94). The EQ-5D-5L index values are anchored at 1.0, corresponding to ‘perfect health’ to a value of minus 1.0. A value of 0 corresponds to a self-reported health status ‘as bad as being dead’, and a value <0 corresponds to a self-reported health status ‘worse than death’.

The lowest index value depends on the value sets used; for Denmark, index values range from −0.757 to 1.0 (98).

EQ VAS is an overall measure of self-reported health, with a score ranging from 0 (worst possible health) to 100 (best imaginable health) on that specific day (98).

EQ-5D-5L is easy to administer, only consisting of five questions and one self-rating of health. It can be obtained by telephone, face-to-face, or by proxy and is available in multiple languages (99).

Assessing cognitive function

We used the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) instrument, Trail-Making Tests A & B (TMT A & B), and the Short Form Informant Questionnaire On Cognitive Decline in the Elderly (IQCODE) to assess cognitive function.

RBANS is the "golden standard" for clinical trials to evaluate cognitive function and detect the presence of cognitive impairment even in patients with mild impairments (100,101). The RBANS has demonstrated adequate reliability and validity in elderly and medical populations and has been used in numerous clinical trials with ICU survivors (66,100,102–105). The RBANS assesses immediate and delayed memory, attention and concentration, visual-spatial construction and language and is based on subtest raw scores; a global cognitive score is generated. The RBANS has a mean score of 100 with a *SD* of 15. Scores can range from 40 to 160, which can be interpreted based on the following classification system: 69 and below – extremely low, 70–79 – borderline, 80–89 – low average, 90–109 – average, 110–119 – high average, 120–129 – superior and 130 and above – very superior (4,66,102). RBANS takes 20–40 minutes to administer. The RBANS takes 20-40 minutes to administer. The material used in the test has been tested and validated for a Scandinavian population.

Executive functions are neurological-based skills associated with independence, self-management, managing time, setting personal goals, paying attention, problem solving and reasoning. These have been reported to be affected in 20-48 % of ICU survivors within the first year after critical illness but are not measured by RBANS(106). TMT A & B have been used in the ICU population to evaluate executive functions (106,107).

A limitation when exploring cognitive function as a long-term outcome after delirium in the ICU is the lack of knowledge concerning the participants' cognitive status prior to delirium in the ICU. We thus used the IQCODE to assess pre-existing cognitive impairments. IQCODE is a questionnaire designed to identify the magnitude of cognitive reduction based on a pre-morbid function level using an informant with a close relationship and knowledge of the patient. It has strong psychometric properties. The informant is asked to compare the patient's present

cognitive abilities with those ten years earlier. The questionnaire consists of 16 items, each scored on a Likert scale of 1 to 5, where 1 is much improvement, and 5 is poor/worsening performance. The total score of the 16 questions is divided by 16 to generate a score from 1 to 5, with higher scores indicating a worsening of cognitive function. An IQCODE $\geq$ 3.5 is defined as cognitive decline (108). The Short IQCODE has strong psychometric and diagnostic properties (109).

Randomisation and Intervention to the AID-ICU trial

The inclusion criteria were adult critically ill patients who were acutely admitted to the ICU and had been diagnosed with delirium, with the screening tool: the Confusion Assessment Method for the ICU (CAM-ICU) or the Intensive Care Delirium Screening Checklist (ICDSC) (32,33). The inclusion and exclusion criteria are listed below in Table 4.

Table 4. The AID-ICU trials inclusion and exclusion criteria (92)

AID-ICU	Inclusion criteria	Exclusion criteria
	– Acute admission to the ICU – Age ≥ 18 years – Diagnosed delirium with either CAM-ICU or ICDSC	– Contraindications to haloperidol (intolerance to haloperidol or additives, known Parkinson's disease or other extrapyramidal symptoms, known QTc prolongation, history of tardive dyskinesia or comatose (non-pharmacological) patients, previous ventricular arrhythmia or torsades de pointes, uncorrected hypokalaemia) – Habitual treatment with any antipsychotic medication or treatment with antipsychotics in the ICU before inclusion – Permanently incompetent (e.g. dementia, mental retardation) – Delirium assessment non--applicable (coma or language barriers) – Withdrawal from active therapy or brain death – Fertile women (women < 50 years) with positive urine human chorionic gonadotropin (hCG) or plasma-hCG – Consent according to national regulations not obtainable – Patients under coercive measures by regulatory authorities – Patients with alcohol-induced delirium (delirium tremens

Patients meeting the inclusion criteria were randomly selected in a ratio of 1:1 to receive either haloperidol or a placebo (isotonic saline). The randomisation was performed at a central location, utilizing a computer-generated assignment sequence with randomly varying block sizes and stratification according to trial site and delirium motor subtype (hyperactive or hypoactive) at inclusion (92).

The patients were randomised to receive haloperidol or placebo (isotonic saline) corresponding to 2.5 mg haloperidol three times daily and additional as-needed doses to a maximum daily dose of 20 mg. Patients were screened for delirium twice daily during the intervention period by healthcare professionals using either the CAM-ICU or ICDSC. Patients received study drugs if they were delirious in the ICU for a maximum of 90 days. Furthermore, an escape protocol was available if needed. The protocols for the AID-ICU trial, the statistical analysis plan, and the main results of the AID-ICU trial have been published (88,92,110).

Study, sample, outcome measures and data collection

RCT Protocol

An RCT Protocol was published prior to the beginning of the AID-ICU's one-year follow-up to increase the transparency and external validity for Study I. Details described the study background, rationale, research objectives and hypotheses, outcomes measures, data collection and analysis.

Study I

One thousand patients were included in the AID-ICU from 16 different ICUs in 4 countries (Denmark, Finland, Italy and the United Kingdom).

The primary analyses were conducted in the intention-to-treat (ITT) population, defined as all randomised patients who received the intervention and consented to use the data. Thirteen patients never received any trial medication, and 25 withdrew their consent and were excluded from the primary analyses. Figure 4 shows the flowchart from randomisation to one-year follow-up.

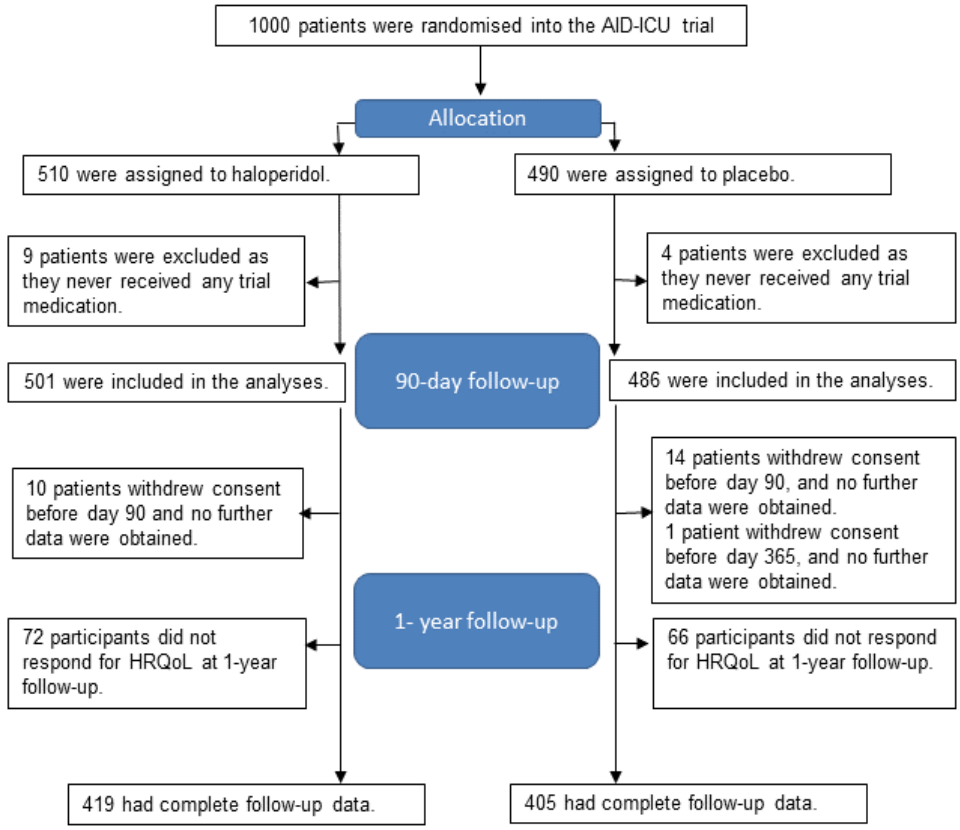

Figure 4. Consort diagram of the flow in the AID-ICU trial.

Outcomes measures

The primary outcome measures were all-cause mortality and HRQoL one year after randomisation. Additional outcomes were differences in HRQoL between survivors only.

Mortality

Vital status on day 365 after randomisation was obtained by research personnel. Deceased patients at day 365 were searched for and checked in electronic medical journals and validated by The Cause of Death Register, and data were entered into a database with a secured electronic case report form. It is mandatory by law to complete a death certificate in any case of a death occurring in Denmark (111). National investigators were responsible for entering data into the database in foreign countries.

HRQoL

Data collection in Denmark was obtained by a small reserch group. We (the author + a physician & research nurses at Zealand University Hospital, Aalborg University Hospital, and Rigshospitalet) collected these data to avoid attrition bias / minimise losses to follow-up. The national investigators were responsible for obtaining HRQoL data for the foreign countries. Data were collected by telephone or during home visits. All research personnel were blinded to the intervention, and data were obtained within a maximum of 30 days after day 365 of randomisation.

Patients who died within the 1-year follow-up were assigned 0 for the HRQoL values, corresponding to a health state as bad as being dead for EQ-5D-5L index values and the lowest possible EQ-VAS value (94,98).

A uniform standard operating procedure (SOP) describing the process of obtaining data concerning HRQoL was developed to enhance the study's rigour.

Study II

Patients from three major Danish participating sites in the AID-ICU trial were eligible for inclusion, and alive at day 365, they were asked to participate.

Three hundred forty-seven patients were alive on day 365 and eligible for this study. However, 189 patients did not participate (Figure 5), and only 135 patients participated in the study exploring cognitive function one year after delirium in the ICU.

Outcome measures

The primary outcome was the global cognition score measured by RBANS. Secondary outcomes were the five cognitive domains of RBANS; Immediate Memory, Delayed Memory, Visuospatial Function, Attention and Verbal Function, and measurement of executive function assessed by TMT A & B.

IQCODE was obtained at randomisation by research personnel who interviewed a nearby family member. Meanwhile, RBANS and TMT A/B were collected during home visits or at the hospital by five trained healthcare professionals (including the author) one year after randomisation. All were first certified by a neuropsychologist to perform RBANS tests.

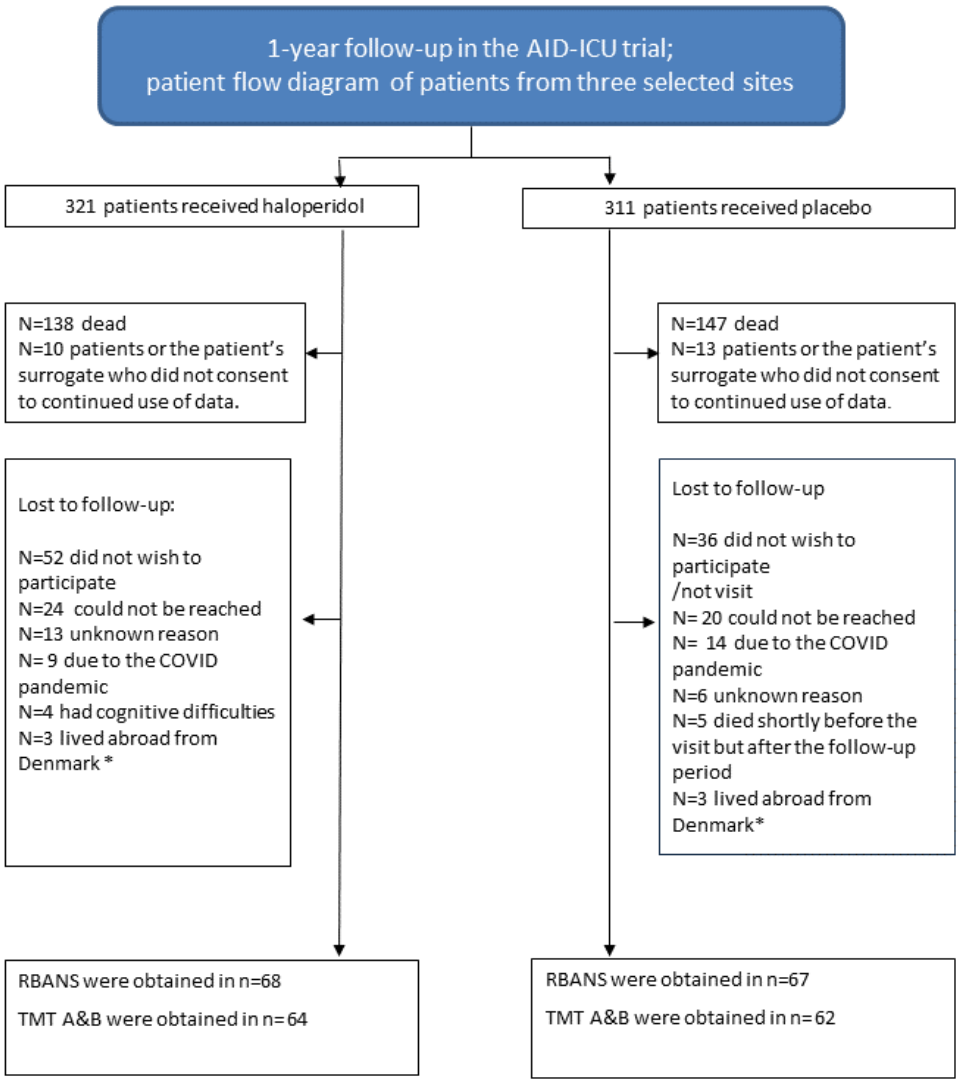

Figure 5. Show the consort diagram of cognitive function. * Greenland or the Faroe Islands

Study III

We used interviews to highlight and gain a comprehensive understanding of the phenomena of recovery and rehabilitation to understand the challenges ICU survivors might face one year later. The participants were recruited from two sites of the AID-ICU trial in Zealand, Denmark, and were all part of the pre-planned 1-year follow-up of the AID-ICU.

We used purposive sampling. The participants were selected with the purpose of providing rich and relevant information for the aim of the study, and the criteria used were gender, age, and demography (112,113).

The study aimed to explore the everyday life experiences of patients who experienced delirium during an ICU stay from discharge until one year later, focusing on patients' health-related quality of life and cognitive function. An interview guide was developed with integrated features from the two of the quantitative instruments used in Study I(EQ-5D) and Study II (RBANS), providing a more deductive approach as we wanted to explore with the participants' own words how they described themself compared to the results of the two instruments used (113,114). The interview guide was supplemented with questions to explore the memory and impact of delirium inspired by Delirium Experience Questionnaire (DEQ) (115) (Table 5). DEQ assesses the distress associated with delirium, qualitatively and quantitatively, and covers elements related to the delirium if the patient remembers being confused and distressed (115).

The author performed the interviews during home visits. Data concerning HRQoL and cognitive function were obtained prior to each interview. A brief introduction to the purpose of the study was given and oral and written consent was obtained. Data became redundant after 15 interviews, and two more interviews were performed to ensure data saturation was obtained (113,116).

The interviews lasted between 12 and 28 min and were digitally recorded and transcribed verbatim.

Table 5. Examples of the Interview guide inspired by the two instruments used In Study I & II supplemented with DEQ (102,115,117).

	Questions	Features from the different instruments
Recovery	How have you regained your functions?	
Delirium	Do you have any recollections or memories from your ICU admission?	Features from DEQ
HRQOL	From discharge until now- Please describe your health and mobility today	Features from EQ domain: Mobility
Cognitive function	Do you have any difficulties in keeping your attention?	Features from RBANS domain: Attention

Reflexivity

The research team consisted of three researchers with more than 15 years of experience in critical care nursing and, therefore, an in-depth knowledge of delirium in the ICU. Furthermore, each researcher has experience in conducting research in context of the long-term follow up on ICU patients with delirium and were familiar with qualitative research.

Data analysis

Descriptive statistics were used to describe the study population in Studies I, II, and III. The patients were stratified by treatment allocation (haloperidol/placebo) in Studies I and II. Numerical data were summarised with median and interquartile range (IQR) and categorical data with numbers and percentages.

We report 95% CIs and consider P-values below 5% statistically significant. All statistical analyses in Studies I and II were performed using IBM SPSS Statistics, version 25 (IBM Corp., Armonk, NY, USA) or R 4.2.3 (R Core Team, Foundation for Statical Computing, Vienna, Austria).

The qualitative research software program NVivo, version 12 (QRS International Pty. Ltd.) was used for the data analysis in Study III.

Study I

Research within critical illness is often challenged by high levels of mortality, we thus, as Colantuoni et al. and Jensen & Lange have recommended, applied a conservative approach to dealing with high levels of mortality and avoiding the so-called truncation-due-to-death problem (118,119). Functional outcomes in RCT-studies with increased mortality and the risk of death before follow-up cannot be assessed, thus making comparisons across the randomised groups complicated because the functional outcomes do not exist, and these will then be truncated due to death. All deceased patients were thus assigned the lowest value in HRQoL data.

The primary analyses were adjusted for stratification variables: site and delirium motor subtypes (hyperactive or hypoactive) at randomisation. We conducted secondary analyses with adjustments of the following additional variables: stratification, sex, age (< 69 years versus ≥ 69 years) and Simplified Mortality Score for the Intensive Care Unit (SMS-ICU;<25 versus≥ 25) (120).

We used logistic and linear regression models with G-computation and bootstrapping (50,000 bootstrap resamples) to calculate sample average treatment effects presented on the absolute (risk differences [RDs] and mean differences [MDs]) and relative (ratios of means [RoMs] and risk ratios [RRs]) scales with 95%

CIs. P-values were derived from the G-computation and bootstrapping procedure for binary outcomes and the Kryger-Jensen and Lange test for continuous outcomes (118).

We supplemented mortality analyses with a Kaplan-Meier plot and a calculation of a hazard ratio from a Cox proportional hazards model adjusted for stratification variables.

Deviations from the RTC protocol were deemed necessary and are presented below:

1. To provide a more intuitive understanding of the impact of the treatment with haloperidol on the outcome mortality, we present sample-average adjusted absolute risk/risk differences instead of odds ratios. These were calculated using logistic regression models with G-computation and non-parametric bootstrapping to estimate confidence intervals (CIs) and P-values.
2. Two strategies for dealing with the expected non-normally distributed numerical outcomes (HRQoL) were specified in the protocol and statistical analysis plan. We planned to use the van Elteren test (adjusted for the stratification variables site and delirium motor subtype) if data were not normally distributed (which was the case) but also using a novel Kryger-Jensen and Lange test if we were challenged with a high proportion of zeroes (due to the high mortality rate). As the mortality was high, we decided to use the Kryger-Jensen and Lange test, which also allows adjustment for the stratification variables. We, therefore, omitted the van Elteren test (118).

Missing data

Death does not generate missing data, and deceased patients were included in the HRQoL analyses unless otherwise stated.

We used complete case analysis for mortality due to limited missing data (2.5%). Fourteen per cent had missing data for the HRQoL outcomes, thus exceeding the predefined threshold of 5%, and Little's test indicated that the data were not missing completely randomly ($P<0.001$).

Study II

We used the RBANS as our primary outcome for assessing cognitive function, which provides a more in-depth evaluation of cognitive functioning across multiple domains and is regarded as "a stand-alone battery" in the context of neuropsychological assessments (66,102).

We performed survivors-only analysis using linear regressions because of a high level of missing data (>55%), which was mainly completely random (due to the COVID-19 pandemic).

We used univariate and multiple linear regression analyses to assess predefined variables associated with impaired cognitive function. In the primary analyses, we used linear regression models adjusted for the stratification variables, site and delirium motor subtype to assess differences between the two groups in the primary and secondary outcomes. We also conducted a secondary analysis of the primary outcome to assess the potential impact of pre-existing cognitive dysfunction measured by IQCODE at randomisation. This was assessed by a linear regression model adjusted for pre-existing cognitive dysfunction and stratification variables.

The RBANS global cognitive score was first reported as a median (using IQR) and assessed between the two groups; however, we also applied the common SD-based cutoff points of 1.5 SD and 2 SD below the age-adjusted population mean of 100 points to explore cognitive impairment in general between the two groups as recommended (66,102).

A neuropsychologist validated one-third of all the RBANS test results.

Study III

We used the framework analysis method (FAM), inspired by Gale et al., supplemented with inductive content analysis during the last data analysis process for the qualitative study.

The FAM is considered a flexible and systematic approach that can be adapted to various research contexts. FAM consists of seven steps: (1) transcription; (2) familiarization with the interview; (3) coding; (4) developing a working analytic framework; (5) applying the analytical framework; (6) charting data into the framework matrix; (7) interpreting the data (114,121).

The FAM often involves a comparative approach, where researchers use a coding framework to analyze each case systematically, categorizing information into codes based on predetermined concepts. The main feature differentiating FAM from other qualitative analysis techniques is its matrix output, which enables researchers to systematically analyze data by participants and themes. As we wanted to explore the everyday life experiences from discharge till one year later, focusing on patients' HRQoL, cognitive function and delirium, we chose a deductive approach to the matrix conception and generated the cases from the two instruments (EQ-5D and RBANS). The codes were the domains from the two instruments (EQ-5D: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression and in RBANS: attention, memory, mobilizing words, visuospatial). Finally, we supplemented with a code called "Recollection of delirium".

An inductive approach was chosen during the last step of the analysis and latent content analysis was applied (114). An inductive approach, also called data-driven, is characterised by searching for patterns, looking for similarities and differences in the data, and going from concrete and specific to abstract and general (121).

Table 6. Example of the final raw matrix.

Case/Codes	EQ-5D Mobility	EQ-5D Self-care	RBANS Attention	RBANS Memory	Recollection of delirum
EQ-VAS>51					
RBANS>70 - 80<					

After creating the matrix meanings, units from each interview were entered in the codes and rows depending on each interviewee's result from the HRQoL and RBANS test obtained before the interview. This formed the initial analytical framework. During this last step, "Interpreting the data," condensation and interpretation of inspired by Graneheim and Lundman generated the final stage in the analysis process, creating sub-themes and then abstracting into one overarching theme (121)**.**

An inductive approach was chosen during the last step of the analysis and lantent content analysis was applied (114). An inductive approach, also called data-driven, is characterised by searching for patterns, looking for similarities and differences in the data, and going from concrete and specific to abstract and general (121).

Table 7. Example of the matrix with quotes within each domain and case.

Cases	Codes	Codes	Codes	
EQ-5D VAS>51	ED-5D Bevægelighed	EQ-5D Mobility	EQ-5D Mobilty	
	Qoutes in Danish	Quotes in English	Condensation	Subtheme
	ID 1: Nu går jeg hver mandag halvanden time om mandagen og hver torsdag i halvanden time og der er ved opvarmning og cykler i og så har vi alle de der maskinerne, og det betaler jeg selv. CB: Så på den måde får du trænet din mobilitet, ved at du træner to gange om ugen… på den måde får du styrke dine mobilitet	ID 1: Now I exercise every Monday an hour and a half and every Thursday for an hour and a half and there's a warm-up and bikes and then we have all those machines, and I pay for that by myself. CB: So in that way you train your mobility by going to a gym twice a week... you get to improve your mobility that way?	All the informants have needed some functional rehabilitation - and they report that it has been a long road and that the municipal provision of services is not enough	Struggling to regain a functional life

Ethical considerations

This thesis is based on an RCT that complied with the ethical principles for medical research involving human subjects as outlined in the Declaration of Helsinki and was approved by relevant health authorities, ethics committees (Danish Ethics committee number: SJ-646), and data-protection agencies in participating countries (76,98). The Declaration of Helsinki states that research involving humans is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments) with the prerequisites of protecting health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. It is further mandatory to provide informed consent (written and oral) and information about the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal (98).

Patients with delirium in the ICU are seen as temporarily incompetent patients in Denmark. Patients were therefore, enrolled after obtaining informed consent from one physician who was independent of the trial (first trial guardian). After that, consent was obtained from the patient's next of kin after enrolment and from a second physician (second trial guardian, also independent of the trial) as soon as possible. Informed consent was obtained from the patients as early as possible after they regained consciousness. This consent also included the one-year follow-up data collection. Consent was obtained according to the national regulations in the foreign countries where the study took place.

A hallmark of delirium is memory loss. Sometimes, this also involves memory loss of ICU admission, making it a challenge when contacting former ICU patients without any recollection of participating in a study during their ICU admission. Furthermore, an ICU admission may sometimes leave the patients with traumatizing experiences of factual and non-factual memories (122). The participants were thus given an explanation (both orally and in written form/a leaflet) prior to each interview about the AID-ICU trial, the reason for a one-year follow-up, and a brief description of delirium and the challenges resulting from this.

Additionally, we aimed to explore patients' cognitive function. If a participant seemed cognitively impaired during the test and had no medical record history to confirm it, we recommended contacting a physician for further examination. One year later, participants who had severe cognitive impairment were excluded from

study II (n=4) based on a judgment by their nearest family member (either wife or husband).

With this follow-up study of the AID-ICU trial, it is believed that the knowledge gained is expected to improve the treatment and management of delirium during and after intensive care and subsequent rehabilitation and recovery.

Furthermore, these studies are in the interest of the individual patient, future patients, and society in order to gain firm evidence of the role of haloperidol in treating delirium. If treatment with haloperidol is not found superior to placebo, future patients will benefit from this trial by avoiding the potential harm of receiving haloperidol for delirium treatment.

Results

Study I

The AID-ICU trial included 1000 patients; 13 patients never received any trial medication and were therefore excluded from the analysis. Consequently, 987 patients were included in the study. A further 25 patients withdrew consent prior to the one-year follow-up.

The baseline characteristics between the two groups were well-balanced. However, there were some differences between the groups. A higher age and a higher prevalence of coexisting conditions, particularly hematologic cancer, were observed among non-survivors, and non-respondents had more baseline risk factors for delirium (e.g., substance abuse, smoking).

We obtained vital status for 96.2% and HRQoL data for 83.3% of the participants. The one-year mortality was 44.7% (224 out of 501) in the haloperidol group and 51.6% (251 of 486) in the placebo group. After adjustment, the absolute risk difference was -6.4 % (95% CI: -12.8 %- points to-0.2 %- points; P=0.045). These findings were broadly consistent across the secondary analyses. Furthermore, the results align with those observed at 90 days in the primary study of the AID-ICU trial. Figure 6 shows a survival curve from randomisation to day 365 (88).

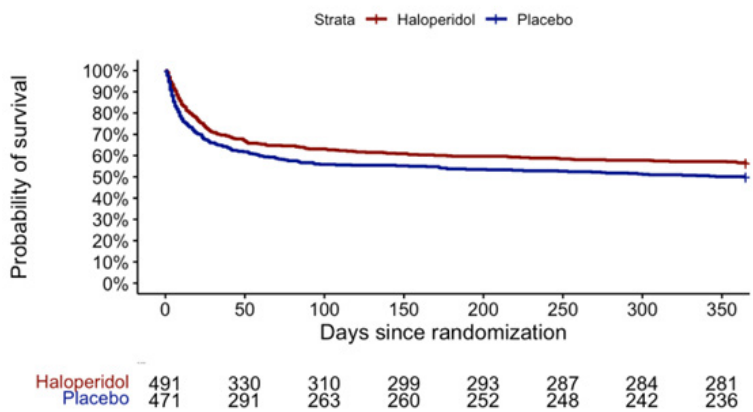

Figure 6. Survival curves in the two groups at one year (day 365). Patients who withdrew consent for further data or were lost to follow-up were censored at the time of withdrawal or loss to follow-up.

At 1-year follow-up the median EQ-5D-5L index value were 0.3 (IQR 0.0 to 0.9) in the haloperidol group and 0.0 (IQR 0.0 to 0.8) in the placebo group, resulting in an adjusted MD of 0.04 (95% CI: -0.03 to 0.11; P=0.091)

Median EQ VAS score were 25.0 in the haloperidol group versus 0.0 in the placebo group, resulting in an adjusted MD of 3.3 (95% CI: -9.3 to 17.5; P =0.142) The results of the sensitivity analyses were consistent with the primary analysis. Best-worst and worst-best sensitivity analyses showed that missing data from non-responders could have influenced the results. Figure 7 shows the distribution of domians in EQ-5D-5L.

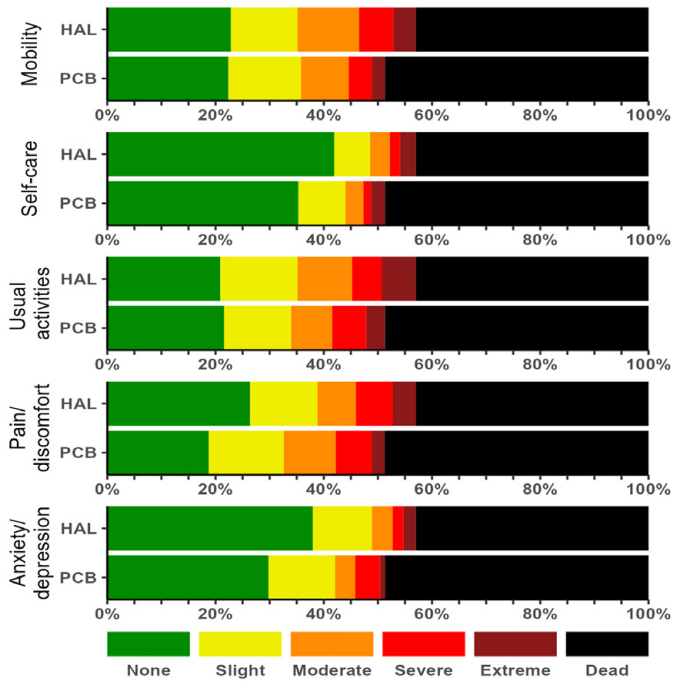

Figure 7. Shows the distribution of the domains of EQ-5D-5L full population.

Study II

A total of 347 of the 632 randomised patients were alive for one year. We obtained data on cognitive function for 135; 68 patients in the haloperidol group, and 67 in the placebo group. We found no statistical difference between groups on either

RBANS global cognitive score (mean difference MD 1.16 (-6.16 to 8.48), P=0.75) or the Trail Making Tests. However, in the secondary outcomes, we found pre-ICU admission cognitive function measured by IQCODE at baseline was associated with lower RBANS global cognitive score (MD -26.99 (-49.13 to – 4.84); P-value= 0.018).

Furthermore, we found that the mean global score in the haloperidol group, was 74 (SD.23), where 59% had a global cognitive score of 1.5 SD below, and where 52% (35/68 patients) had a global cognitive score of 2 SD below the normative mean. The mean global score in the placebo group was 72 (SD.20), where 60% had a global cognitive score of 1.5 SD below, and 40% (28/67) of those had a global cognitive score of 2.0 SD below the normative mean.

In conclusion, we found that treating delirium with haloperidol did not influence a potentially cognitive decline in acutely ill patients with delirium in the ICU one year, but in both groups, a high proportion of the patients' global cognitive scores were below 2 SD the normative mean indicating mild to severe cognitive impairment.

Study III

Nine women and eight men participated in this study. The median age was 69 years (interquartile range (IQR), 57-73.5), and the median length of stay in the ICU was eight days (IQR 5.5-26.5).

They all reported a struggle returning to everyday life and, for some participants, an adaptation to a new normality from hospital discharge one year later. None of the participants knew the challenges they would face once discharged from the hospital. They described needing more information about the challenges they could/would experience in order to better understand their situation and the struggles they experienced during recovery. This information was important for the patients themselves but also for staff in a primary care setting. One theme emerged from the analysis '*From enduring to adapting'* with three subthemes: *'Struggling to regain a functional life', 'Struggling to regain normal cognition'* and *'Distressing manifestations from the ICU'*. The experience of hallucinations was still very present. The experiences were still vivid and intense, with impressive details. As one participant described:

"Every night, the nurses would be dressed as cats, and the doctors as dogs, and then the bed would be placed vertically, and they would run around it"(I13).

Discussion

Methodological considerations

The general purpose of scientific research is to generate knowledge. This thesis is based on a quantitative and qualitative research design and methods together with various ontological and epistemological perspectives. Two different concepts are thus necessary to apply to discuss these studies' limitations and strengths.

Concepts such as validity will be discussed to evaluate the quality of the studies with a quantitative approach, and concepts such as trustworthiness will be discussed to evaluate the quality of the study with a qualitative approach (123).

The experimental design

Randomised clinical trials are considered to be the golden standard in research. The only difference between the groups is the intervention, which in study I & II concerns two groups of patients where one group received haloperidol and the other placebo.

However, the way a study is conducted, the measurements that are used, and which data analysis is applied, will determine the findings and thus influence the interpretation and conclusion of the study (123). The findings of a study will be free from ambiguity in the ideal world, but in reality, different elements can affect the validity of the study and interfere with the interpretation of the results. When a researcher can anticipate potential threats to validity and introduce different features to mitigate these threats, then the validity is strengthened.

Besides the validity of an instrument, Shadish et al. have proposed four types of validity for assessing a study: internal , external, construct, and statistical conclusion validity. These four types are not mutually exclusive, and the same problem in a study (e.g. attrition) may threaten more than one type of validity (124). Some of the challenges to the studies in this thesis are discussed below.

Validity of the instruments

The psychometric properties of any instrument or test (medical, neuropsychological, or other) must be explored and shown to be adequate to ensure its accuracy and consistency in order to be clinically valuable. Two crucial elements are validity and reliability. Validity refers to the degree to which an instrument measures what it is supposed to measure, whereas reliability refers to the consistency of the measure (123).

Delirium screening

Clinical trials investigating treatment of delirium are mainly based on delirium assessment tools; therefore, the generalizability relies on the instrument used. All randomised patients were screened for delirium with either the CAM-ICU or the ICDSC to be included in the AID-ICU trial. Both are recommended, well-established screening instruments and have been translated into different languages with a high level of reliability and validity (40,125). Furthermore, both instruments have a high pooled sensitivity and specificity; however, CAM-ICU is superior in excluding patients without delirium and detecting delirium in patients receiving mechanical ventilation (34,125).

At the start-up of the AID-ICU trial, nurses and physicians involved in the participating sites received a brief introduction and a refresher course on using delirium assessment tools to enhance the instrument's reliability. Studies have shown that although CCRNs and physicians view themselves as competent in using both instruments, they require ongoing training as they keep questioning the instrument's validity, especially CAM-ICU (126,127).

According to the study and international recommendations (PADIS guidelines), patients should be screened twice a day, and when there are changes in the level of the patient’s consciousness (40,92). However, delirium is a dynamic condition with fluctuations in symptoms and where the timing and frequency of delirium screening can impact the detection of delirium (125).

Seventy-seven per cent of the patients in the AID-ICU trial were assessed with CAM-ICU. However, there are several limitations when using CAM-ICU. Firstly, its dichotomous approach to detecting delirium provides a current statement of the presence of delirium. Delirious patients outside the screening point could thus have been missed. Secondly, CAM-ICU lacks an ordinal grading of the severity of delirium. Patients with low levels of severity symptoms of delirium could potentially be missed (128). Thirdly, CAM-ICU requires an interaction with the patient that, for some, is found to be embarrassing and demeaning to one's professional role, which may have yielded lower screening scores of patients during the AID-ICU trial (126). Fourthly, the patients may be confused by other internal (e.g. pain) and external factors (e.g. the ICU environment) (128). Finally, in both

instruments there is a risk of false-positive screening (e.g., sedation or sedation-related confusion) (128,129).

ICDSC is based on observations during routine care and involves nurses using their professional judgment. But the nurses' judgments are subjected and, thereby, a risk of bias and thus a limitation. However, a limitation. However, a limitation of ICDSC is a lower level of sensitivity in the detection of delirium in intubated/non-verbal speaking patients, which might affect the outcome of the screening (129). These limitations of the delirium screening may have influenced the results and, thereby the validity of this thesis.

HRQoL

EQ-5D was recommended for use in ICU settings at the time of start-up (76,130). A strength is that EQ-5D is a short, brief instrument with a self-rating of the patient's health status, is translated into many languages and with many country-specific population preference scoring systems (76,130,131). It is less burdensome than other HRQoL instruments (e.g. SF-36)(132).

However, two systematic reviews have recently investigated the quality of the HRQoL instruments used in critical care settings, showing that the data on the psychometric properties of these instruments, including EQ-5D, are sparse and generally of poor to fair quality and, therefore, a limitation (132,133).

Further, EQ-5D is a generic HRQoL questionnaire that provides a broad overview of health status but may lack specificity for capturing differences of a specific health condition, e.g., cognitive difficulties e.g., cognitive difficulties, but may also be challenged by fluctuations in health, meaning that the patients can have good and bad days, thus therefore a limitation.

To ensure consistency and reliability, a SOP was developed. Only three sites in Denmark (from a total of 12) collected HRQoL data for this study, and the author introduced and discussed the SOP at each site.

RBANS

We chose a comprehensive neurological test battery in Study II to investigate the patients' cognitive function. A strength is that the RBANS is designed to assess a broader range of cognitive functions and is considered a "stand-alone" tool for this evaluation (66). However, a limitation is the lack of validation of RBANS in the context of ICU survivors. Further, is RBANS a comprehensive instrument and time-consuming for the participants. This could be a limitation, as ICU survivors may be/ are a frail population (81). However, the RBANS has been validated for use in patients with mild cognitive impairment, including Alzheimer's disease and traumatic brain injury and was therefore used in this study (101,102,134).

Using psychologists to assess the RBANS might have been more appropriate but was not done due to limited resources. Further, RBANS is designed for other healthcare professionals to administer as long as they have been trained (104). A neuropsychologist trained the research personnel, including the author. Same neuropsychologist also validated the results in 1/3 of the RBANS. An SOP was also developed to enhance the reliability of the data collected. Finally, we screened for cognitive impairment in this study and did not use the test result for diagnostic purposes.

When designing Study II, we wanted to use a neuropsychological test to evaluate a broad range of cognitive functions. However, RBANS is time and resource-consuming if all the patients of the AID-ICU trial were to have particpated in this study. Obtaining data concerning cognitive function by using a brief instrument by telephone could have enhanced the data collection but might not have provided a comprehensive picture of the patients' cognitive function.

TMT A&B

A strength is that TMT A & B tests are simple, easy to administer, and valuable for exploring cognitive functions such as executive functions and attention. However, a major limitation with TMT B is that patients with language or literacy difficulties may struggle with this task, making it challenging to differentiate between cognitive impairments and language/literacy difficulties. We did not examine whether the patients had language or literacy difficulties prior to the tests; and this is thus a limitation. Furthermore, TMT A& B has not yet been validated for use in ICU survivors but has been validated in patients with traumatic brain injury (135). The level of education may be a confounding factor and was not obtained for every patient, so our results may thus be influenced.

In general, if the level of education, sex, and preadmission coexisting conditions are not taken into account when exploring cognitive function in ICU survivors, then this may lead to an overestimation of the incidence of cognitive decline and thus constitute a limitation (4).

Internal validity

The strength of the AID-ICU trial and the two follow-up studies (Studies I and II) reported in this thesis is the robust methodology from trial initiation to trial completion. The RCT Protocol serves as a strength for the research described in Study I.

Study I

The data analysis in Study I has been performed in the ITT population to increase internal validity. ITT analysis helps to preserve the randomised treatment

assignment, avoid selection bias and provide a more conservative estimate of the treatment effects (136).

We had high level of completeness of data on the primary outcomes (97.5 % for mortality and 83.5% for HRQoL), and the statistical analyses were performed in adherence to the ITT principle, thus constituting a strength of the study.

There are several threats to internal validity, and one is selection bias. To eliminate this, the randomisation was centralised and web-based according to the computer-generated allocation sequence list and varying block size and was stratified according to trial site and delirium motor subtype (hyperactive or hypoactive) (92). Another possible selection bias may arise during inclusion into the AID-ICU because of the screening tools used. Both instruments have limitations, as mentioned above, and therefore, patients could have been erroneously included or excluded from the study.

Notably and intentionally, no adjustment for any post-baseline variables (including potential mediators in the 12-month follow-up period) was made, as adjustment for post-randomisation variables in an experimental context (i.e., a randomised clinical trial) is discouraged and inappropriate in this context, as the resulting inferences would no longer be causally interpretable (137).

Study II

Cognitive impairment is a complex condition with different cognitive disturbances in memory and executive functions. One major limitation is the absence of a clear definition when investigating cognitive impairment in ICU survivors and the lack of a validated instrument for assessing cognitive function (71). We adopted the definition expressed by Morandi et al. in 2012 (66).

The methodology is the same as in Study I and thus this study's strength is the randomisation process. A further strength is that all research personnel were blinded to the intervention. To increase internal validity, data concerning pre-admission cognitive status was obtained; however, this was only for 65% of the patients (n=88), thus a limitation to internal validity.

However, a major limitation of Study II is the attrition, where only 39% of ICU survivors wanted to participate. The reasons were mainly due to the COVID-19 pandemic (n = 24 but also during the subsequent varying periods of the pandemic (n=88)). Anothor limitation to the internal validity, was that data concerning pre-admission cognitive status was only obtained for 65% of the patients (n=88).

We did not obtain any medical history at the one-year follow-up, which can thus be seen as a limitation. Consequently, the risk of confounding factors such as the use of e.g. benzodiazepines could influence the tests and therefore the results of the tests.

External validity.

A strength that enhances the generalisability of the present studies is the inclusion criteria for the AID-ICU trial. The patients included were heterogeneous in several aspects, such as admission diagnosis, illness severity, and age, thus increasing the study's external validity. Additionally, participants were recruited from mixed ICUs, where 55% of patients had hypoactive delirium, and 45% had hyperactive delirium (45%), reflecting a broad and diverse sample of ICU patients with delirium.

However, the majority of the patients were recruited from general ICUs in Denmark, limiting the external validity, and thus the result is mostly applicable to a population that is similar to those in Danish ICUs with delirium.

Construct validity

We hypothesised that haloperidol would decrease mortality but increase HRQoL and cognitive function. In the AID-ICU trial the hypothesis was that haloperiodol would shorten the duration of delirium (92). We saw an early separation in the survival curve early in AID-ICU trial continuing to day 365. As a result of this, a plausible explanation is the effect of haloperidol on delirium could be linked to the management of delirium. Haloperidol's sedative effect may help manage agitation, a common symptom of hyperactive delirium but also has an impact on acute psychotic episodes, which both (hypo/ hyper)types of delirium may experience. As delirium is debilitating and distressing for patients, minimising these events of delirium could potentially influence the patient's psychological outcomes after critical illness and hereby influcence long-term HRQoL(48). Unfortunately, this was not the case.

Furthermore, the findings in study II could not be translated into an improvement in cognitive function one year later. Manage delirium with haloperidol may alleviate symptoms associated with delirium and hereby reduce the severity of delirium, but does not prevent the course of cognitive impairment. Delirium and cognitive impairment are intertwined, and shortening the duration and severity of delirium could potentially have had a positive impact on cognition.

One of the strengths in RCTs is the randomisation, which balances known and unknown risk factors/confounders in the two groups, so the only difference between the two groups is the intervention given to the patients, in this case, either haloperidol or placebo. The risk of progression of chronic diseases (frailty, dementia), ICU readmission or hospital admissions should be equal in the two groups unless the intervention has an effect on these events one year later (123).

Statistical conclusion validity

Statistical conclusion validity involves applying adequate sampling procedures, appropriate statistical tests, and reliable measurement procedures to ensure reliable and accurate conclusions. Two types of errors can compromise statistical validity in a study: type I and type II errors.

Type I errors occur when the null hypothesis is mistakenly rejected, indicating differences in the data even though no differences exist in the population. The risk of incorrectly rejecting the null hypothesis is associated with the p-value. The significance level was below 0.05 in Studies I & II. There is thus a 5% chance of erroneously rejecting the null hypothesis in the analyses conducted in Studies I & II (123,136). Nonetheless, the power calculation for the AID-ICU trial did not account for the one-year follow-up, thus constituting a limitation, and there is a risk of a type I error in Study I. Furthermore, using a p-value less than 0.01 for rejecting the null hypothesis could have indicated a higher level of confidence of the result (136).

We used complete case analysis to deal with missing data in mortality, which was limited (2.5%), and used multiple imputations for the HRQoL outcomes, where 14% had missing data. Both of these procedures can be seen as a strength.

A major threat in follow-up studies is mortality and attrition. As one-year mortality varies within ICU survival from 10 to 40% (24,138), the risk of high mortality was considered in Study I, and as a result of this the risk of influencing the HRQoL outcome was also considered. We thus chose to assign the deceased patients the lowest value in EQ-5D in the analysis to avoid misleading results in Study I.

With a type II error, the null hypothesis is not rejected when it is actually true, meaning that differences in the data are not shown even though there are differences in the population. Type II errors are related to the statistical power in terms of sample size and effect size. Small differences are difficult to detect with a small sample size, so there is a risk for a type II error in Study II (123,136).

Trustworthiness

Lincoln and Guba's framework was applied to enhance the trustworthiness of the qualitative approach. There are four criteria: credibility, dependability, confirmability and transferability (123).

Credibility

Credibility refers to the confidence of the findings. A way to enhance credibility is by triangulation. Firstly, the participants were purposely sampled and selected with varying characteristics regarding gender, age, and demography to increase the possibility of receiving rich and varied descriptions related to the research question.- Furthermore, we used the participants' data from the two tests performed before each

interview as a data source for developing the matrix in the analysis. The author conducted all the interviews to ensure data quality. For data analysis, we provided a thorough description of this process. Finally, we used research triangulation, in terms of three nurses each with different work experiences: ICU, delirium, and qualitative research (123,139).

Dependability

Dependability refers to the study's consistency and stability (reliability) that should be reported in detail. To minimize the risk and strengthen dependability, a semi-structured interview guide was used in all interview sessions. A detailed description of the study process was provided, as well as a description of how the research study was conducted with different approaches. Our study may be considered a "prototype model" using the quantitative data to create a qualitative matrix (139).

Confirmability.

Confirmability refers to the study's objectivity, meaning that the findings represent the participants' perspectives rather than being biased by the researchers' perspectives. However, the existence of the researcher's biases is inevitable. The authors' preunderstanding was continuously discussed in the research group during the analysis process in order to limit its' impact. Furthermore, the participants' voices were used as quotes to enhance and visualise the basis of the interpretations and thus support confirmability (123,139).

Transferability

Transferability refers to the generalizability of the data and the extent to which the findings can be transferred or applicable to other settings. A broad description of the phenomenon and participants were provided to give others a proper understanding of it (123,139). However, one limitation is that only Danish speaking patients were invited to participate in the study, which may constitute a limitation.

Discussion of the findings

This thesis aimed to determine the long-term effects of haloperidol treatment in acutely admitted adult patients with delirium in the ICU on mortality, HRQoL and to describe these patients' experiences of their quality of life.

The sedation approach for mechanically ventilated ICU patients has shifted from deep sedation to lighter or no sedation since 2000. This paradigm change reflected a 'less is more' strategy driven by a growing body of evidence supporting the advantages of lighter sedation (140). Delirium was then often unrecognised or attributed to the effects of sedation or underlying medical conditions. A growing

recognition of the distinct features of delirium became apparent in the ICU and led to the development of delirium screening assessments in the ICU. Research has demonstrated since then that delirium in ICU patients is associated with deteriorated outcomes and that delirium imposes a substantial burden on patients, their families, healthcare systems, and society. This emphasises the importance of early detection and management of delirium (23,33,39,70,141).

Research has expanded during the last decades and included a focus on the long-term outcomes of delirium in ICU survivors, but also an understanding of PICS and its impact on patients' cognitive, mental, and physical health has become an integral part of critical care research (2,57).

The findings will be discussed in three themes: Intensive care Delirium, Long-term outcomes and recovery.

Intensive Care Delirium

The results of this thesis show that treatment with haloperidol for delirium reduces mortality, while highly relevant patient-centred outcomes such as HRQoL and cognitive function did not improve. It is, thus, essential to continue focusing on preventing and treating delirium in the ICU.

Delirium during critical illness is associated with unintentional removal of devices/catheters, complications to mechanical ventilation, e.g. self-extubation, nosocomial pneumonia, increased duration of mechanical ventilation, and prolonged length of stay in ICU and hospital (23,30,31,142). Delirium significantly contributes to various long-term impairments with long-term mortality and morbidity (30,31,39,91,141).

Delirium in the ICU is highly prevalent, affecting more than 40-50 % of all ICU patients, where hypoactive delirium is the most prevalent of motor subtypes (50%) (19,39). Hypoactive delirium is most challenging to detect and requires the use of a validated tool to avoid the risk of misinterpretation (e.g., the patient being depressed or tired) (39). Research has showen that hypoactive delirium has been suggested to be linked to the poorest survival prognosis compared to mixed- and hyperactive delirium, which was highlighted in a systematic review by Krewulak et al., who found a higher mortality in patients with hypoactive delirium (39,143). Patients with hypoactive delirium may not get the correct treatment and nursing care due to the misinterpretation of this condition.

A recently published Chinese cross-sectional study exploring knowledge, attitudes, and practices regarding hypoactive delirium among CCRNs showed a need for greater understanding and continuing education regarding related factors and clinical symptoms, prevention, assessment and risk factors (144). Being a Chinese study limits the generalisability to a Nordic CCRN population. However, Danish

CCRNs have raised concerns regarding using the CAM-ICU and potential deficiencies in delirium detection (126). Moreover, a newly published Danish survey exploring CCRNs' perception of different methods for delirium screening showed that despite CCRNs viewing themselves as competent in delirium screening the use of ICDSC broadened their clinical understanding of delirium. This suggests that choosing an instrument that resonates with the nurses' observations and practises and perpetuates ongoing education and training is highly relevant (127). The CCRNs are the patients' primary caregivers in the ICU, and the patients are dependent upon their accurate monitoring of delirium in terms of being either hypoactive or hyperactive in order to receive the correct care and treatment and thus hopefully improve survival.

Hyperactive delirium is easily recognized due to the nature of the increased psychomotor agitation, which is a dangerous condition with a high risk of self-harm and potentially compromising care and treatment (145).

There is a lack of evidence-based nursing procedures concerning the different subtypes of delirium, and in particular, how to work with patients with hypoactive delirium. Still, it should be underscored and recommended that the A2F bundle be applied to focus on managing delirium and exploring the causes of delirium (22,40,144).

Finally, the discussion about treating hypoactive delirious patients with haloperidol is a subject of ongoing debate and has also been the subject of criticism of the AID-ICU trial. Nonetheless, it is not uncommon for patients to experience different kinds of motor subtypes of delirium, leading to mixed delirium, which, in a scoping review by La Cour et al. showed were more likely to receive benzodiazepines and propofol, two highly potential medications for delirium development. Hypoactive delirium should thus receive the same attention as hyperactive delirium (19). Future research should focus on a differentiated delirium-targeted pharmacological strategy.

Long-term outcomes

Haloperidol has been used in the ICU for several decades. It is indisputably the most-studied antipsychotic treatment of delirium in the ICU, which is now supplemented with evidence about the long-term outcomes as reported in this thesis (146).

Study I is the first RCT to assess haloperidol's effect on long-term mortality, showing improved survival. The survival curve in Figure 6 (page 46) showed an early clear separation between the two intervention groups, which could indicate that haloperidol affects delirium management, and this effect is translated into improved long-term survival. Although the mechanism of haloperidol is still not fully understood, it reduces psychomotor agitation, which is essential for patients with hyperactive delirium. In the newly published *Efficacy of haloperidol*

to decrease the burden of delirium in adult critically ill patients, the EuRIDICE trial, the risk of self-harm and other agitation-related events in patients with delirium in the ICU treatment with haloperidol versus placebo(isotonic saline) showed that haloperidol decreases agitation (147). Similar results were reported in the RCT, *Effect of intravenous haloperidol on the duration of delirium and coma in critically ill patients*, the Hope-ICU trial, which assessed the prophylactic effect of haloperidol (148). Reducing agitation or agitation-related events may benefit the patients and thereby being translated into improved survival. Further, using haloperidol for treating delirium-associated symptoms, such as agitation, may also minimize exposure to multiple sedating agents, thus mitigating potential interactions and avoiding polypharmacy (146,147).

The use of pharmacological interventions to treat delirium are not recommended for routine use. Still, managing delirium in the ICU is frequently done pharmacologically, with haloperidol being most common, and the results from Study I add to the knowledge that haloperidol is safe for both types of delirium (hypoactive and hyperactive delirium) and improves survival in the long-term, but not HRQoL.

Despite an increase in RCTs focusing on survival in critically ill patients, there is limited evidence concerning other highly relevant patient-centred outcomes, such as HRQoL in these studies (149). It is essential to recognize that improved survival does not necessarily equate to enhanced HRQoL, as highlighted in the systematic review by Pallanch et al. (153). One potential explanation for the results of Study I could be that more severely ill patients survived in the haloperidol group compared to the placebo group. These survivors may have experienced greater levels of disability, translating into lower HRQoL assessments.

The results of Study II showed that ICU survivors were challenged with impaired cognitive functions despite allocation to the AID-ICU trial. These findings add to the sustainable evidence that delirium and cognitive impairment are interconnected and not influenced by pharmacological treatment (4,6,59,66,70). It is crucial to prevent delirium in the ICU to minimize the risk of impaired cognitive function until the underlying mechanisms of delirium and cognitive impairment are identified. There is an increasing focus on interventions with cognitive training to prevent and manage delirium in the ICU. However, these interventions still lack sufficient evidence and must be explored in larger RCTs (150,151). A small RCT recently examined the feasibility of occupational therapist-guided cognitive interventions in critically ill patients using simple cognitive training (e.g. memory, playing cards, suduko) (151). These were found feasible, and CCRNs could easily apply such interventions in their daily routine care and interaction with the patient.

Furthermore, there is also a need for systematic assessment of the patient's cognitive function when admitted to the ICU to determine which patients are at risk of developing cognitive impairment to initiate relevant cognitive rehabilitation.

Knowledge about HRQoL and cognitive functions is important for patient-centred outcomes and relevant for discussing critical illness and survival. There is a lack of knowledge about these factors' associations with changes in quality of life and their impact on recovery from critical illness. Further, there is a need to move beyond critical illness. As recommended by Herridge et al. in their review article on outcomes after critical illness, they see critical illness as a phase of an illness encompassing both pre- and post-ICU stay. The dissemination of knowledge concerning outcomes and recovery after critical illness is still limited, and there is a need to broaden this knowledge (2). This underlines the need to assess these long-term outcomes in future randomised clinical trials and explore patient-centred outcomes at baseline to determine, e.g., HRQoL before critical illness in order to explore the trajectory they experience.

Recovery

The findings in Study III underscore the ongoing challenges ICU survivors experience from ICU discharge to one year later. These include lacking information about critical illness, what to expect during recovery, feeling lost during the transition from hospital to home/primary care, and requiring information to regain themselves or adapt to new life circumstances. The participants described a difficult recovery phase with a high level of dependency in the beginning due to a loss of physical functioning to still being challenged with a functional loss. None of them had regained the same level of physical functioning as they had prior to their critical illness. Some participants struggled with cognitive challenges such as memory loss and concentration problems but demonstrated various adaptive strategies to encounter these challenges. Finally, some of them still had memories of their hallucinations from their delirium, which a few of them experienced as distressing memories.

Ortega et al. explored the lived experience of patients with delirium in the ICU in a meta-ethnographic synthesis in 2020 and showed that critical ill patients with delirium experienced being confronted with intense existential challenges. They were potentially overlooked by care providers and described a persisting unaddressed thought about their experience during ICU admission but also post-discharge emphasising the importance of communicating about recovery and delirium (45).

Critical illness has a profound impact on a patient's recovery, not only in relation to the impairments within physical, cognitive and mental health but also to the effect on quality of life, returning to work, social engagement, and the patient's family and each patient surviving critical illness has a unique recovery (53,65). The complexity of PICS challenges the rehabilitation process. The understanding of the essential meaning of the transition the patients experience from critical illness to their

recovery phase to the impact of PICS on ICU survivors is still limited, and future research exploring this is warranted.

Healthcare professionals are crucial in assisting ICU survivors in enduring, building resilience, and adapting to the changes during their recovery trajectory. Surviving critical illness is a challenge that triggers a phase of shock, pre-resilience, and endurance intertwined with the recovery process. The transition from ICU to hospital ward and home presents challenges, and patients face a decline in various functions during critical illness.

The CCRN provides comfort and ensures the correct care and treatment for critically ill patients. During this phase of critical illness, there is a need to support the patient in enduring to survive, which means providing support and care for the patient to survive (152). The next phase, enduring to live, entails the patient using all their energy to focus on getting through the challenging situation. Protective coping strategies, both internal and external, are vital to find themselves again during this phase. The patient will most lightly leave the ICU during this phase and be transferred to the ward. Patients are often discharged from the ICU to a hospital ward without knowing or perhaps remembering what has happened. Some patients have bizarre and frightening memories of hallucinations, whereas other patients have amnesia from their ICU admission. In addition, delirium is often not addressed after an episode/or during ICU admission, leaving the patients vulnerable (45,153). Patients who recall their delirium episode may feel bewildered not knowing what has happened and may, therefore, experience increased distress related to the delirium. In contrast, the patient's perspective on not remembering needs to be explored in a research context because no recollection of their delirium/ ICU admission does not necessarily mean no distress or discomfort associated with the amnesia. Lacking memories of ICU has been related to developing PTSD (1).

Transferring patients to the ward is a part of nursing care, and CCRN nurses play a vital role in improving and securing the patient during this transition. Hence, a CCRN could draw upon interventions to increase resilience (e.g. information about ICU survivorship or basic ADL education) as with her knowledge and understanding of the patient's situation, knowledge about the forward coming recovery process and, importantly, in addressing the possibility of delirium and what it might entail (1,45).

A major challenge for ICU survivors is the additional transition to other healthcare providers and settings and the absence of clear responsibility following ICU discharge (11). The heterogeneous patient population in the ICU challenges the aftermath of designing a clear pathway for recovery and rehabilitation (11). Strategies for ICU follow-up within hospital admission are currently not an integral part of patient therapy after critical illness. However, there is a consensus that ICU healthcare professionals should manage ICU follow-up services in-hospital and

after discharge, and additionally, nurse-led ICU follow-up services have been found to improve Qol; however, evidence is sparse (1,2,11).

Simple nursing interventions, such as diaries or re-visiting the ICU, have been found to be beneficial for ICU-survivors, helping ICU survivors " to understand and make sense of ICU admission and the critical illness" (154–156). The use of diaries in the ICU has thus been the subject of debate about the ability ot minimising the risk of ICU survivors developing PTSD. Still, research has lacked quality and sufficient evidence (157). Nevertheless, CCRNs could easily manage interventions like these in the context of an ICU follow-up service.

Limited evidence exists concerning ICU survivors' challenges during the transition from ICU to hospital ward to home and which coping strategies they apply (55). Using the RAM framework to enhance ICU survivorship could involve designing nursing interventions to facilitate and promote adaptive responses, implementing cognitive rehabilitation training, ensuring physical training, and providing patient education to manage potential challenges during recovery. The RAM framework also emphasises an ongoing evaluation of the interventions to assess their effectiveness in promoting adaptation to monitor a progress, identify areas for improvement or challenges and thus modify the interventions to ensure that a patient-centred approach and an awareness for changing needs is provided if required. This necessitates a collaborative and interdisciplinary approach, customising interventions to address ICU survivors' unique needs for patient-centred care (82,86).

If (nurse-led) ICU follow-up services became an integrated part of ICU therapy, different positive coping strategies (e.g. problem-focus coping aiming to increase the resources available to manage everyday life) could be applied (158). Interventions to promote resilience e.g. social support, could help improve adaptation to new life changes or interventions with information about the ICU-stay, delirium, the recovery process, and the aspect of PICS could potentially enhance empowerment, self-efficacy, and acceptance (82,154,159). Furthermore, this intervention could provide important information about the transition (ICU to home), mitigate many unknown certainties experienced during recovery, and guide the patients with interventions to increase self-management (55). Finally, a follow-up service could screen the patients for different PICS-related challenges, e.g., cognitive function and physical function, and bridge the multidisciplinary approach to provide more targeted rehabilitation for each patient.

There is limited knowledge concerning ICU follow-up services in Scandinavia. Egerod et al. conducted a Scandinavian survey exploring the models of ICU follow up in 2012, which showed mainly bottom-up initiatives conducted by semi-volunteers (160). There is a need for ICU follow-up services to become more structural and uniform and an integral part of ICU therapy despite this extending beyond the normal ICU services. This could be justified by emphasizing the

possibility for enhancing recovery for ICU survivors. Notably and importantly, ICU follow-up should not be limited to only nursing interventions but should entail cooperation between multidisciplinary healthcare professionals and focus on a person-centred approach acknowledging that one size does not fit all (2,42). However, conceptualising a model for nurse-led ICU follow-up services goes beyond the sphere of this thesis, but nursing researchers play an essential role in exploring and identifying predictors for adaptation and designing a model of ICU follow-up.

Conclusion

In conclusion, this thesis contributes new data and a greater understanding of the impact of delirium and delirium treatment in the ICU, focusing on the long-term outcomes one year later. The findings showed that treatment with haloperidol in patients with delirium in the ICU influenced their long-term survival. Notably, it did not impact their HRQoL or cognitive function one year later. Concurrently, patients expressed that their recovery journey from critical illness posed challenges, extending from discharge to one year later, marked by numerous uncertainties and a lack of clarity on appropriate actions to take.

If delirious patients in the ICU are to be treated pharmacologically, haloperidol is the best-studied antipsychotic treatment supported by the evidence and its influence on long-term survival. Our results have notably shown that cognitive function was impaired in both groups even though haloperidol reduced mortality; this pharmacological treatment does not influence the underlying mechanisms of delirium that affect cognition. On the contrary, these results add to the knowledge that patients with delirium in the ICU are at a high risk of developing new or worsened morbidities, especially within the cognitive domain of PICS, but also with the physical domain of PICS. Thus, this thesis underscores the continuous need to prevent and treat ICU delirium.

This thesis also shows that ICU survivors find themselves in an unpredictable life situation after critical illness, striving to regain their lives as normal as possible. The aftermath for ICU survivors is filled with adversity. Nonetheless, CCRN play an essential role in supporting ICU survivors to strengthen their comprehension of their situation, and relatively simple nursing interventions could help identify the specific challenges ICU survivors may encounter. Further, if CCRN participates in designing interventions to enhance the patients' adaptation and resilience after critical illness, it could potentially mitigate the development of symptoms from PICS and assist the patients in the transition across healthcare settings.

Future research

Delirium and cognitive impairment are undeniably intertwined, and firstly, interventions to prevent and treat delirium must be prioritised. There is an ongoing need to continue educating healthcare professionals about delirium. Quality improvement initiatives using virtual reality have been found to be a powerful educational tool for healthcare professionals. Secondly, it is imperative that non-pharmacological interventions focusing on cognitive training within the ICU and, shortly after, should be designed and investigated. However, besides the need for more research to explore the effect of cognitive training during and after delirium in the ICU, these interventions could easily be adapted to nursing care in the ICU.

HRQoL is a multidimensional concept that can provide information on a patient's current health status. Interventions exploring long-term outcomes should consider a number of issues in the design process, e.g., sample size for long-term studies and the assessment of HRQoL at baseline and one year later. This could provide important knowledge about a deterioration or an improvement in a patient's HRQoL in the long-term.

The magnitude of cognitive impairment after ICU still challenges critical care settings and there is an ongoing need to gain a better insight into this problem. Research investigating the pre-/post-cognitive status in patients experiencing delirium in ICU are therefore warranted to establish the magnitude of cognitive impairment, supplemented with qualitative research to gain in-depth knowledge of the patient's experiences of cognitive impairment to identify ways to manage cognitive impairment in the recovery phase.

It is imperative to gain a better understanding of the experiences of ICU survivors recovering from critical illness and how they approach and adapt to changes in their lives. Using qualitative research may enable an exploration of which coping strategies ICU survivors use in recovery. Notably, understanding and exploring the experiences of transitions across healthcare settings may help identify which factors may facilitate a better recovery process and knowledge of the recovery.

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Summary in Danish

Baggrund

Akut kritiske syge patienter, som indlægges på en intensiv afdeling, er i stor risiko for at udvikle delirium. Delirium er en akut forstyrrelse i hjernen, hvor symptomerne er kendetegnet ved forstyrrelser i opmærksomheden, bevidstheden og døgnrytmen. Delirium er forbundet med øget sygelighed, som eksempelvis nedsat kognitiv funktion og dødelighed. Patienter, som udvikler delirium på en intensiv afdeling, behandles oftest med et antipsykosik medicin, kaldet haloperidol, trods begrænset viden om dets effekt og langtidsvirkningerne.

For at undersøge haloperidols fordele og ulemper til behandling af delirium hos patienter på intensiv afdeling, er der blevet gennemført et randomiseret, placebo-kontrolleret multicenter forsøg, "Agents Intervening against Delirium in the Intensive Care Unit (AID-ICU)" som fandt, at behandling med haloperidol ikke førte til signifikant flere dage i live udenfor hospitalet. Man fandt en lavere dødelighed blandt patienter i haloperidol gruppen, samt at det er et sikkert medicinsk præparat at give (sammenlignet med placebo , som var saltvand) til behandling af delirium. Denne afhandling undersøger langtidsopfølgning af AID-ICU studiet, som her rapporteres i tre del-studier. Formålet med de tre studier var: (*studie 1)* at undersøge langtidsvirkning af haloperidol i forhold dødelighed og helbredsrelatered livskvalitets hos akut kritisk syge patienter med delirium på intensiv afdeling*, (studie 2*) at undersøge langvirkning af haloperidol i forhold til kognitiv funktion hos en gruppe udvalgte deltagere fra AID-ICU studiet og *(studie 3)* at undersøge tidligere intensive patienters oplevelse af livet fra udskrivelse til et år efter kritisk sygdom.

Metode

Et år efter inklusion til studiet, blev patienternes vital status undersøgt via nationale registre. Patienter, som var i live, blev kontaktet via telefon og inviteret til at deltage i et studie vedrørende deres helbredsrelaterede livskvalitet (*studie 1*). Yderligere blev en gruppe af danske patienter inviteret til at deltage i et studie vedrørende deres kognitive funktion(*studie 2*). De patienter, som deltog, fik målt deres kognitive

funktion ud fra bl.a. the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). Yderligere deltog en gruppe af disse patienter i et kvalitativt studie, hvor deltagerne blev interviewet (*studie 3*).

Resultat

Resultatet viste, at patienter, som havde modtaget haloperidol i studiet, havde en bedre overlevelse, end dem, som fik placebo medicin. Vi fandt ingen forskel mellem de to grupper i forhold til livskvalitet eller kognitiv funktion. Dog viste studiet, som undersøgte kognitive funktion, at patienterne uanset hvilken af de to behandlinger de fik, at deres kognitive funktion var forringet. Patienterne fra det kvalitative studie fortalte, at livet efter kritisk sygdom var en kamp, hvor man skulle genvinde mange tabte funktioner, som både var af fysisk karakter, men også kognitivt. Men derudover manglede patienterne viden om forløbet efter kritisk sygdom, hvilke tiltag man kunne gøre for at fremme genoptræning, og at især primærsektor manglede viden omkring kritisk sygdom og livet derefter.

Konklusion

Studierne i denne ph.d. afhandling har bidraget med yderligere viden om haloperidol og dets langtidsvirkning sammenlignet med placebo. Derudover har disse studier givet et indblik i et skrøbeligt efterforløb, hvor patienterne kæmper med flere udfordringer, både i forhold til dem selv, og i forhold til primær og sekundær sektors håndtering af dem efter kritisk sygdom.

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