Dissertation

Potential Role of Alcohol-Associated Biomarkers in Predicting ICU-Delirium and Sex-Specific Differences in Short-Term Mortality After ICU-Delirium

submitted by

Dr. med univ. Nikolaus Schreiber

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Assoz. Prof. Priv. Doz. Dr. Philipp Eller, MBA

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Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used.
Throughout this thesis and in all related publications I followed the “Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz“.

In the writing process of this thesis generative Artificial Intelligence (AI) (ChatGPT-4) was used as a language editing service to improve the readability and language of parts of the manuscript. No confidential information or results were disclosed to or shared with ChatGPT. All the output was carefully reviewed by myself, and I take full responsibility for the content of this thesis.

Graz, 24.10.2024 Dr. med. univ. Nikolaus Schreiber eh

Disclosures

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List of abbreviations

95% Confidence interval (95% CI)

Acetylcholinesterase (AChE)

Acute Physiology and Chronic Health Evaluation (APACHE)

American Association of Anesthesiologists (ASA)

Area under the curve (AUC)

Area under the receiver operating characteristic (AUROC)

Beth Israel Deaconess Medical Center (BIDMC)

Blood-brain barrier (BBB)

CAM-Severity score (CAM-S)

Carbohydrate-deficient transferrin (CDT)

C-reactive protein (CRP)

Confusion Assessment Method for the ICU (CAM-ICU)

Credible interval (CrI)

Delirium Rating Scale-Revised-98 (DRS-R98)

Default mode network (DMN)

Diagnostic and Statistical Manual of Mental Disorders (DSM-5)

Early Prediction Model for Delirium (E-PRE-DELIRIC)

Health related quality of life (HRQoL)

Hemoglobin (Hgb)

Hazard ratio (HR)

Intensive Care Delirium Screening Checklist (ICDSC)

Intensive care unit (ICU)

Interleukin (IL)

Massachusetts Institute of Technology (MIT)

Medical Information Mart for Intensive Care-IV (MIMIC-IV)

Memorial Delirium Assessment Scale (MDAS)

Modifying Delirium Using Simvastatin (MoDUS) trial

National Institute on Aging-Alzheimer's Association (NIA-AA)

Neurofilament light protein (NfL)

Neuron-specific enolase (NSE)

Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (PADIS)

Prediction Model for Delirium (PRE-DELIRIC)

Reactive oxygen species (ROS)

Richmond Agitation-Sedation Scale (RASS)

S100 calcium-binding protein B (S-100β)

Severe-acute respiratory-syndrome-coronavirus-type- 2 (SARS-CoV-2)

Simplified Acute Physiology Score II (SAPS II)

Standardized mean difference (SMD)

Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)

Superoxide dismutase (SOD)

Sequential Organ Failure Assessment (SOFA)

Tumor necrosis factor alpha (TNF-alpha)

Variance inflation factor (VIF)

γ-glutamyltransferase (γGT)

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Abstract

Introduction

Delirium is a major problem in modern critical care medicine. No study to date established the predictive role of alcohol associated biomarkers, Carbohydrate-deficient transferrin (CDT) and the γ-glutamyltransferase-CDT derived Anttila-Index, for intensive care unit (ICU)-delirium. Furthermore, the role of sex related disparities in outcomes after ICU-delirium is unclear.

Methods

In a first project, a prospective observational study, including 343 consecutive patients admitted to our medical ICU between February and November 2022, was conducted the occurrence of delirium was assessed using the Confusion Assessment Method for the ICU (CAM-ICU), its association with biomarkers of alcohol abuse measured on the day of ICU admission was investigated. In a second project, a retrospective cohort study using the Medical Information Mart for Intensive Care-IV (MIMIC-IV) database was conducted. The primary outcome was 30-day mortality following delirium onset. To control for baseline differences in demographics, illness severity, and comorbidities, we applied 1:1 propensity score matching. Cox proportional hazards regression models were used to evaluate the association between sex and mortality.

Results

In the first project, CDT, and particularly the derived Anttila Index, were shown to be independently associated with the development of delirium, prolonged delirium duration, and increased mortality in critically ill patients. Results of the second project in more than 7000 patients suggest, that women with ICU-delirium have a significantly higher risk of short-term mortality than men.

Zusammenfassung

Einleitung

Das Delir stellt ein schwerwiegendes Problem in der modernen Intensivmedizin dar. Bisher hat keine Studie die prädiktive Rolle von alkoholassoziierten Biomarkern, wie dem Carbohydrate-deficient transferin (CDT) und dem aus dem γ-Glutamyltransferase-CDT abgeleiteten Anttila-Index, für Delir auf der Intensivstation (ICU) etabliert. Darüber hinaus ist die Rolle geschlechtsspezifischer Unterschiede bezüglich der Outcomes nach einem Delir auf der Intensivstation unklar.

Methoden

In einem ersten Projekt wurde eine prospektive Beobachtungsstudie durchgeführt, die 343 aufeinanderfolgende PatientInnen umfasste, die zwischen Februar und November 2022 auf unserer medizinischen Intensivstation aufgenommen wurden. Das Auftreten von Delir wurde mit der Confusion Assessment Method for the ICU (CAM-ICU) bewertet und seine Assoziation mit Biomarkern für exzessiven Alkoholkonsum, die am Tag der Aufnahme auf der Intensivstation gemessen wurden, untersucht. In einem zweiten Projekt wurde eine retrospektive Kohortenstudie unter Verwendung der Medical Information Mart for Intensive Care-IV (MIMIC-IV) Datenbank durchgeführt. Das primäre Zielgröße war die 30-Tage-Mortalität nach Delir-Beginn. Um für Unterschiede bezüglich Demografie, Krankheitsschwere und Komorbiditäten zu kontrollieren, wurde 1:1 Propensity Score Matching angewandt. Cox-Proportional-Hazard-Regression Modelle wurden verwendet, um den Zusammenhang zwischen Geschlecht und Mortalität zu evaluieren.

Ergebnisse

Im ersten Projekt wurde gezeigt, dass CDT und insbesondere der abgeleitete Anttila-Index unabhängig mit der Entwicklung von Delir, einer verlängerten Delir-Dauer und einer erhöhten Sterblichkeit bei kritisch kranken PatientInnen assoziiert sind. Die Ergebnisse des zweiten Projekts, das mehr als 7000 PatientInnen umfasste, deuten darauf hin, dass Frauen mit ICU-Delir ein signifikant höheres Risiko für eine 30-Tage Mortalität aufweisen als Männer.

Introduction

Definition

The term 'delirium' finds its roots in the Latin word *delirare*, which means 'to go out of the furrow' — implying a deviation from a straight path or a state of derangement (2).

Delirium is a complex neuropsychiatric syndrome characterized by the sudden onset of cognitive deficits and is linked to increased days on mechanical ventilation, length of hospital stay, cost of care, long-term cognitive impairment, requirement for postdischarge institutionalization, and mortality (3,4).

As per the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (5), delirium is characterized by a primary disruption in attention, which is the foremost mandatory feature. Delirium develops rapidly and is accompanied by additional impairments in cognition. These cognitive disturbances cannot be more adequately accounted for by an existing, established, or evolving neurocognitive disorder. Moreover, they do not manifest in the context of severely reduced arousal.

The diagnosis excludes cases where there is evidence from the patient's history, physical examination, or laboratory findings indicating that the disturbance is a direct physiological consequence of another medical condition, substance intoxication, or withdrawal (6).

Individuals may exhibit varying levels of altered arousal, ranging from diminished responsiveness bordering on near-coma, to heightened vigilance and pronounced agitation (2).

Furthermore, the course of delirium is characterized by distressing symptoms of psychosis, such as delusions and hallucinations. The features of delirium are known to fluctuate both in their presence and intensity (4).

In the ICU, delirium can manifest in different forms: hyperactive (characterized by agitation and restlessness), hypoactive (marked by flat affect, apathy, lethargy, and decreased responsiveness), or a mixed state where patients oscillate between hyperactive and hypoactive states (2).

Prevalence

Delirium represents a frequently encountered clinical entity as estimations concerning incidence in the ICU range between 20% and 80% across different institutions and study populations (3).

Historically, delirium was observed in 60–80% of mechanically ventilated patients (7–9) and in 20–50% of ICU patients with lower severity of illness (10,11). The diverse prevalence values of delirium observed across different settings underscore the interplay between the characteristics of the patients involved—varying in terms of age and frailty—and the quantity and severity of the factors precipitating the onset of delirium (2).

The widespread use of validated diagnostic tools globally, with translations available in over 30 languages, along with changes in routine ICU management to mitigate the culture of excessive sedation and immobility, has led to a reduction of delirium rates by approximately 25% in many ICUs (12).

Regarding the various delirium subtypes, a study conducted in a medical intensive care unit (ICU) identified the two primary types as mixed, representing 54.9% of cases, and hypoactive, observed in 43.5% of delirious patients (13).

Risk factors

Delirium risk stems from predisposing factors, which are patients' inherent characteristics, and precipitating factors, which include acute insults, injuries, or drug effects. (2)

The presence and intensity of predisposing factors influence the degree of precipitating factors needed for delirium to develop. For example, an elderly patient already showing signs of cognitive decline might experience delirium with relatively minor triggers such as mild hypoxia or a urinary tract infection (14).

Conversely, a younger, healthier individual typically requires more severe precipitating factors, like sepsis or multiple traumas, to develop delirium.

Key predisposing risk factors include advanced age, cognitive dysfunction, and existing hypertension. Other potential predisposing factors, such as nicotine and alcohol consumption, a higher American Association of Anesthesiologists (ASA) classification grade, and cardiac diseases, have been suggested, but research in these areas is not extensive (14).

Precipitating factors for delirium fall into three distinct categories:

- Factors related to acute illness: These include a history of coma; a higher level of illness severity, often measured by the Acute Physiology and Chronic Health Evaluation (APACHE) score; instances of multiple trauma; sepsis; the necessity for mechanical

ventilation; pain experiences; and systemic hypoperfusion leading to metabolic acidosis (15).

- Medication-related factors: The risk increases with the dosage of benzodiazepines. Drugs such as anticholinergics, opioids, and corticosteroids are also suspected to contribute to delirium onset, although there are some contradictory studies in this regard (16).
- Environmental factors: Conditions such as elevated noise levels, insufficient daylight exposure, and being admitted to a general ward instead of a private room have been linked to a higher risk of delirium. (15,16)

It's crucial to recognize that while most triggering factors can be modified or controlled, predisposing risk factors are generally non-modifiable.

Subtypes of delirium

Currently, the most prevalent approach to categorizing delirium involves differentiating it by psychomotor subtypes (17). The concept of hypoactive and hyperactive subtypes was initially put forth by Lipowski in 1983 (18), with the introduction of the mixed subtype following in 1990 (19).

Additionally, there's a classification for patients who don't exhibit psychomotor disturbances, labeled as 'no subtype' (20).

Variations in incidence, severity, and the degree of symptom fluctuation are noted among these subtypes. Notably, the hypoactive and mixed subtypes are often associated with more severe outcomes and a higher demand for medical resources (3,21).

However, a systematic review focusing on ICU studies highlighted the challenges in making robust assessments of outcomes across these subtypes due to inconsistencies in reporting and variations in methodological quality (22).

Bowman et al. recommend refining the delirium classification by integrating various phenotypes and their underlying mechanisms. They emphasize the importance of distinguishing ‘clinical’ subphenotypes, based on symptom clusters as for instance the coexistence of alcohol consumption and malnutrition, and ‘mechanistic’ subphenotypes, related to the pathophysiology of delirium (17).

The integration of these subphenotypes may lead to the identification of an endotype. They further highlight advancements in genomic, transcriptomic, proteomic, and metabolomic technologies as key tools in identifying these disease subgroups or subphenotypes. Their proposed framework suggests that delirium can be effectively subdivided into subphenotypes based on clinical or biological characteristics, leading to the identification of treatable traits (17).

This approach aligns with the innovative conceptual model of critical illness presented by Maslove et al., who suggest a shift away from traditional syndrome-based frameworks (23).

Maslove et al. argue for a model that prioritizes underlying biological changes in critical illness, supported by translational evidence, including research on respiratory failure in severe-acute respiratory-syndrome-coronavirus-type- 2 (SARS-CoV-2) infection. This model aims to foster a deeper understanding of critical illness pathobiology, improve patient outcomes, and refine clinical practices by focusing on precise, treatable aspects of critical conditions (23).

Machine learning-based subtypes, identified through analysis of highly granular and extensive datasets, can uncover significant, previously unnoticed heterogeneity. This approach has enhanced our knowledge of other critical care conditions like acute respiratory distress syndrome (ARDS) and sepsis (24,25).

A recent study translated this to the context of ICU-delirium. In this study, researchers analyzed data from a large, multicenter prospective cohort of ICU patients with respiratory failure or shock who experienced delirium. They used pre-diagnosis data in an unsupervised latent class model to identify four distinct delirium subtypes and then compared demographic data, clinical characteristics, and outcomes among these subtypes.

The study involved 731 patients, with a median age of 63 years and a median Sequential Organ Failure Assessment score of 8.0. Among them, 83.4% were on mechanical ventilation. The four-class model showed that subtype 1 encompassed 50% of patients, subtype 2 comprised 18%, subtype 3 accounted for 17%, and subtype 4 included 14%. Subtype 2, which had higher rates of shock and kidney impairment, also had the highest mortality rate at 33%. Subtype 4, associated with higher benzodiazepine and opioid use, experienced the longest duration of delirium (6 days) and coma (4 days).

All four subtypes corresponded to previously recognized psychomotor and risk factor-based subtypes, and clinically significant cognitive impairment was observed across all groups.

However, the severity of cognitive impairment did not vary significantly between subtypes at the 3-month and 12-month follow-up points (26).

Pathogenesis of delirium

At least six neuropathophysiological hypotheses have been proposed to explain delirium, though their mechanisms remain poorly understood. Rather than being competitive, these theories should be seen as complementary and may help define subphenotypes by underlying mechanisms (17).

For instance, the ***neuroinflammation hypothesis*** may enable the categorization of delirium into inflammatory or non-inflammatory subtypes, as the levels of biomarkers such as C-reactive protein (CRP) and pro-inflammatory cytokines differ depending on inflammation presence. Elevated CRP levels are linked to longer delirium or coma periods in ICU patients (27,28).

The ***neuronal aging hypothesis*** suggests that age-related decreases in cerebral blood flow and capillary density lead to diminished brain volume, particularly in the hippocampus and superior frontal lobe, which are crucial for memory and behavior (29). Long delirium episodes have been associated with brain atrophy in these regions, though it's unclear whether this is a cause or effect (17,29–31).

The ***oxidative stress hypothesis*** associates delirium with increased levels of reactive oxygen species in the hippocampus, while the concentrations of protective enzymes like superoxide dismutase (SOD) are reduced (32–34).

The ***neurotransmitter hypothesis*** involves disruptions in serotonergic, dopaminergic, and cholinergic systems. A deficiency of tetrahydrobiopterin for instance, crucial for dopamine and serotonin synthesis, correlates with both Alzheimer's and delirium (17,35,36).

In addition, melatonin dysregulation could further explain differences in delirium symptoms, as studies show altered levels of melatonin and its metabolite 6-sulfatoxymelatonin in patients with hyperactive delirium (37).

Lastly, the ***network dysconnectivity hypothesis*** attributes delirium symptoms to disruptions in brain networks, specifically the default mode network (DMN) (17). This network, which includes brain regions like the posterior cingulate cortex and the medial temporal lobe, becomes less connected during delirium episodes (38). Reduced connectivity between subcortical regions impairs attention and consciousness (17,38).

Overall, these hypotheses suggest complementary perspectives on the nature and development of delirium, paving the way for categorization and improved treatments.

On the cellular level, microglial cells, which may already be primed by pre-existing brain pathologies, can become further activated by acute inflammatory responses. These cells release pro-inflammatory cytokines, reactive oxygen species (ROS), and reactive nitrogen species, impacting neighboring brain tissue and neuronal function (39).

These mediators may also directly influence astrocytes. Astrocytes, especially those sensitized by chronic brain conditions, respond to acute inflammatory triggers by releasing higher levels of chemokines, potentially attracting more peripheral inflammatory cells to the brain (2).

In such a state, astrocytes might also reduce their support for neuronal energy metabolism. Moreover, vascular functions can be compromised due to pre-existing degenerative issues or new stressors like systemic inflammation, leading to endothelial damage and blood-brain barrier (BBB) compromise (2).

The vascular supply of oxygen and glucose may also be affected due to microvascular dysfunction or impaired neurovascular coupling, contributing to a state of metabolic insufficiency (40).

Collectively, these processes lead to the primary observable outcome in delirium: acute neuronal dysfunction and the disintegration of neural networks (2).

Diagnosis and delirium detection

The 2018 Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU (PADIS) Guidelines advocate for routine delirium monitoring in adult ICU patients (41). These guidelines recommend using either the CAM-ICU (7) or the Intensive Care Delirium Screening Checklist (ICDSC) (10) to carry out this monitoring (41).

The CAM-ICU, an adaptation of the Confusion Assessment Method (42), was specifically designed to suit both verbal and non-verbal ICU patients. Originally introduced by Ely et al. in 2001, this tool evaluates the same four key features as its predecessor: acute changes or fluctuations in mental status, inattention, disorganized thinking, and an altered level of consciousness. However, it does so in a more concise format that is well-suited for the ICU environment.

The CAM-ICU was first validated in a study involving 96 adult patients at the Vanderbilt University Medical Center, specifically within medical or coronary ICUs. In this study, critical care nurses conducted 471 paired evaluations and compared their findings with assessments by delirium experts, who used the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria. Against the reference standard for diagnosing delirium, the CAM-ICU demonstrated a sensitivity of 100% and 93%, specificity of 98% and 100%, and exhibited high interrater reliability with a kappa coefficient (κ) of 0.96 (95% CI, 0.92–0.99) (7).
The ICDSC evaluates eight diagnostic characteristics of delirium throughout an entire nursing shift. These characteristics include altered level of consciousness, inattention, disorientation, psychosis, altered psychomotor activity, inappropriate speech or mood, sleep disturbance, and symptom fluctuation (10). In its initial validation, the ICDSC was administered to 93 patients and the results were compared to psychiatric evaluations. The identification of four or more of the listed features resulted in a sensitivity of 99% and a specificity of 64% for detecting delirium (10). Additionally, a systematic review of studies involving ICU patients reported a pooled sensitivity of 74% and specificity of 82% for the ICDSC (43).
Detecting hypoactive delirium poses a particular challenge. Without the use of a validated screening tool, it may be overlooked, as its clinical presentation could be mistakenly attributed to fatigue or depression. Importantly, hypoactive delirium is associated with more severe and perilous outcomes.

Assessment of Delirium Severity

Delirium severity is a multifaceted concept that includes several potential parameters, such as the extent of cognitive impairment, arousal level, delirium duration, the number of diagnostic criteria present, and the distress experienced by patients (44). The primary instruments used most frequently are CAM-based tools (42), the Delirium Rating Scale-Revised-98 (DRS-R98) (45), and the Memorial Delirium Assessment Scale (MDAS) (46).
The CAM-Severity (CAM-S) score measures the intensity of delirium symptoms, with a range of 0–7 for the short form and 0–19 for the long form (47).
The DRS-R-98 is a clinician-rated assessment tool consisting of 16 items. It includes 13 severity items that gauge the intensity of delirium symptoms and 3 diagnostic items to aid in identifying the presence of delirium (45).

The Memorial Delirium Assessment Scale (MDAS) is a ten-item, clinician-rated scale that uses a four-point scoring system to quantify the severity of delirium in medically ill patients. Its total possible score ranges from 0 to 30 (46).

The CAM-ICU-7 is a severity scoring system adapted from the CAM-ICU, validated in 518 adult patients across medical, surgical, and progressive ICUs in three academic medical centers. Patients underwent twice-daily assessments using both the CAM-ICU and Richmond Agitation-Sedation Scale (RASS). The CAM-ICU-7 score, ranging from 0 to 7, was derived from these assessments and validated against the DRS-R98. The CAM-ICU-7 demonstrated strong internal consistency (Cronbach's alpha = 0.85) and good correlation with DRS-R-98 scores (correlation coefficient = 0.64). It showed high predictive validity, revealing increased odds of in-hospital mortality (OR = 1.47, 95% CI = 1.30–1.66) and reduced odds of discharge to home (OR = 0.8, 95% CI = 0.72–0.9) after adjusting for co-factors. Additionally, longer ICU stays were associated with higher CAM-ICU-7 scores (p = 0.001) (48).

Risk assessment and Prediction of ICU-Delirium

As for now, three predictive models have been developed to help clinicians prevent and manage delirium: the Prediction Model for Delirium (PRE-DELIRIC) (49) , the Early Prediction Model for Delirium (E-PRE-DELIRIC) (50), and the Lanzhou Model (51).

The PRE-DELIRIC model includes ten predictors: age, APACHE II score, admission group (medical, surgical, trauma, neurologic), emergency admission, infection, coma, sedation, morphine use, urea level, and metabolic acidosis.

The E-PRE-DELIRIC model features nine predictors: age, history of cognitive impairment, history of alcohol abuse, blood urea nitrogen, admission group (medical, surgical, trauma, neurologic), emergency admission, mean arterial pressure, corticosteroid use, and respiratory failure.

The Lanzhou Model incorporates eleven predictors: age, APACHE II score, mechanical ventilation, emergency surgery, coma, multiple trauma, metabolic acidosis, history of hypertension, history of delirium, history of dementia, and dexmedetomidine use.

These predictive models were validated in routine clinical practice through a prospective observational study involving 455 ICU patients. The PRE-DELIRIC model demonstrated an area under the receiver operating characteristic (AUROC) curve of 0.79 (95% CI, 0.75–0.83), while the E-PRE-DELIRIC showed an AUROC curve of 0.72 (95% CI, 0.67–0.77). The Lanzhou Model

had an AUROC curve of 0.77 (95% CI, 0.72–0.81). However, the practicality of these models can be limited for real-time clinical action, particularly when applied to ICU patients who have already been admitted for more than 24 hours (52).

Using large clinical databases, recently two new models for predicting delirium in the ICU using machine learning models were developed. The first model, which predicts delirium within the first 24 hours, outperformed the adapted PRE-DELIRIC and showed good calibration with a contemporary dataset. The second model, a dynamic tool that continuously updates delirium risk estimates, demonstrated higher discrimination than PRE-DELIRIC model and performed as well or better compared to existing models. Both models were generally validated well with two external datasets, particularly the more recent one. However, the dynamic model showed limited calibration in the validation cohorts, where the actual probability of delirium was much lower than the predicted probability at high levels (53).

Recent research has explored a wide range of biomarkers in postoperative and critical care delirium. (4,54).

Several biomarkers have been studied in critical care settings, such as neurofilament light protein (NfL), CRP, various interleukins (IL) (IL-1, IL-6, IL-8, IL-10), plasma tau, neuron-specific enolase (NSE), and acetylcholinesterase (55).

A study in 2020 found that high levels of certain biomarkers (IL-6, IL-8, IL-10, tumor necrosis factor alpha (TNF-alpha), CRP, and S100 calcium-binding protein B (S-100β)) were associated with reduced delirium/coma-free days and increased delirium severity as assessed by the CAM-ICU-7 within one week and 30 days after enrollment. By the time of hospital discharge, only IL-6, IL-8, and IL-10 remained linked to delirium severity. Additionally, high levels of IL-8 and S-100β were associated with higher in-hospital mortality, while Insulin Like Growth factor 1 (IGF-1) for instance showed no association with either outcome. In conclusion, the study suggests that biomarkers of systemic inflammation, astrocyte, and glial activation are associated with longer delirium duration, increased severity, and in-hospital mortality (56).

In 2021, Chan et al. conducted a meta-analysis of ICU delirium biomarkers aligned with the National Institute on Aging-Alzheimer's Association (NIA-AA) Research Framework. They included 38 studies, and 8 of these were suitable for meta-analysis. Significant associations with ICU delirium were found for amyloid β-peptide 1–40 (standardized mean difference (SMD): 0.42, 95% CI: 0.09–0.75), IL-1 receptor antagonist (SMD: 0.58, 95% CI: 0.21–0.94), and

IL-6 (SMD: 0.31, 95% CI: 0.06–0.56). This analysis highlights potential overlapping mechanisms between delirium and Alzheimer's disease. Chan et al. suggested integrating diagnostic methods from Alzheimer's research into ICU assessments of post-ICU cognitive dysfunction (57).

In 2022, Page et al. conducted a secondary analysis of the Modifying Delirium Using Simvastatin (MoDUS) trial, an RCT investigating simvastatin versus placebo in ICU delirium. They examined the relationship between NfL levels and days spent in delirium or coma. Higher NfL levels were linked to these conditions, and the AUC for NfL predicting 6-month mortality was 0.81 (95% CI: 0.7, 0.9). The authors concluded that NfL levels measured within the first three days of admission could help identify patients at risk for poor clinical outcomes (58).

Later in 2022, Hughes et al. reported a landmark study AChE activity as a potential indicator of delirium in the ICU. Comparing 272 ICU patients with delirium against those with normal mental status, the study found higher absolute AChE levels in delirious patients (OR: 1.64, 95% CI: 1.11–2.43, p=0.045). However, AChE normalized to hemoglobin (Hgb) (AChE/Hgb) and butyrylcholinesterase were not associated with delirium. No biomarkers predicted long-term cognitive dysfunction or quality of life after ICU discharge. Nevertheless, this study was the first to show a connection between AChE and delirium in the ICU, supporting the theory that the cholinergic pathway plays a role in delirium (59).

As emphasized by Kotfis et al., additional research on biomarkers is necessary. Future progress in delirium monitoring will focus on developing and integrating reliable biomarkers that can consistently and accurately identify patients at risk of delirium. These advancements will help enhance early detection and management, ultimately improving patient outcomes (54).

Pharmacologic Delirium Prevention

The neurotransmitter hypothesis has paved the way for research into the efficacy of antipsychotic medications for delirium prevention. Haloperidol, as an example, primarily functions by blocking dopamine receptors, while atypical antipsychotics inhibit serotonin, dopamine, alpha-1 adrenergic, and histamine receptors (4).

Numerous studies have examined the effectiveness of antipsychotic medication and other central nervous system receptor targets in delirium prevention (60–64). However, none have consistently shown a significant reduction in delirium. Consequently, the PADIS guidelines

recommend against using haloperidol, atypical antipsychotics, dexmedetomidine, statins, or ketamine for the prevention of delirium in critically ill adults (41).

Two multicenter randomized controlled trials need to be highlighted in this context:

The double-blind, placebo-controlled randomized trial known as HOPE-ICU was conducted to assess the impact of haloperidol on preventing delirium. In this study, patients were assigned to receive either 2.5 mg of haloperidol or a 0.9% saline placebo intravenously every 8 hours, provided they required mechanical ventilation within 7 hours of admission. The results showed no significant difference between the two groups in the number of days patients were alive and free from delirium and coma, with the haloperidol group having a median of 5 days (IQR 0–10) and the placebo group having a median of 6 days (IQR 0–11) ($p = 0.53$) (60).

The REDUCE trial (Prophylactic Haloperidol Use for Delirium in Patients at High Risk for Delirium) was a randomized, double-blind, placebo-controlled study involving 1,789 critically ill patients. Participants received either prophylactic haloperidol at doses of 1 mg or 2 mg, or a placebo. The 1-mg haloperidol group was discontinued early due to futility. There was no significant difference in median survival over 28 days between the 2-mg haloperidol group and the placebo group (95% CI, 0–0; $p = 0.93$), with a hazard ratio of 1.003 (95% CI, 0.78–1.30; $p = 0.82$). Additionally, none of the 15 secondary outcomes showed statistical differences among the three groups. These outcomes included the incidence of delirium (mean difference 1.5%; 95% CI, −3.6% to 6.7%), delirium- and coma-free days (mean difference 0 days; 95% CI, 0–0 days), and the duration of mechanical ventilation, ICU stay, and hospital stay (mean difference 0 days; 95% CI, 0–0 days for all three measures). Adverse events were similar across all groups (61).

Certain multicenter studies have shown promising results for the central alpha-2-agonist dexmedetomidine.

The MENDS randomized controlled trial involved 106 adult ICU patients on mechanical ventilation at two tertiary care centers between August 2004 and April 2006. Patients were sedated with either dexmedetomidine or lorazepam for up to 120 hours, targeting a specific level on the Richmond Agitation-Sedation Scale (RASS). Delirium was assessed twice daily using the CAM-ICU (65).

Results showed that patients sedated with dexmedetomidine had significantly more days alive without delirium or coma (median 7.0 vs. 3.0 days; $P = .01$) and a lower prevalence of coma (63% vs. 92%; $P < .001$) compared to those sedated with lorazepam. They also spent a higher

percentage of days close to their sedation target (80% vs. 67%; p=0.04). While 28-day mortality was lower in the dexmedetomidine group (17% vs. 27%; p=0.18), this was not statistically significant, and the cost of care was similar between groups (65).

Another randomized, double-blind, placebo-controlled trial was conducted with 700 elderly patients admitted to the ICU after non-cardiac surgery at two tertiary-care hospitals in China. Patients were randomized to receive either dexmedetomidine or a placebo from ICU admission on the day of surgery until 0800 h on postoperative day 1. The incidence of delirium during the first seven postoperative days was significantly lower in the dexmedetomidine group (32 [9%] of 350 patients) compared to the placebo group (79 [23%] of 350 patients; odds ratio [OR] 0.35, 95% CI 0.22–0.54; p < 0.0001) (63).

A third multicenter, double-blind, placebo-controlled trial randomized 100 critically ill patients without delirium to receive either nocturnal dexmedetomidine or a placebo. A significantly higher proportion of patients in the dexmedetomidine group remained delirium-free during their ICU stay (dexmedetomidine: 40 [80%] of 50 patients; placebo: 27 [54%] of 50 patients; relative risk 0.44, 95% CI 0.23–0.82; p = 0.006) (64).

The authors of the PADIS guidelines considered the incidence and duration of delirium, duration of mechanical ventilation, ICU length of stay, and mortality as the most critical outcomes. Although there was a consistent decrease in the incidence of delirium, the PADIS guideline committee determined that none of the studies reported a meaningful difference in any of the other important clinical outcomes (41). Additionally, many of these studies predominantly included surgical patients, who generally have a lower severity of illness compared to medical patients.

These findings should further be considered in the context of the SPICE III study and its post hoc analysis, which indicated higher mortality for patients younger than 65 years treated with dexmedetomidine (66,67). This even prompted the issuance of a health alert in Europe and New Zealand (68).

Non pharmacologic management and prevention of ICU-delirium

Although no pharmacologic agents have been proven to significantly affect delirium, implementing a bundle of non-pharmacologic strategies has shown effectiveness. As a result, this bundle approach has become a cornerstone of ICU care (41).

One example of a multi-component strategy is the A2F bundle, which consists of six steps: A, assess, prevent, and manage pain; B, both spontaneous awakening and spontaneous breathing trials; C, choice of analgesic and sedation; D, delirium: assess, prevent, and manage; E, early mobility and exercise; and F, family engagement. This easily memorized bundle was designed to facilitate the implementation of recommendations from various guidelines. Studies conducted at a single center, across multiple hospitals within a single regional system, and within a large nationwide collaborative have demonstrated that this bundle improves a range of patient outcomes (4,41).

A prospective cohort quality improvement study involving 6064 patients, both ventilated and non-ventilated, was conducted at seven community hospitals. The study found that patients had a 7% higher odds of hospital survival for every 10% increase in total bundle compliance (odds ratio: 1.07; 95% CI: 1.04–1.11; $p < 0.001$). Additionally, patients exhibited a 15% higher hospital survival rate for every 10% increase in partial bundle compliance (odds ratio: 1.15; 95% CI: 1.09–1.22; $p < 0.001$). Both total bundle compliance (incident rate ratio: 1.02; 95% CI: 1.01–1.04; $p = 0.004$) and partial bundle compliance (incident rate ratio: 1.15; 95% CI: 1.09–1.22; $p < 0.001$) were associated with more days alive and free from delirium and coma (69).

In a prospective, multicenter quality improvement collaborative involving 68 academic, community, and federal ICUs over a 20-month collection period, the performance of the complete A2F bundle was associated with a lower likelihood of death within 7 days (HR 0.32; CI, 0.17–0.62), next-day mechanical ventilation (OR 0.28; CI, 0.22–0.36), coma (OR 0.35; CI, 0.22–0.56), delirium (OR 0.60; CI, 0.49–0.72), physical restraint use (OR 0.37; CI, 0.30–0.46), ICU readmission (OR 0.54; CI, 0.37–0.79), and discharge to a facility other than home (OR 0.64; CI, 0.51–0.80). A dose-response relationship was observed, with higher proportional bundle performance leading to improvements in each clinical outcome ($p < 0.002$) (70).

While the A2F bundle is widely believed to be effective, there is, however, currently no single randomized controlled trial (RCT) that demonstrates its benefit.

Consequently, two recently published meta-analyses conclude that bundle interventions are ineffective in reducing the prevalence and duration of ICU delirium (71,72).

This is why recent discussions have identified future goals for ICU delirium research and care, emphasizing the inclusion of all the aforementioned non-pharmacological interventions and practices, including the A2F bundle (73).

Pharmacologic Management

Similar to the data on ICU delirium prevention, no large trials have demonstrated that any pharmacologic agents can effectively treat delirium in the ICU setting. Consequently, the PADIS guidelines advise against the routine use of haloperidol, atypical antipsychotics, or statins for treating delirium (41).

Two recent major trials evaluated the efficacy of Haloperidol in the treatment of ICU-Delirium. The Modifying the Impact of ICU-Associated Neurological Dysfunction-USA (MIND-USA) Study was a multicenter, randomized, placebo-controlled trial involving 566 patients with acute respiratory failure or shock. The study compared the effects of haloperidol, ziprasidone, and placebo on the treatment of delirium. The adjusted median number of days alive without delirium or coma was 8.5 (95% CI, 5.6–9.9) in the placebo group, 7.9 (95% CI, 4.4–9.6) in the haloperidol group, and 8.7 (95% CI, 5.9–10.0) in the ziprasidone group, with a p-value of 0.26. During the study, 60% of patients experienced hypoactive delirium and 40% experienced hyperactive delirium at some point. There were no significant differences between the groups in terms of duration of mechanical ventilation, ICU or hospital length of stay, time to ICU readmission, or mortality at 30 and 90 days compared with placebo. Additionally, occurrences of arrhythmias, Parkinsonism (extrapyramidal symptoms), neuroleptic malignant syndrome, study drug discontinuation, and other safety concerns were extremely low across all three groups (12).

The AID-ICU trial, a multicenter, blinded, placebo-controlled study randomly assigned patients with manifest delirium to receive either intravenous haloperidol (2.5 mg three times daily, with additional doses up to a total maximum of 20 mg daily) or a placebo. The treatment continued in the ICU if delirium persisted and was given as needed for recurrences. The primary outcome was the number of days patients were alive and out of the hospital at 90 days post-randomization.

In this study, 1000 patients were randomized, with 510 receiving haloperidol and 490 receiving a placebo. The final analysis included 987 patients. At 90 days, patients in the haloperidol group had a mean of 35.8 days alive and out of the hospital (95% CI, 32.9 to 38.6), compared to 32.9 days (95% CI, 29.9 to 35.8) in the placebo group. The adjusted mean difference was 2.9 days (95% CI, −1.2 to 7.0; P = 0.22). Mortality at 90 days was 36.3% in the haloperidol group versus 43.3% in the placebo group, with an adjusted absolute difference of −6.9 percentage

points (95% CI, −13.0 to −0.6). Serious adverse reactions were rare, occurring in 11 patients in the haloperidol group and 9 patients in the placebo group (74).

A preplanned Bayesian reanalysis of the AID-ICU trial provided further insights into the primary outcome of days alive and out of the hospital at 90 days. The mean difference was 2.9 days (95% credible interval (CrI), -1.1 to 6.9), with a 92% probability of any benefit and an 82% probability of a clinically important benefit. The risk difference for mortality was -6.8 percentage points (95% CrI, -12.8 to -0.8), with probabilities of 99% for any benefit and 94% for clinically important benefit. The adjusted risk difference for serious adverse reactions was 0.3 percentage points (95% CrI, -1.3 to 1.9), with a 98% probability of no clinically important difference. Sensitivity analyses using different priors confirmed these findings, showing more than 83% probability of benefit and less than 17% probability of harm with haloperidol treatment (75).

Neither the MIND-USA nor the AID-ICU trial were specifically designed to detect differences in mortality, as it was not the primary outcome of interest. However, considering the similarities in both the design and the non-mortality outcomes of the two trials, it is unexpected that they produced differing estimates regarding the effect of haloperidol on mortality.

Potential explanations for these differing results include the following: Compared to participants in the MIND-USA trial, those in the AID-ICU trial were significantly older, exhibited hyperactive delirium more frequently at the time of randomization, and were less commonly mechanically ventilated. In the MIND-USA trial, a higher mechanical ventilation rate (95%) and earlier recruitment and randomization relative to ICU admission suggest that participants were more likely to be sedated when randomized. This sedation likely accounts for the higher proportion of participants with hypoactive delirium at randomization in the MIND-USA trial compared to the AID-ICU trial (76).

One may speculate that haloperidol might decrease mortality by reducing psychomotor agitation, thereby lowering metabolic rate and the risk of self-harm. Additionally, haloperidol could minimize the need for multiple sedating agents and the potential adverse interactions associated with polypharmacy, which can be particularly beneficial for susceptible patients (76).

Meta-analyzed data from the MIND-USA, AID-ICU, and three other placebo-controlled randomized controlled trials estimated the effect on mortality, showing a relative risk reduction of 0.89 (96.7% CI 0.77 to 1.03) with moderate certainty evidence (77). So, despite

the completion of two large placebo-controlled trials and one updated systematic review, uncertainty remains about the effects of haloperidol in delirious ICU patients.

Significantly, neither of these trials rigorously assessed key delirium-related outcomes, such as agitation-related complications or the development of psychotic symptoms. Despite haloperidol commonly being used to address these clinical issues in routine practice, these outcomes remain critical from the perspectives of both clinicians and patients (78).

Therefore, Smit et al. conducted another multi-center, double-blind, placebo-controlled, randomized clinical trial at eight Dutch ICUs from February 2018 to January 2020 to evaluate the efficacy and safety of haloperidol in treating delirium and its associated symptoms and outcomes in critically ill adults (79).

Patients were randomized to receive either intravenous haloperidol or a placebo every 8 hours, with doses adjusted based on persistent delirium. The primary outcome was ICU delirium- and coma-free days within 14 days post-randomization, with secondary outcomes including sedative use, patient-initiated extubation, adverse events, mechanical ventilation, ICU stay length, 28-day mortality, and long-term outcomes up to one year.

The trial was terminated early due to futility in achieving the primary endpoint, enrolling 132 patients. Like AID-ICU and MIND-USA, haloperidol did not significantly increase delirium- and coma-free days. However, haloperidol-treated patients were less likely to receive benzodiazepines and showed favorable trends in other secondary outcomes related to agitation, though confidence intervals included potential harm. No differences in adverse drug events were observed (79).

The authors concluded that further research regarding long term outcomes and agitation-related events is needed (79).

Outcomes

Delirium in critically ill patients is a significant independent predictor of mortality, extended hospital stays, recurrent hospitalizations, long-term cognitive decline, and increased healthcare costs (4). However, the interplay between ICU-delirium and patient outcomes is complex and the literature has partially been contradictory.

A prospective cohort study involving 275 adults in medical and coronary ICUs investigated the impact of delirium on mortality and hospital stay duration. Delirium developed in 183 patients (81.7%) during their ICU stay. After adjusting for variables such as age, illness severity,

comorbidities, coma, and the use of sedation or analgesia, delirium was found to be independently associated with higher six-month mortality (adjusted HR, 3.2; 95% CI, 1.4–7.7; p=0.008), prolonged hospital stays (adjusted HR, 2.0; 95% CI, 1.4–3.0; p<0.001), and extended post-ICU stays (adjusted HR, 1.6; 95% CI, 1.2–2.3; p=0.009) (8).

Further studies specifically evaluated the differential severity of illness prior to delirium onset, partially demonstrating that ICU-delirium may not be directly and casually related to mortality. For instance, Klein Kouwenberg et al. demonstrated that in patients experiencing more than two days of delirium in the ICU, there was a significant risk of mortality attributable to delirium (80).

A large retrospective cohort study involving 6323 ICU patients evaluated the association between delirium subtypes and 90-day mortality after adjusting for covariates. The study found that only mixed delirium, and not hyperactive, hypoactive, or rapidly reversible delirium, was associated with 90-day mortality [HR 1.57 (95% CI: 1.51–2.14)] (81).

The BRAIN-ICU study conducted by Pandharipande et al. assessed long-term cognitive impairment in patients after critical illness. Of 812 patients with respiratory failure or shock enrolled in the study, 74% developed delirium during their stay at the hospital. The authors demonstrated that a longer duration of delirium was independently associated with worse global cognition at 3 and 12 months and worse executive function at 3 and 12 months (82).

Recently, long term outcome data of the two randomized, placebo-controlled trials that evaluated the efficacy and safety of haloperidol for the treatment of delirium in ICU patients, the AID-ICU study and the MIND-USA study, were published.

In the 1-year follow-up study of the AID-ICU trial, the long-term effects of haloperidol versus placebo on mortality and health related quality of life (HRQoL) in acutely admitted adult ICU patients with delirium were assessed. Haloperidol was found to reduce mortality but did not statistically significantly improve HRQoL, although the HRQoL results had higher uncertainty (83).

Because the MIND-USA trial showed no difference in mortality between treatment groups, survivor-only analyses were conducted. The 1-year follow-up study showed that neither haloperidol nor ziprasidone had a significant effect on cognitive, functional, psychological, or quality-of-life outcomes among survivors. The authors conclude that, along with insufficient evidence of short-term benefits and the frequent inappropriate continuation of antipsychotics

at hospital discharge, their findings indicate that antipsychotics should not be routinely used to treat delirium in critically ill adults (84).

The conflicting results of antipsychotic use on short- and long-term mortality in patients with ICU delirium highlight the need for further research to understand the complex relationship between delirium and patient outcomes. Future studies should aim to identify delirium subtypes to better determine the potential heterogeneity of treatment effects.

Sex specific differences in ICU-Delirium

In this context, sex refers to the biological differences between males and females, determined by genetics, hormones, and anatomy, whereas gender encompasses the sociocultural roles, relationships, and behaviors shaped by societal norms and expectations (85).

The literature shows some variability regarding whether sex influences the risk of ICU delirium. While several studies suggest no significant sex differences among patients who develop delirium, others have identified male sex as a potential risk factor, with some research indicating a higher risk among women (86). Findings regarding the impact of sex on the duration of ICU delirium are also inconsistent. For example, Liu et al. found no significant differences in delirium duration between men and women (87). Similarly, delirium severity among hospitalized patients does not appear to differ by sex (88). The evidence surrounding sex differences in delirium subtypes (hypoactive, hyperactive, or mixed) is also unclear. Some studies suggest women are more prone to hypoactive delirium, particularly in acute medical settings, while others report no gender differences in ICU delirium subtypes (22,89). Agitation and hyperactive delirium, on the other hand, are more frequently observed in men, who are also more likely to be treated with antipsychotic medications due to the visibility of hyperactive symptoms and safety concerns related to agitation (90).

A study identified a reverse relationship between the proportion of female patients admitted with a particular diagnosis (stratified to nine major diagnostic categories) and their hospital mortality rates when compared to men with the same condition. This effect, influenced by gender minorities, worked in both directions: women had a higher mortality risk when admitted for diagnoses that were less common among them (such as cardiac surgery), whereas men were more likely to die when admitted for conditions that were rarer among men (such as metabolic disorders) (91).

Whether this pattern extends to ICU delirium remains unproven. No study to date for instance has specifically explored sex specific differences in outcomes of patients with ICU-delirium and more data is needed.

Alcohol and ICU-Delirium

While alcohol consumption is generally considered a predisposing factor for the development of ICU delirium (Hughes et al.), the available data on this relationship are limited and somewhat inconclusive. While some studies indicate that alcohol abuse and dependence significantly elevate the risk of delirium, this association is not consistently observed. A meta-analysis of twelve prospective studies involving 3144 patients indicated a trend towards a higher risk of delirium with alcohol use, especially when analyzed using multivariate methods (92).

However, a multicenter observational study involving patients admitted to medical, surgical, cardiac, neurological, and trauma ICUs did not confirm this link (93).

Moreover, only one study so far has examined the association between laboratory markers of chronic alcoholism, such as elevated gamma-glutamyl transferase and thrombocytopenia, and an increased risk of delirium (94). The relationship between other alcohol consumption-related biomarkers and ICU delirium remains unclear.

Establishing a correlation between these biomarkers and ICU delirium, however, could have significant therapeutic implications. For instance, if ICU delirium is strongly influenced by alcohol consumption, it may theoretically respond better to benzodiazepine therapy. Yet so far, this hypothesis is unproven and remains to be established.

Biomarkers of alcohol abuse

Identifying and monitoring alcohol abuse is critical for effective intervention and treatment, particularly in the context of critical care. In such settings, biomarkers play a crucial role by providing objective, quantifiable measures of alcohol consumption and its physiological effects. Unlike self-reported measures, which are often used to quantify alcohol use but may not be reliable in critically ill patients, biomarkers may offer a more dependable alternative. This reliability is essential in critical care, where accurate information is vital for appropriate medical decision-making and treatment planning.

Carbohydrate-deficient transferrin represents one of the most studied and widely used biomarkers to detect recent excessive alcohol use. Carbohydrate-deficient transferrin is particularly sensitive to heavy alcohol intake exceeding 40 grams per day, which equates to approximately 5-7 standard drinks daily (95,96).

Carbohydrate-deficient transferrin is a form of the glycoprotein transferrin, which normally transports iron in the bloodstream. Alcohol consumption interferes with the attachment of sialic acid to transferrin, leading to the production of CDT being deficient in carbohydrate sialic acid (97).

Carbohydrate-deficient transferrin levels remain elevated for up to three weeks following alcohol consumption. Individuals with chronic alcohol use exhibit higher CDT levels compared to non-drinkers (95).

The diagnostic accuracy of CDT is notable, with specificity exceeding 90% and sensitivity around 80% for detecting heavy alcohol abuse, defined as the consumption of 60 grams of alcohol per day (97).

CDT is measure by high performance liquid chromatography and the results are provided as the percentage of serum disialotransferrin to all transferrin fractions (%CDT). A cut-off value of 1.7% is used to differentiate between subjects with and without excessive alcohol consumption (98).

Anttila and colleagues proposed combining CDT and γ-glutamyltransferase (γGT) measurements in a mathematical equation $(0.8\ x\ ln(GT) + 1.3\ x\ ln(CDT))$ to improve the diagnostic accuracy of excessive alcohol abuse disorder. The herein referred to Anttila-Index with an established cut-off of 4.0 offers higher sensitivity compared to %CDT alone (99).

No study so far examined the relationship between those biomarkers of alcohol consumption and the development of ICU-delirium.

Rationale and outline of this thesis project

This thesis is structured in two sub-projects.

Rationale for the first project:

Describing delirium subphenotypes through the application of predisposing and precipitating risk factors could greatly enhance our understanding of how symptoms are linked to various etiologies and guide research into the underlying pathophysiological mechanisms of delirium. This process necessitates robust recording and comprehensive testing for the presence of

known risk factors, as well as consideration for unknown or unidentified ones. Additionally, identifying biomarkers in blood plasma could help in identifying patients most at risk of developing delirium (17).

Differentiation between alcohol-withdrawal associated delirium and delirium of different origins is paramount, as therapeutic consequences may be directly implied (100). Benzodiazepines have been shown to be effective in the treatment of alcohol-withdrawal associated delirium, whereas their application for other indications is considered a trigger for delirium (100–102). Therefore, it is necessary to differentiate between subphenotypes of ICU-delirium and to establish a prediction tool to assess the risk for development of alcohol-withdrawal associated delirium in the ICU.

In the ICU setting, traditional methods of diagnosis based on self-reported surveys and questionnaires can be challenged by the acute illness, making diligent history-taking often not feasible. The unreliable diagnosis of alcoholism by medical history taking can obscure the opportunity to identify it as a contributing factor for ICU-delirium and may hinder the implementation of preventive measures targeting this specific risk factor. Consequently, it is rational to explore alcohol-associated biomarkers as a means of identifying patients at risk of ICU-delirium.

To our knowledge, no study has evaluated the association of these alcohol abuse-associated biomarkers and the occurrence of ICU-delirium. The purpose of the first project hence was to conduct a prospective observational study to investigate the potential role of these parameters, especially CDT, for predicting delirium in the setting of a medical ICU.

Rationale for the second project:

In recent years, sex and gender-specific differences in ICU care have gained increasing attention in the literature (103). Notable differences between how men and women experience, respond to, and recover from critical care conditions such as cardiogenic shock, sepsis, and acute kidney injury have been elucidated (103). Within the context of personalized medicine, it seems essential to understand and address both sex and gender differences in the ICU, enabling tailored management that promotes equitable, patient-focused care. Despite this, the impact of sex-specific factors on ICU delirium and associated outcomes is still not well understood, as outlined above. The purpose of the second project hence was to investigate whether critically ill patients with ICU delirium show sex-specific differences in short-term

mortality. This analysis was conducted using a large, publicly accessible dataset, with the aim of producing highly reproducible results to support open science and encourage transparency in research.

Methods

First project

Study population and study design

The first project was a prospective observational study conducted in the ICU of the Department of Internal Medicine, Medical University Graz, Austria.

The study adhered to the ethical guidelines set by the university's Ethics Committee and the principles of the Helsinki Declaration of 1975. The study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement (104).

All patients admitted to the ICU between February 2022 and November 2022 were assessed for eligibility. The inclusion criteria included: (1) admission to the medical ICU, (2) fluency in German, (3) age 18 years or older, and (4) providing written informed consent. Patients were excluded if they: (1) had been hospitalized for more than one week prior to ICU admission (due to time-dependent changes in CDT levels), (2) had pre-existing conditions like mental retardation or dementia, or (3) did not provide informed consent. The study protocol received approval from the Ethics Committee of the Medical University of Graz on August 6, 2021 (approval number: #33-395 ex 20/21). Additionally, the study was registered with the German Clinical Trial Register under the identifier DRKS00027015 on October 28, 2021 (https://drks.de/search/de/trial/DRKS00027015).

Upon ICU admission, demographic information and laboratory data were collected from all critically ill patients. All personal data were pseudonymized. Measurements of CDT were blinded to prevent any bias during the assessment of delirium, and data were only unblinded after the study concluded and the last patient was discharged. For determining the appropriate sample size, we followed the formula for logistic regression in observational studies: n = 100 + 50i, where "i" refers to the number of independent variables in the final model (105). With five independent variables planned in our models, our target sample size was 350 patients (details in the statistical plan section).

Outcomes

The outcomes for this study included the occurrence of delirium, duration of delirium, length of stay in the ICU, total length of hospital stay, in-hospital mortality, and 30-day survival rate. Cognitive status was assessed every 12 hours by critical care nurses and intensivists, all of whom were blinded to the CDT biochemical results. Delirium was evaluated using the Confusion Assessment Method for the ICU (CAM-ICU) (7), which defines delirium as an acute change or fluctuation in mental status along with inattention, plus either disorganized thinking or an altered level of consciousness (RASS scores of -3 or higher, and a positive CAM-ICU result). Patients who were comatose, with a RASS score of -4 or -5, and who did not regain consciousness during their ICU stay, were excluded from further analysis, as it was not possible to obtain informed consent or conduct CAM-ICU assessments on them.

Laboratory testing

All laboratory analyses were conducted at the Clinical Institute for Medical and Chemical Laboratory Diagnostics at the Medical University of Graz. Full blood count measurements were performed using a XN-1000 analyzer (Sysmex Austria GmbH, Vienna, Austria), while other biochemical markers were analyzed on a Cobas 8000 fully automated system (Roche Diagnostics, Vienna, Austria).

Carbohydrate-deficient transferrin levels were measured upon ICU-admission using high-performance liquid chromatography (HPLC) with the ClinRep® HPLC Complete Kit for CDT (Recipe, Munich, Germany). This method aligns with the reference measurement procedure proposed by the International Federation of Clinical Chemistry and Laboratory Medicine's Working Group on CDT Standardization. CDT results were expressed as the percentage of serum disialotransferrin relative to total transferrin fractions (98). Following the recommendations of Helander et al., a cutoff value of 1.7% was used to distinguish patients with excessive alcohol consumption from those without (98).

In addition, the Anttila-Index (γGT-%CDT-index) was calculated using the following equation: γGT-%CDT-index = 0.8ln(γGT) + 1.3ln(%CDT) (99). A cutoff value of 4, as proposed by Anttila et al., was applied to further identify excessive alcohol consumption.

Statistical analysis

All statistical analyses for this project were conducted using R software (version 4.2.1; R Core Team, 2022). Baseline demographic and clinical characteristics were reported as means and standard deviations, medians with interquartile ranges (25th-75th percentiles) for continuous variables, and as proportions for categorical variables. For comparisons of continuous variables, independent samples t-tests were employed for normally distributed data, while rank-sum tests were used for non-normally distributed data. Chi-square and Fisher's exact tests were applied to compare categorical variables. Effect sizes were evaluated using Cramer's V.

The association between alcohol-related biomarkers and delirium was investigated through both unadjusted and adjusted multivariable logistic regression models. Predicted probabilities were plotted to aid in interpreting the model results. To avoid multicollinearity, variance inflation factor (VIF) analysis was performed to check for independence and low correlation between variables. The goodness of fit for the models was assessed using the Hosmer-Lemeshow test. Receiver operating characteristic (ROC) analysis was used to evaluate the discriminatory and predictive power of the variables, and the area under the ROC curve (AUROC) was calculated. Optimal cut-off points were determined using the Youden Index (106).

To examine the relationship between alcohol biomarkers and hospital mortality, multivariable Cox proportional hazards regression was employed. The proportional hazards assumption was evaluated using Schoenfeld residuals. Kaplan-Meier survival analysis was used to compare the 30-day overall survival between groups with dichotomized alcohol abuse markers, with the log-rank test applied for group comparisons. A p-value of less than 0.05 was considered statistically significant.

Covariates

For the multivariable models, potential covariates were selected a priori based on previous research and clinical expertise, focusing on factors that could influence the development of delirium and mortality. The covariates included age, use of mechanical ventilation, serum albumin levels, and the Sequential Organ Failure Assessment (SOFA) score. The SOFA score, which ranges from 0 to 24, was chosen due to its ability to account for illness severity, with higher scores indicating more severe disease and increased risk of death. This score also

adjusts for several key confounding factors, such as platelet count, oxygenation index, and sedation status (16,107).

Second project

Data source and study design

To ensure transparency and reproducibility, we utilized data from the publicly available Medical Information Mart for Intensive Care-IV (MIMIC-IV) database (108), which is hosted on the PhysioNet platform (109). The MIMIC-IV dataset, developed by the Massachusetts Institute of Technology (MIT), contains detailed clinical data for over 60,000 critically ill patients admitted to the ICUs at Beth Israel Deaconess Medical Center (BIDMC) between 2008 and 2019. Access to this database is granted to researchers who complete the necessary "protecting human subjects" training and agree to the data use agreement.

The MIMIC-IV database received approval from the institutional review boards of both Beth Israel Deaconess Medical Center (protocol 2001-P-001699/14) and MIT (protocol No. 0403000206). As the data is deidentified, individual patient consent was waived. We accessed the MIMIC-IV data through PostgreSQL, retrieving relevant variables using SQL queries provided by the official MIMIC GitHub repository. Subsequent data cleaning and analysis were performed using Python version 3.12.4.

The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (104) for observational research and has been registered on the Open Science Framework (https://osf.io/g6fr8). The code necessary to replicate this analysis is openly available at (https://github.com/schrnik/sex_specific_differences_delirium).

Study population

Patients aged 18 years or older who were admitted to the ICU and screened positive for delirium during their stay, as assessed by either the Confusion Assessment Method for the ICU (CAM-ICU) (7) or the Intensive Care Delirium Screening Checklist (ICDSC) (10), were included in the analysis. Patients were excluded if they screened negative for delirium, lacked documentation of delirium screening, or had incomplete data necessary for time-to-event analysis.

Outcome

The study's censoring date was set at a maximum of 30 days from the onset of delirium. The primary outcome of interest was 30-day all-cause mortality following the onset of delirium. This was defined as the time from delirium onset to death from any cause, or to the censoring date for patients who were still alive 30 days after the onset of delirium.

Statistical analysis

Continuous variables were reported as medians with interquartile ranges (IQRs) and were compared between sexes using the Wilcoxon rank-sum test. Categorical variables were presented as counts and percentages and compared using the Chi-Square test. The differences between groups were quantified using standardized mean differences (SMDs).

To investigate the association between sex and 30-day mortality, we conducted Cox proportional hazards regression, with results expressed as hazard ratios (HRs) along with 95% confidence intervals (CIs). The proportional hazards assumption was tested using Schoenfeld residuals.

Kaplan-Meier curves were used to visualize survival probabilities, and the log-rank test was applied to evaluate differences between sexes.

To account for potential imbalances in baseline characteristics, illness severity, and comorbidities between sexes, we implemented propensity score matching (PSM). The propensity score was derived from a multivariable logistic regression model with sex as the dependent variable. By matching on the propensity score, we aimed to achieve similar distributions of baseline covariates between female and male patients (110,111).

The logistic regression model covariates were selected based on prior research (86) and included age, illness severity (Simplified Acute Physiology Score [SAPS] II), invasive ventilation prior to delirium onset, Charlson Comorbidity Index, admission type (surgical vs. medical), presence of sepsis at admission, coronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, liver disease, diabetes, renal disease, malignant cancer, metastatic solid tumor, and acquired immunodeficiency syndrome (AIDS).

We performed 1:1 nearest-neighbor matching with a caliper width of 0.1. After matching, balance between groups was evaluated by reassessing SMDs within the matched cohort to confirm that baseline covariates were well-balanced between the sexes.

As sensitivity analysis, we calculated the E-value to quantify the potential impact of unmeasured confounding on the observed associations (112). The E-value represents the minimum strength of association, measured on the risk ratio scale, that an unmeasured confounder would need to have with both the exposure and the outcome—while accounting for the measured covariates—to fully explain away the observed exposure-outcome relationship. In simpler terms, confounders with associations weaker than the E-value would be insufficient to eliminate the observed association.

Results

First project

Baseline characteristics of the study population

As illustrated in the patient flow diagram **(Figure 1)**, we initially screened 412 critically ill patients upon admission to our medical ICU. Of these, 69 patients were excluded due to lack of informed consent, presence of dementia, missing CDT values, or a hospital stay exceeding seven days before ICU admission. Additionally, comatose patients who passed away with a RASS score of -4 or -5 before CAM-ICU assessment could be conducted were categorized as lacking informed consent. This resulted in a final cohort of 343 patients. Among them, 35% (n=121) developed delirium during their ICU stay. The admission diagnoses are outlined in **Table 1**, while the demographic and clinical characteristics of the study cohort are presented in **Table 2**.

Only 35% (119/343) of the included patients were female, and the sex distribution between the delirium and non-delirium groups was comparable (p=0.193). Patients who developed delirium had significantly higher SAPS3, TISS28, and SOFA scores at the time of ICU admission (p<0.001 for each). These patients also required mechanical ventilation and deep sedation more frequently (p<0.001 for both). As expected, both ICU length of stay and overall hospital length of stay were significantly longer for patients with delirium (p<0.001 for both). ICU mortality was nearly three times higher in delirious patients compared to those without delirium (18% vs. 5%, p<0.001), with the overall ICU mortality rate for the entire study population being around 10%.

Laboratory data at ICU admission are detailed in **Table 3.** Patients who developed ICU delirium exhibited significantly lower platelet counts (p<0.001), reduced oxygenation index (p=0.007),

and lower serum albumin levels ($p<0.001$). Inflammatory markers such as C-reactive protein and procalcitonin were elevated ($p=0.005$ and $p=0.006$, respectively), as were serum creatinine ($p=0.014$) and urea levels ($p=0.021$) in delirious patients compared to those without delirium.

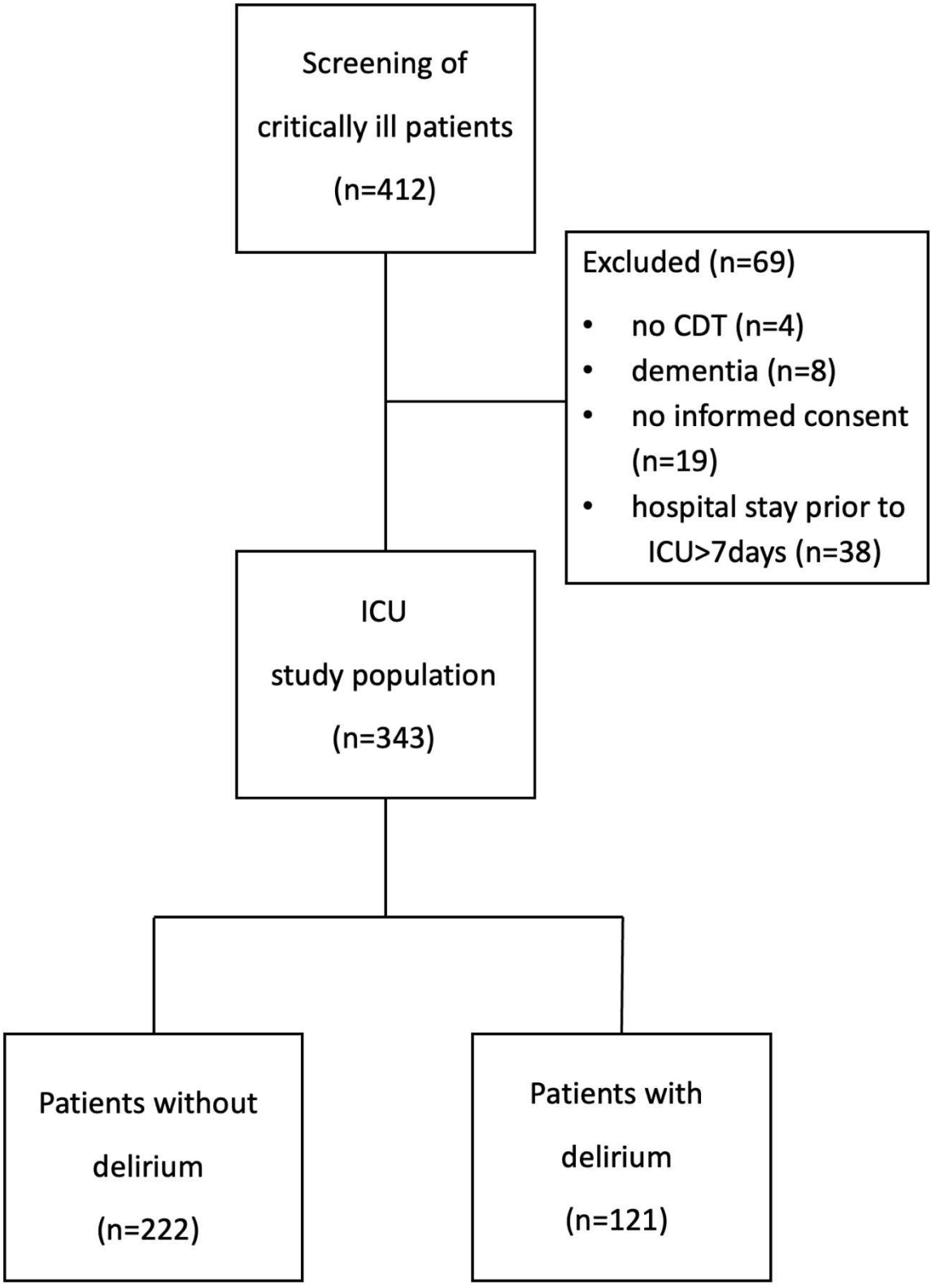


Figure 1. Patient flow chart. (adapted from (1))

Table 1 - Admission Diagnosis of the study population (adapted from (1))

Diagnosis on ICU admission	**N=343**
AKI	13 (3.8%)
Apoplex	5 (1.5%)
Arrhythmia	5 (1.5%)
Cancer	11 (3.2%)
Cardiac arrest	9 (2.6%)
Cirrhosis	9 (2.6%)
COPD	39 (11%)
COVID 19	18 (5.2%)
Diabetic coma	14 (4.1%)
Electrolyte abnormality	18 (5.2%)
GI Bleeding	22 (6.4%)
Heart Failure	12 (3.5%)
Intoxication	47 (14%)
NSTEMI	15 (4.4%)
Other	14 (4.1%)
PAE	7 (2.0%)
Pneumonia	29 (8.5%)
Sepsis	38 (11%)
STEMI	18 (5.2%)

Table 1. Admission Diagnosis of the study population. Proportions are depicted as percent. Abbreviations: AKI= Acute kidney injury, COPD=chronic obstructive pulmonary disease, COVID 19=Corona virus disease 2019, SAPS=simplified acute physiology score, TISS=therapeutic intervention scoring system, SOFA=sequential organ failure assessment, RASS=Richmond agitation-sedation scale.

Table 2 - Demographic and clinical characteristics of the study population (adapted from (1))

Demographic and baseline characteristics	Study population [n=343]	Patients w/o delirium [n=222]	Patients with delirium [n=121]	p-value*
Age [years]	64 [52; 73]	63.5 [51; 73]	64 [52; 73]	0.988
Sex female [%]	34.7	37.4	29.8	0.193
Body mass index [kg/m^2]	24 [22; 27]	24 [22; 27]	24 [22; 27]	0.639
SAPS3	51 [43; 62]	49 [42; 59]	57 [46; 67]	**<0.001**
TISS-28	31 [25; 34.5]	30 [24; 33]	34 [27; 38]	**<0.001**
SOFA Score	4 [2; 7]	3 [1; 5]	7 [4; 10]	**<0.001**
Age >65 years [%]	44.6	44.6	44.6	0.998
Mechanical ventilation [%]	20.4	12.2	35.6	**<0.001**
Deep sedation [RASS-5] [%]	19.8	11.3	35.6	**<0.001**
ICU-length of stay [d]	3 [2;6]	3 [2;4]	5 [3;9]	**<0.001**
Hospital-length of stay [d]	9 [4; 17]	8 [4; 13]	11 [5; 22]	**<0.001**
ICU-mortality [%]	9.9	5.4	18.2	**<0.001**
Hospital-mortality [%]	14.0	9.0	23.1	**<0.001**

Table 2. **Demographic and clinical characteristics of the study population**. Median values are shown with 25th and 75th percentile in brackets. *Chi-Square-Test or rank-sum test as appropriate. Abbreviations: w/o= without, SAPS=simplified acute physiology score, TISS=therapeutic intervention scoring system, SOFA=sequential organ failure assessment, RASS=Richmond agitation-sedation scale.

Table 3. Laboratory parameters of the study population (adapted from (1))

Laboratory parameters	Study population [n=343]	Patients w/o delirium [n=222]	Patients with delirium [n=121]	p-value*
Leucocytes [G/L]	10.3 [7.4; 14.5]	10.5 [7.7; 14.5]	10.1 [7.0; 14.7]	0.701
Hemoglobin [g/dL]	11.9 ± 2.8	12.0 ± 2.8	11.6 ± 2.9	0.151
Platelets [G/L]	210 [154; 277]	227 [172; 296]	184 [121; 244]	**<0.001**
C-reactive protein [mg/L]	15.7 [3.7; 88.1]	11.8 [2.8; 77.6]	25.5 [6.6; 103.6]	**0.005**
Procalcitonin [ng/mL]	0.24 [0.07; 1.12]	0.19 [0.06; 0.79]	0.42 [0.11; 2.21]	**0.006**
Sodium [mmol/L]	138 [134; 140]	137 [134; 140]	138 [134; 141]	0.196
Potassium [mmol/L]	4.1 [3.8; 4.7]	4.1 [3.8; 4.6]	4.2 [3.7; 4.8]	0.767
Calcium [mmol/L]	2.22 [2.11; 2.3]	2.23 [2.15; 2.31]	2.20 [2.07; 2.29]	0.065
Phosphate [mmol/L]	1.14 [0.93; 1.40]	1.09 [0.92; 1.36]	1.19 [0.94; 1.51]	0.111
Creatinine [mg/dL]	1.01 [0.79; 1.59]	0.99 [0.79; 1.42]	1.20 [0.81; 2.04]	**0.014**
Urea [mg/dL]	41 [27; 66]	38 [27; 57]	50 [27; 84]	**0.021**
Bilirubin [mg/dL]	0.56 [0.35; 1.04]	0.55 [0.34; 0.97]	0.58 [0.36; 1.33]	0.143
γ glutamyltransferase [U/L]	48 [24; 102]	42 [24; 82]	56 [26; 156]	**0.006**
Aspartate transaminase [U/L]	35 [22; 75]	31 [20; 67]	41 [25; 92]	**0.014**
Alanine transaminase [U/L]	26 [17; 44]	26 [17; 42]	29 [16; 49]	0.688
Amylase [U/L]	22 [14; 35]	23 [15; 33]	20 [12; 41]	0.317
Creatine kinase [U/L]	110 [60; 273]	101 [58; 235.25]	130 [64.50; 367.5]	0.077
Lactate dehydrogenase [U/L]	231 [179; 346]	224.5 [177; 333]	256 [186; 365]	0.199
Prothrombin time INR	1.05 [0.97; 1.22]	1.04 [0.96; 1.18]	1.08 [1; 1.27]	**0.008**
Protein [g/dL]	6.1 ± 0.8	6.2 ± 0.8	5.9 ± 0.8	**0.010**
Albumin [g/dL]	3.4 [3.0; 3.8]	3.5 [3.1; 3.9]	3.2 [2.8; 3.7]	**<0.001**
Lactate [mmol/L]	1.1 [0.70; 1.85]	1.1 [0.70; 1.75]	1.2 [0.73; 2.15]	0.236
Oxygenation index [mm Hg]	306 [204; 400]	323 [218; 410]	283 [173; 377]	**0.007**
CDT [%]	1.19 [0.94; 1.50]	1.14 [0.93; 1.40]	1.28 [0.96; 1.79]	**0.011**
Anttila-Index	3.32 [2.67; 4.08]	3.22 [2.58; 3.84]	3.69 [2.79; 4.42]	**0.001**

Table 3. Laboratory parameters of study population. Parameters are given as means ± SD or medians with 25th and 75th percentile in brackets. *Rank-sum test or t-test, as appropriate. Abbreviations: w/o= without, INR=international normalized ratio, CDT=carbohydrate-deficient transferrin.

Biomarkers of alcohol abuse are associated with development of ICU-delirium

Consistent with our hypothesis, CDT levels were significantly higher in patients who developed ICU delirium compared to those without delirium (p=0.011). In fact, 52% (33/63) of patients with CDT levels above 1.7% experienced delirium during their ICU stay, while only 31% (88/280) of patients with CDT levels below 1.7% developed delirium (p=0.002). Additionally, the Anttila Index was notably elevated in patients with delirium, with a median value of 3.69 in delirious patients compared to 3.22 in those without delirium (p=0.001). Patients with an Anttila Index over 4 had a significantly higher incidence of delirium (49%, 45/91) compared to those with an Anttila Index below 4 (30%, 76/249) (p=0.002). (The Anttila Index could not be calculated for 3 patients due to missing γ-glutamyltransferase data).

In our study, a documented history of alcohol abuse was noted in only 16% (55/343) of patients. However, 27% of patients (91/340) had an Anttila Index above the threshold, indicating possible excessive alcohol consumption. The correlation between documented alcohol abuse and an Anttila Index above 4 showed a Cramer's V of 0.23, suggesting only a moderate association. These findings reinforce our hypothesis that diagnosing alcohol abuse can be difficult in acute care settings, especially considering the strong diagnostic utility of the Anttila Index in identifying excessive alcohol use (99).

In unadjusted binary logistic regression analysis, we observed that both an increase in CDT levels per percentage point (OR 1.34, 95% CI 1.10–1.69) and CDT levels above 1.7% (OR 2.40, 95% CI 1.38–4.20) were significantly associated with ICU delirium development (p=0.008 and p=0.002, respectively). Similarly, each unit increase in the Anttila Index (OR 1.47, 95% CI 1.21–1.79) and Anttila Index levels above 4 (OR 2.23, 95% CI 1.36–3.65) were strongly associated with delirium (p<0.001 and p=0.001, respectively). The results from unadjusted logistic regression analysis can be found in **Table 4**.

Figure 2 shows the relationship between predicted probabilities of delirium occurrence and alcohol abuse biomarkers, SOFA scores, and serum albumin levels based on unadjusted logistic regression. Importantly, in our multivariable models adjusting for SOFA scores, age, mechanical ventilation, and serum albumin, CDT values above 1.7%, CDT per percent increase, and the Anttila Index per unit increase remained significantly associated with development of delirium **(Figure 3).**

Table 4. Univariable logistic regression models for development of ICU-delirium (adapted from (1))

Binary logistic regression	**ICU delirium**		
	Odds ratio	**95% Confidence interval**	**p-value**
CDT (per one percent increase)	1.34	1.10 - 1.69	**0.008**
CDT > 1.7%	2.40	1.38 - 4.20	**0.002**
Anttila-Index	1.47	1.21 - 1.79	**<0.001**
Anttila-Index > 4	2.23	1.36 - 3.65	**0.001**
SAPS3 (per five points increase)	1.2	1.11 - 1.31	**<0.001**
TISS-28 (per one point increase)	1.07	1.04 - 1.11	**<0.001**
SOFA (per one point increase)	1.25	1.18 - 1.34	**<0.001**
Mechanical ventilation	3.98	2.32 - 6.96	**<0.001**
Deep sedation (RASS -5)	4.34	2.50 - 7.68	**<0.001**
Age (per 10 year increase)	1.02	0.89 - 1.16	0.823
Female gender	0.71	0.44 - 1.14	0.157
Procalcitonin (per 10 ng/mL increase)	1.13	0.97 - 1.36	0.141
C-reactive protein (per 50mg/L increase)	1.11	0.96 - 1.24	0.061
Creatinine (per one mg/dL increase)	1.04	0.95 - 1.15	0.389
Prothrombin time INR (per one unit increase)	1.10	0.65 - 1.82	0.700
Urea (per 10 mg/dL increase)	1.02	0.99 - 1.06	0.188
γ-glutamyltransferase (per 100 U/L increase)	1.29	1.11 - 1.56	**0.005**
Aspartate transaminase (per 50 U/L increase)	1.00	0.98 - 1.02	0.937
Albumin (per one g/dL increase)	0.50	0.34 - 0.73	**<0.001**

Figure 2. Potential predictors for development of ICU-delirium (adapted from (1))

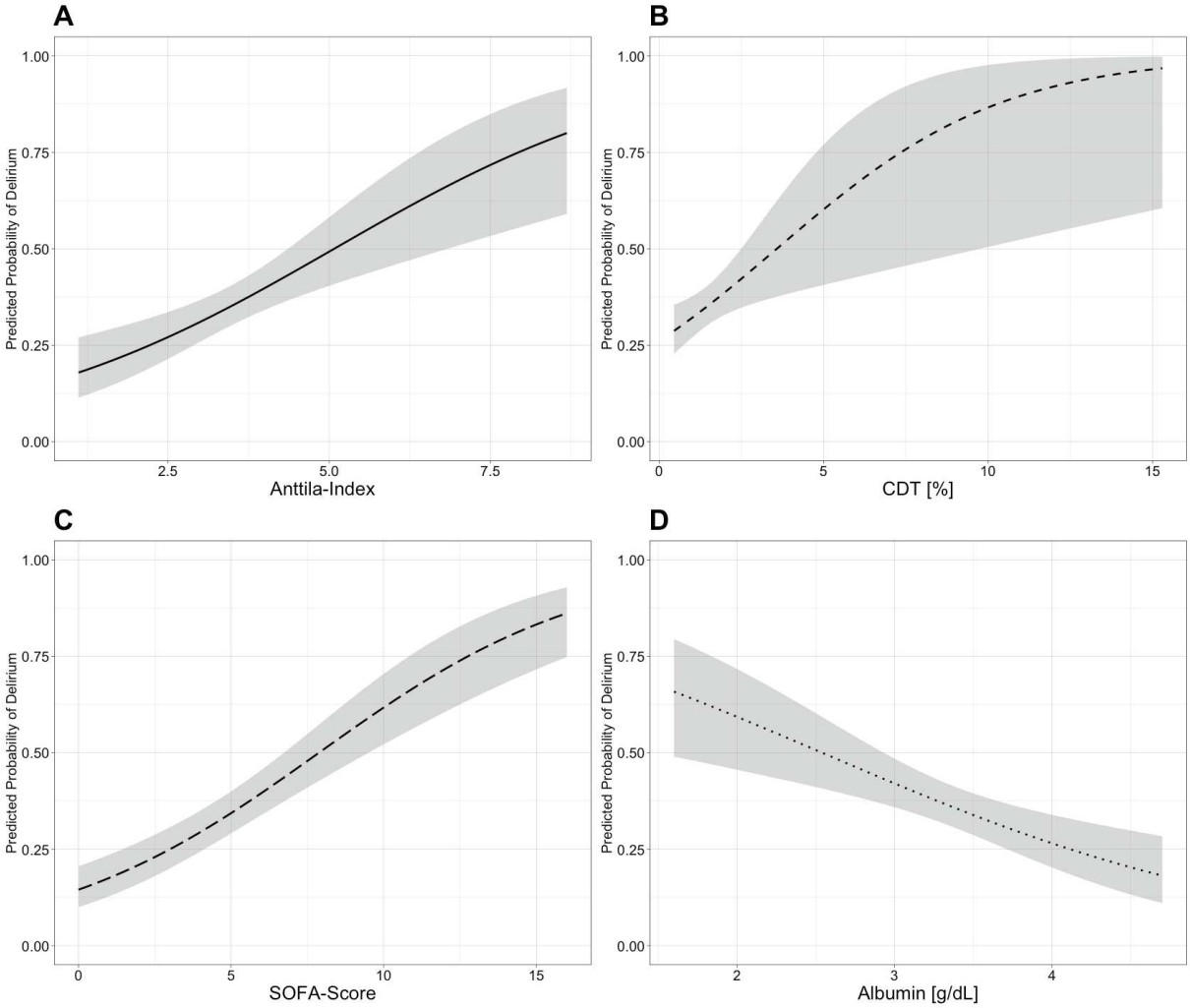


Figure 2. Potential predictors for development of ICU-delirium. (adapted from (1))

Predicted probabilities to develop ICU delirium were derived from binary logistic regression for A) Anttila-Index ($p < 0.001$), B) carbohydrate-deficient transferrin (CDT) ($p=0.008$), C) Sequential Organ Failure Assessment (SOFA)-score ($p < 0.001$), and D) serum albumin ($p < 0.001$), respectively. Shaded areas depict 95% confidence intervals.

Figure 3. Carbohydrate-deficient transferrin and Anttila-Index are potential predictors of ICU-delirium (adapted from (1))

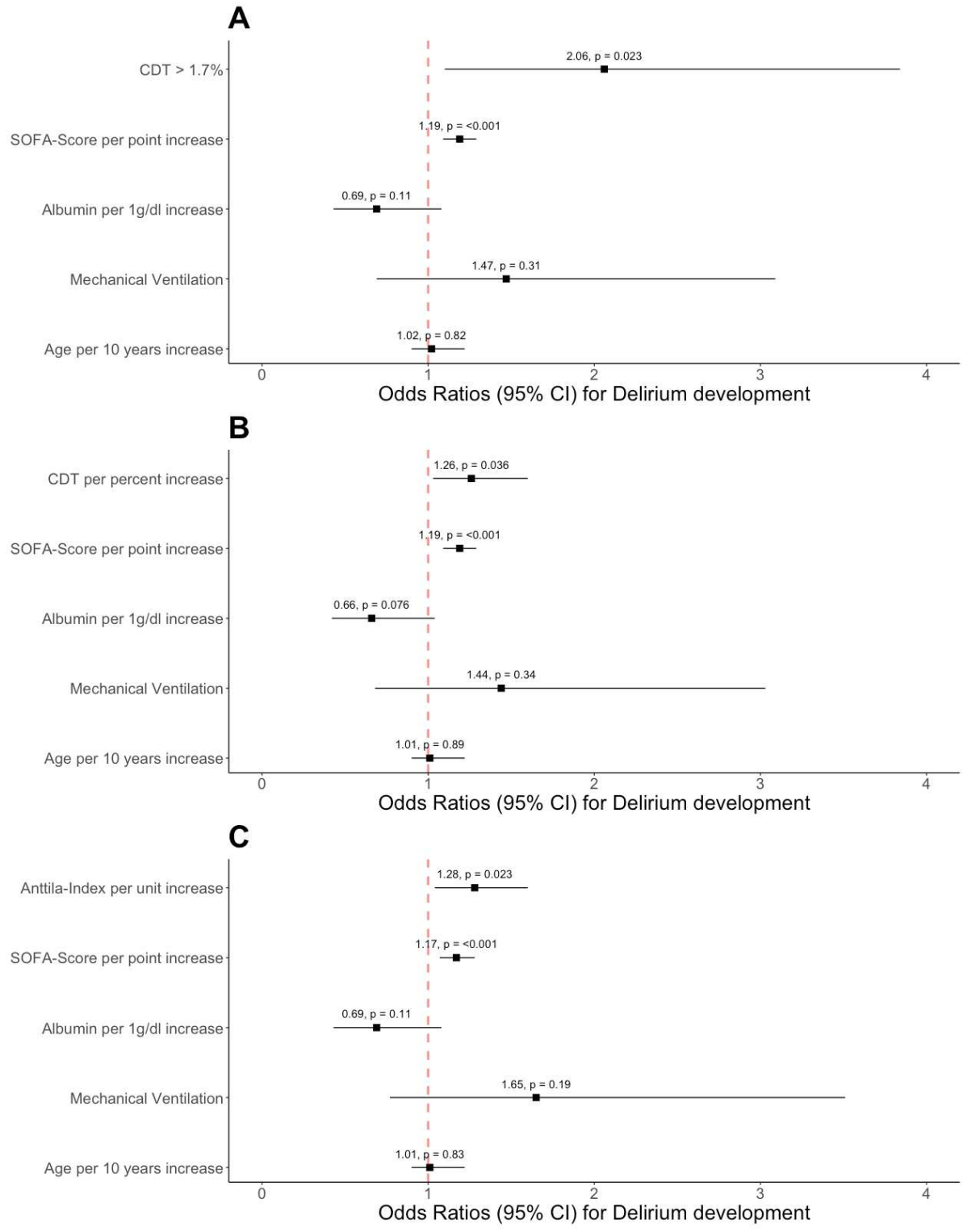


Figure 3. Carbohydrate-deficient transferrin and Anttila-Index are potential predictors of ICU-delirium

Multivariable logistic regression models for A) carbohydrate-deficient transferrin (CDT) above cutoff 1.7% (OR 2.06, 95% CI 1.10 - 3.84, p=0.023), B) CDT per percent increase (OR 1.26, 95% CI 1.03 - 1.60, p=0.036), and C) Anttila-Index per unit increase (OR 1.28, 95% CI 1.04 - 1.60, p=0.023) after adjustment for Sequential Organ Failure Assessment (SOFA)-score, serum albumin, mechanical ventilation and age. P-values of Hosmer-Lemeshow-Tests were 0.74, 0.83, and 0.98, respectively.

Predictive Performance of CDT and Anttila-Index

The predictive capabilities of CDT and the Anttila Index were assessed through Receiver Operating Characteristic (ROC) curve analysis, with the area under the ROC curve (AUROC) used to evaluate performance. The AUROC for CDT was 0.75 (95% CI: 0.69 – 0.81), while the Anttila Index had an AUROC of 0.74 (95% CI: 0.68 – 0.80).

Optimal cutoff values for both biomarkers were identified using the Youden Index. For CDT, the ideal threshold was 1.79%, which corresponded to a sensitivity of 0.65 and a specificity of 0.75. Similarly, the Anttila Index had an optimal cutoff of 3.61, with a sensitivity of 0.66 and specificity of 0.74 in predicting the development of ICU delirium. The corresponding ROC curves for these analyses are depicted in **Figure 4.**

Figure 4: Receiver operating characteristic curves for CDT [%] and the Anttila-Index (adapted from (1))

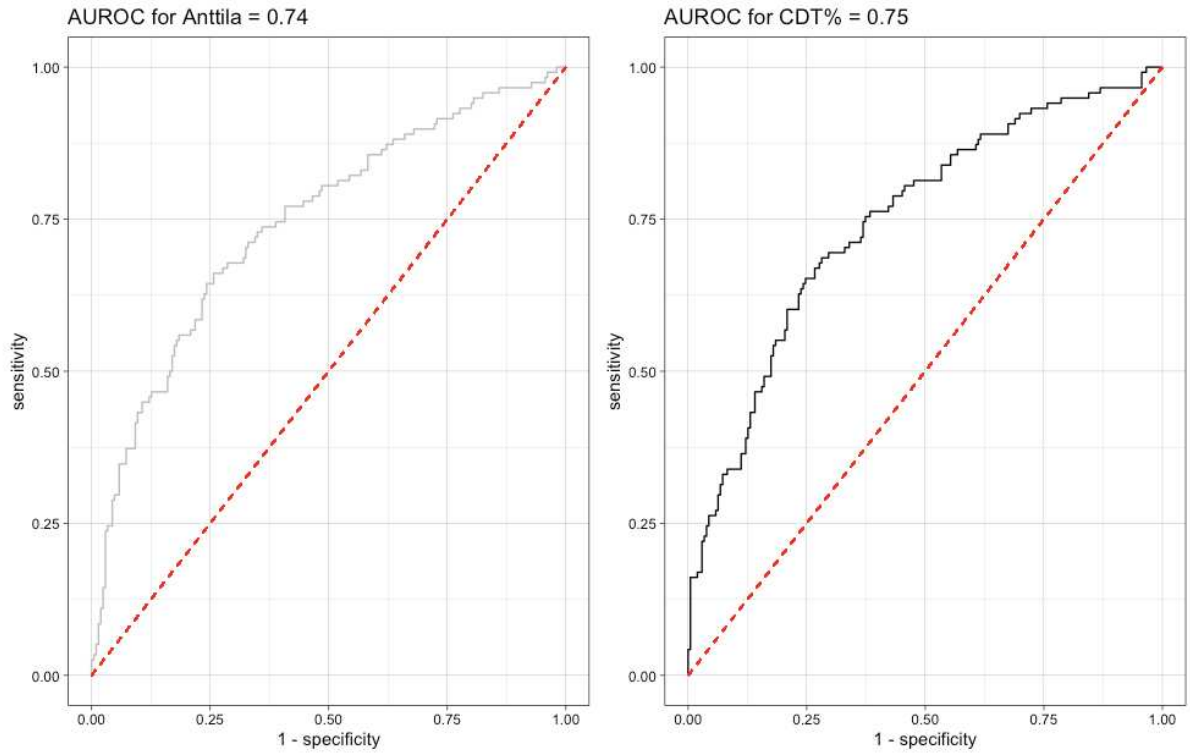


Figure 4: Receiver operating characteristic curves for CDT [%] and the Anttila-Index.

Receiver operating characteristic (ROC) curves to evaluate the predictive and discriminative ability of CDT (black line) and the Anttila-Index (grey line) for development of ICU-delirium are shown. Respective areas under the receiver operating characteristic curves (AUROC) are depicted as well. Abbreviations: AUROC= area under the receiver operating characteristic curve, ROC = receiver operating characteristic, CDT= Carbohydrate-deficient transferrin, ICU= Intensive care unit

Higher Anttila-Index and CDT-Levels are linked to longer Delirium duration

In our cohort, the median duration of delirium was 3 days [2–5 days]. Based on recent studies involving critically ill patients, which reported delirium durations ranging from 4 to 11 days with a median of 5 days, and considering that the 75th percentile of delirium duration in our study population was 5 days, we defined "prolonged ICU delirium" as delirium lasting 5 or more days. Of the 121 patients who developed delirium, 34 remained CAM-ICU positive for 5 days or longer.

Covariate-adjusted logistic regression analysis, focusing only on patients who were CAM-ICU positive, revealed that each one-unit increase in the Anttila Index was associated with a 1.70-fold higher odds (95% CI 1.21–2.51, p=0.004) of developing delirium lasting 5 or more days, after adjusting for SOFA score, mechanical ventilation, age, and albumin levels. Additionally, a 1% increase in CDT levels was associated with a 1.34-fold higher odds (95% CI 1.04–1.84, p=0.042) of experiencing prolonged ICU delirium.

Anttila-Index and CDT are linked to mortality in critically ill patients

In our study, 14% of the patients admitted to the ICU did not survive their hospital stay. Mortality rates were significantly higher among patients who developed delirium, with a 23% death rate in the delirium group compared to 9% in the non-delirium group (p<0.001). An Anttila Index above 4 was linked to a twofold increase in the risk of death during the hospital stay compared to an Anttila Index below 4, based on adjusted Cox proportional hazards analysis (HR 2.20, 95% CI 1.21–4.00, p=0.010). Additionally, both CDT levels per percent increase and the Anttila Index as continuous variables were significantly associated with hospital mortality (**Table 5**).

As shown in the Kaplan-Meier curve (**Figure 5**), the 30-day survival rate was 77% for patients with an Anttila Index above 4, compared to 69% for those with an Anttila Index below 4 (p=0.036 by log-rank test).

Table 5. Adjusted hazard ratios for hospital mortality (adapted from (1))

Adjusted Cox proportional hazard model			
		Hospital mortality	
	Hazard ratio	**95% Confidence interval**	**p-value**
Anttila-Index > 4	2.20	1.21 - 4.00	**0.010**
SOFA Score per one point increase	1.11	1.03 - 1.20	**0.008**
Age per 10 years increase	2.16	1.63 - 2.84	**<0.001**
Albumin per g/dL increase	0.75	0.45 - 1.27	0.284
Mechanical ventilation	1.46	0.65 - 3.25	0.359
		Hospital mortality	
	Hazard ratio	**95% Confidence interval**	**p-value**
Anttila per unit increase	1.36	1.05 - 1.74	**0.018**
SOFA per point increase	1.12	1.03 - 1.21	**0.005**
Age per 10 years increase	2.16	1.63 - 2.84	**<0.001**
Albumin per g/dL increase	0.74	0.44 - 1.25	0.265
Mechanical ventilation	1.37	0.63 - 2.97	0.423
		Hospital mortality	
	Hazard ratio	**95% Confidence interval**	**p-value**
CDT per percent increase	1.19	1.01 - 1.40	**0.034**
SOFA per point increase	1.12	1.04 - 1.21	**0.003**
Age per 10 years increase	2.16	1.48 – 2.84	**<0.001**
Albumin per g/dL increase	0.72	0.42 - 1.21	0.210
Mechanical ventilation	1.20	0.55 - 2.63	0.647

Table 5. Adjusted hazard ratios for hospital mortality. Anttila-Index above 4 is independently associated with higher risk for death during stay at the hospital in cox proportional hazard analysis. (HR 2.20, 95% CI 1.21 - 4.00, p=0.010). Moreover CDT (per percent increase, HR 1.19, 95% CI 1.01 - 1.40, p=0.034) and Anttila-Index (per unit increase, HR 1.36, 95% CI 1.05 - 1.74, p=0.018) as continuous variables were independently associated with higher risk for death. Furthermore SOFA-score and age remained significantly associated with death in all our adjusted models. Abbreviations: CDT=carbohydrate-deficient transferrin, SOFA=sequential organ failure assessment, HR=hazard ratio.

Figure 5. Figure 5: Kaplan-Meier survival curve (adapted from (1))

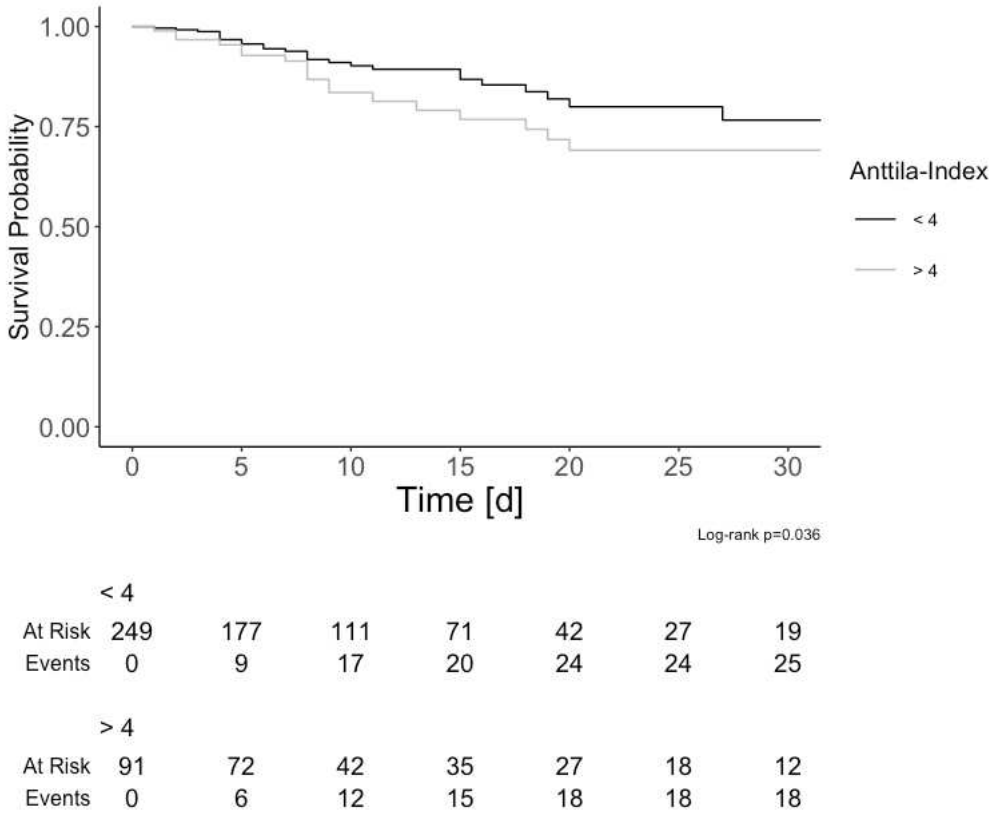


Figure 5: Kaplan-Meier survival curve. 30-day Kaplan-Meier survival estimates for critically ill patients with Anttila-Index below 4 (black line) and Anttila-Index above 4 (grey line). Three patients were not considered because of missing values for γ-glutamyltransferase.

Second project

Characteristics of the study cohort

A total of 8950 ICU patients developed delirium during their stay and were eligible for analysis **(Study Flow Chart 2, Figure 6**). Of these, 42.6% were female. Women were significantly older than men (median age: 71 [58–81] vs. 66 [54–77], p<0.001) and had higher illness severity (SAPS II: 39.0 [31.0–50.0] vs. 38.0 [30.0–49.0], p<0.001), though they were less likely to receive invasive ventilation (48.4% vs. 53.5%, p<0.001). The baseline demographics and comorbidities of the entire cohort, stratified by sex, are detailed in **Table 6**.

Sex specific differences in short term mortality after ICU-Delirium

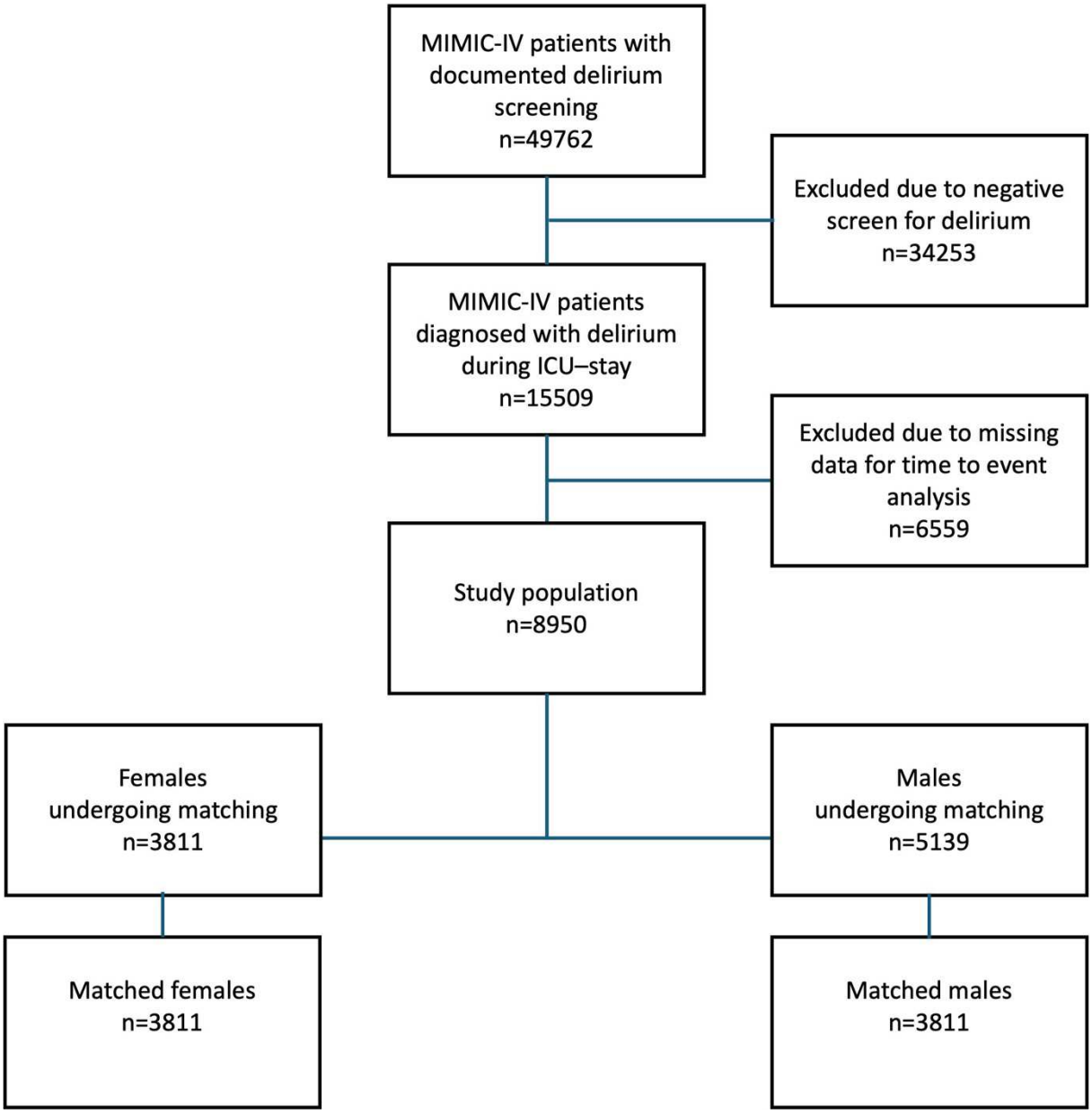
At 30 days, 992 of 3811 females and 1202 of 5139 males (26.0% vs. 23.4%, p=0.004) had died, resulting in a crude HR of 1.16 (95% CI 1.071–1.267, p<0.001) (**Figure 7**). After propensity score matching, the cohort included 3811 females and 3811 males. In the matched cohort, 909 males and 992 females had died after 30 days, corresponding to a HR of 1.14 (95% CI 1.046–1.252, p=0.003) for female sex.

Baseline characteristics in the matched cohort were well-balanced, with all SMDs <0.1 (**Figure 8**). The distribution of the propensity score before and after matching is shown in **Figure 9.**

Sensitivity Analysis

For the hazard ratio of 1.16 (95% CI 1.071–1.267) for 30-day mortality in females, the E-value was calculated to be 1.45, indicating that any unmeasured confounder would need to have a relative risk of at least 1.45 with both gender and mortality to explain away the observed effect.

Figure 6. Study Flow Chart 2



Abbreviations: ICU – Intensive Care Unit; MIMIC-IV - Medical Information Mart for Intensive Care-IV;

Table 6. Demographics, illness severity and comorbidities stratified by sex.

Variable	Overall n=8950	Female n=3811	Male=5139
Age	68.0 [56.0 - 79.0]	71.0 [58.0 - 81.0]	66.0 [54.0 - 77.0]
Comorbidity and Illness severity scores			
Charlson Comorbidity Index	5.0 [3.0 - 7.0]	5.0 [3.0-7.0]	5.0 [3.0 - 7.0]
SAPS II	39.0 [31.0 - 49.0]	39.0 [31.0-50.0]	38.0 [30.0 - 49.0]
Diagnosis, admission and treatment modality			
Type of admission			
Surgical	2208 (24.7%)	912 (23.9%)	1296 (25.2%)
Medical	6742 (75.3%)	2899 (76.1%)	3843 (74.8%)
Invasive ventilation before onset of delirium	4593 (51.3%)	1843 (48.4%)	2750 (53.5%)
Sepsis at admission	6477 (72.4%)	2699 (70.8%)	3778 (73.5%)
Comorbidities			
Peripheral vascular disease	1008 (11.3%)	382 (10.0%)	626 (12.2%)
Coronary artery disease	1507 (16.8%)	533 (14.0%)	974 (19.0%)
Cerebrovascular disease	1961 (21.9%)	923 (24.2%)	1038 (20.2%)
Congestive heart failure	2478 (27.7%)	1057 (27.7%)	1421 (27.7%)
Renal disease	1750 (19.6%)	645 (16.9%)	1105 (21.5%)
Dementia	671 (7.5%)	346 (9.1%)	325 (6.3%)
Chronic pulmonary disease	2226 (24.9%)	1104 (29.0%)	1122 (21.8%)
Malignant cancer	1004 (11.2%)	386 (10.1%)	618 (12.0%)
Rheumatic disease	276 (3.1%)	185 (4.9%)	91 (1.8%)
Peptic ulcer disease	252 (2.8%)	107 (2.8%)	145 (2.8%)
Mild liver disease	1201 (13.4%)	424 (11.1%)	777 (15.1%)
Severe liver disease	630 (7.0%)	225 (5.9%)	405 (7.9%)

Diabetes without complications	1981 (22.1%)	836 (21.9%)	1145 (22.3%)
Diabetes with complications	916 (10.2%)	330 (8.7%)	586 (11.4%)
Paraplegia	838 (9.4%)	388 (10.2%)	450 (8.8%)
Metastatic solid tumor	449 (5.0%)	189 (5.0%)	260 (5.1%)
Acquired immune deficiency syndrome (AIDS)	35 (0.4%)	10 (0.3%)	25 (0.5%)

For continuous variables medians with 25^{th}-75^{th} percentile in brackets are depicted, whereas for categorical variables absolute values and percent in brackets are presented.

Abbreviations: AIDS - Acquired immune deficiency syndrome; SAPS II - Simplified Acute Physiology Score II

Figure 7. Kaplan-Meier Survival Curve by Sex.

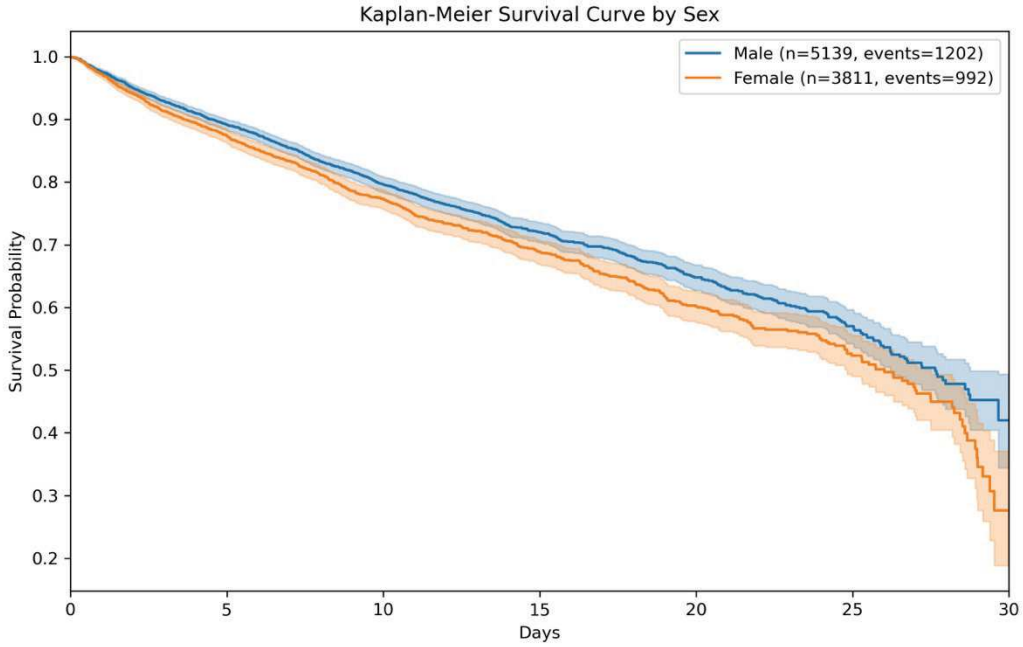


Figure 7. Kaplan-Meier Survival Curve by Sex. 30-day survival probability after delirium onset compared between male patients (in blue) and female patients (in orange). 95%-Confidence Intervals are depicted as shaded areas. Log-Rank Test p-value = 0.0004.

Figure 8. Standardized Mean Differences before and after matching

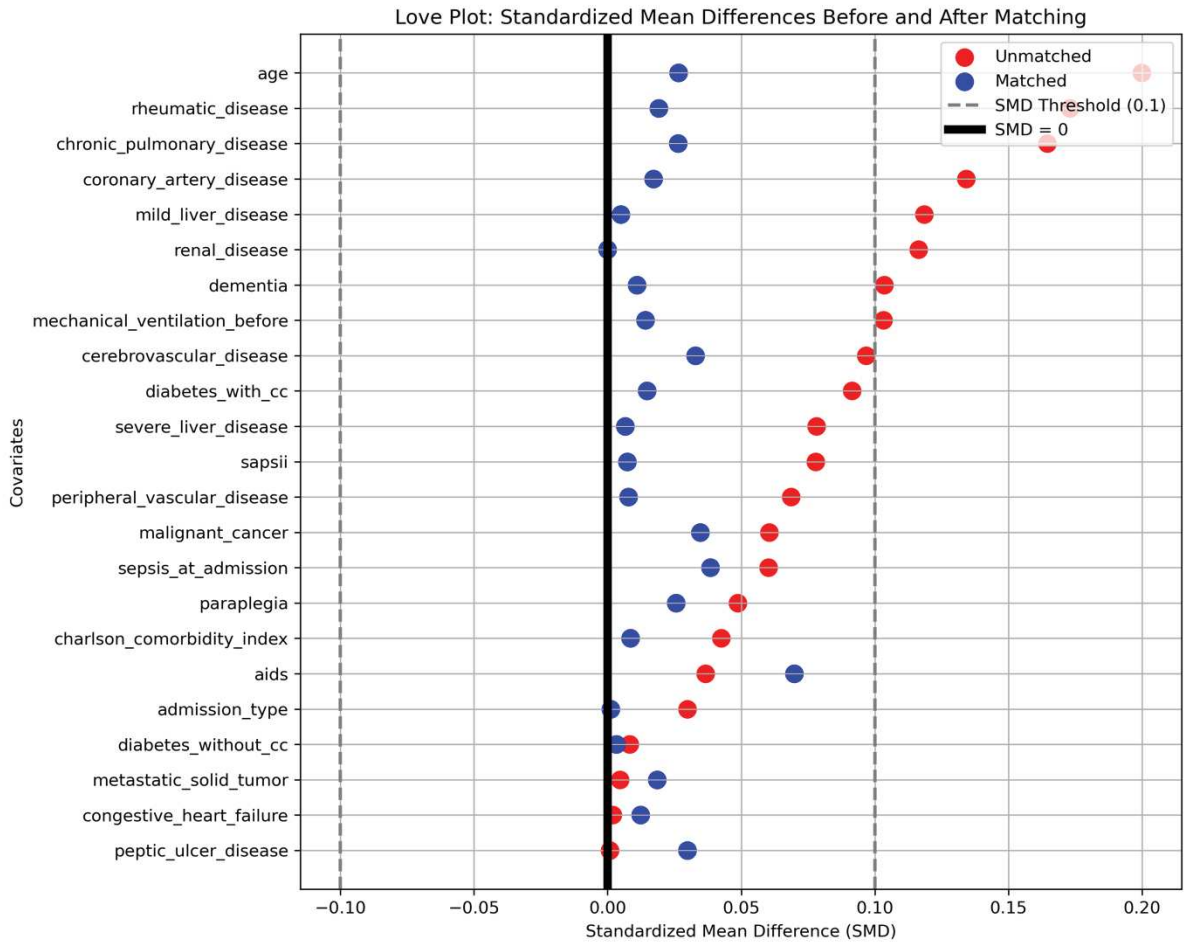


Figure 8. Standardized Mean Differences before and after matching. Love-plot displaying the standardized mean differences (SMDs) of all covariates included in the propensity score model, comparing females and males in both the unmatched cohort (n=8950, red dots) and the matched cohort (n=7622, blue dots).

Abbreviations: SMD – Standardized mean difference;

Figure 9. Distribution of the propensity score before and after matching

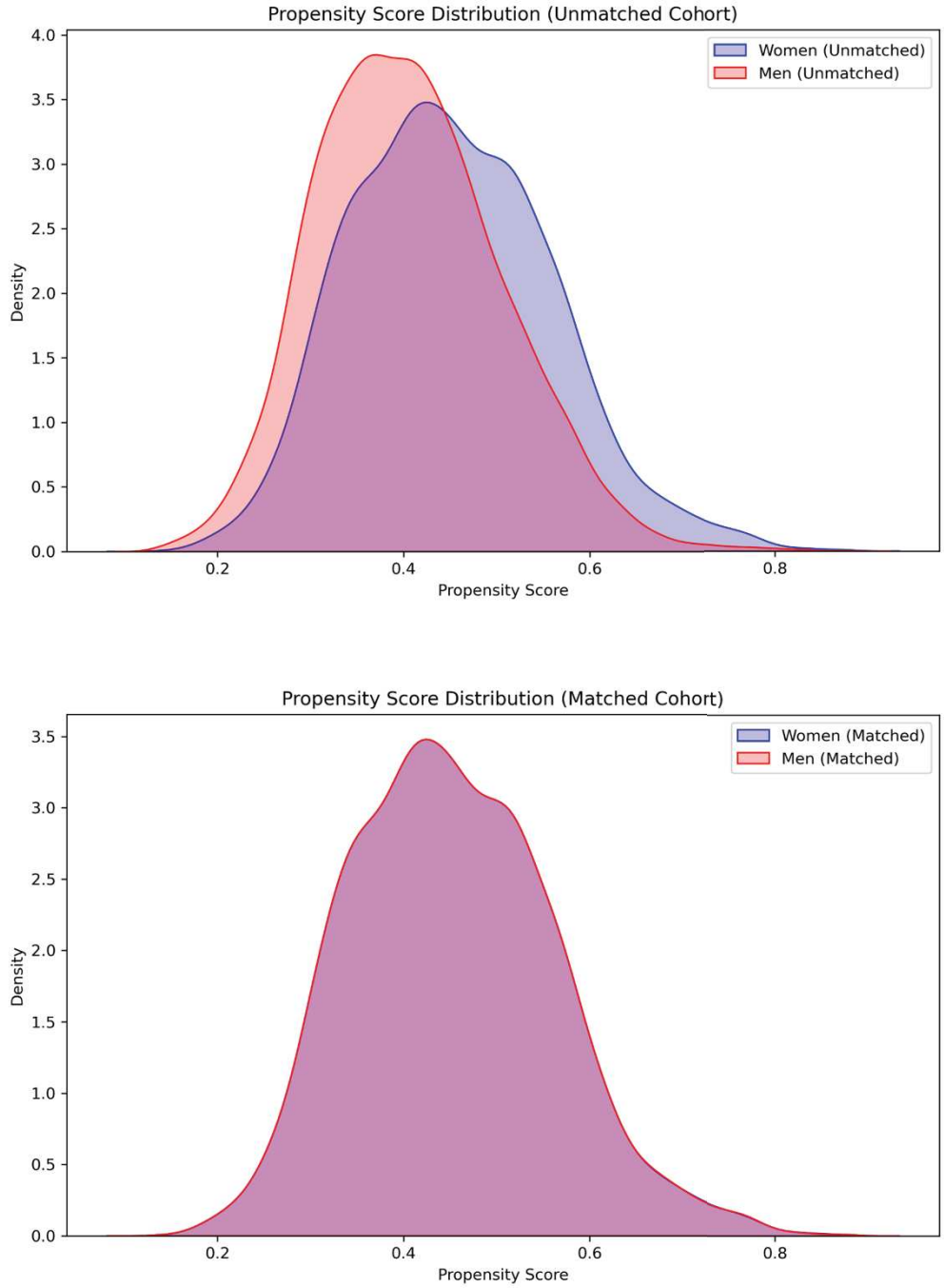


Figure 9. Distribution of the propensity score before and after matching. Density plots of the propensity score for female patients (blue) and male patients (red) in the unmatched cohort (upper panel) and matched cohort (lower panel). The propensity score was derived from a multivariable logistic regression model with sex as the outcome variable.

Discussion

The findings from the first project, a prospective observational study, clearly indicate that elevated CDT levels, and particularly the Anttila Index at the time of ICU admission, were strongly associated with an increased risk of delirium, prolonged delirium duration, and higher hospital mortality. The second project, a retrospective cohort analysis based on clinical data science using a large, publicly available dataset, revealed a significantly higher adjusted risk of short-term mortality for women with ICU delirium compared to men.

Both findings, although not directly related, represent novel and previously unexplored scientific achievements that contribute to the knowledge and advancement in the field of ICU delirium.

Initially, the findings from both projects will be discussed separately and contextualized within the existing body of literature. Following this, the less obvious connection between the two will be explored in relation to the current critical care literature, highlighting potential implications.

First project- Biomarkers of alcohol abuse potentially predict delirium, delirium duration and mortality in critically ill patients

Our findings suggest that these biomarkers may play a potential role in predicting ICU delirium and other critical outcomes. Furthermore, consistent with previous studies (8), we demonstrate that delirium is associated with a substantial disease burden, including prolonged ICU and hospital stays, and, most notably, elevated ICU and hospital mortality rates.

Bowman and colleagues advocate for the clinical and biological subphenotyping of delirium to clarify the causal links between symptoms, risk factors, and underlying biological mechanisms (17). Alcohol abuse is a well-established risk factor for the onset of delirium; however, definitions of alcohol abuse vary considerably across studies (16). Additionally, assessing alcohol use disorder in a structured manner within critical care environments may often be impractical and challenging. A logical consequence of complexity of these assessments may be under-documentation. Our study reflects this issue, as we observed a gap between the proportion of patients with elevated alcohol-associated biomarkers and those with a documented history of alcohol abuse. This inconsistency is further evidenced by a moderate correlation (Cramer's V = 0.23) between documented alcohol abuse and an Anttila Index above

4. These findings emphasize the need for a biomarker-based approach to assess delirium risk in critically ill patients.

While previous studies suggest an increased risk of delirium associated with benzodiazepine use (102), our findings lead as to propose that a potential delirium subphenotype identified by elevated CDT and Anttila Index at ICU admission may actually benefit from early benzodiazepine use as a preventive measure. However, this hypothesis requires validation in future controlled clinical trials.

Strengths and limitations

Our study has several strengths and limitations. The RASS and CAM-ICU assessments were conducted by trained medical staff who were blinded to the biochemical analysis of CDT, ensuring that the delirium evaluations were unbiased and unaffected by knowledge of the biomarker results. Additionally, we used prospectively collected data to investigate the potential relationship between alcohol consumption-related markers and the occurrence of delirium. Notably, our findings hold significant clinical relevance for intensivists, as both CDT and the Anttila Index are readily accessible biomarkers that can help identify patients at high risk for developing delirium, allowing for the early implementation of preventive strategies.

While previous model-based predictions for ICU delirium have demonstrated moderate to good discriminative ability (49,52), their practical utility for real-time clinical decisions has been questioned (4). This reinforces the need for a more straightforward approach to assessing delirium risk, as proposed in our study.

Several limitations warrant consideration when interpreting our data:

(i) ICU delirium is a complex clinical syndrome characterized by acute brain dysfunction, resulting from a multifaceted interaction of numerous, sometimes obscure, pathophysiological mechanisms. This complexity makes accurate prediction challenging. Firstly, the ability of single biomarkers to predict ICU delirium is limited due to the multifactorial nature of its pathogenesis and the presence of various confounding factors (113). Our results reflect these challenges, as evidenced by the modest discriminative performance of CDT (AUROC 0.75) and the Anttila Index (AUROC 0.74). While these AUROC values do not indicate exceptional discrimination, they do suggest a meaningful capacity to identify patients at a higher risk for delirium. Thus, despite the complexities of delirium's pathogenesis, our findings remain

clinically relevant for risk identification. Secondly, the statistical modelling of delirium in the ICU is complicated by multiple confounders. To address this, we selected covariates a priori, based on clinical expertise and evidence. For instance, we used the SOFA score—a well-validated measure of illness severity—as a covariate, instead of admission diagnosis, given its robust association with delirium development (86). Additionally, other established risk factors, such as mechanical ventilation, age, and serum albumin (a strong predictor of ICU delirium not included in SOFA), were incorporated to balance the model's complexity and maintain interpretability (86,107). This approach helped address issues related to collinearity and redundancy.

(ii) The single-centre, single-ICU design of our study restricted the cohort to critically ill medical patients, which restricts the generalizability of our findings, particularly for surgical patients. However, it is worth noting that surgery, especially emergency surgery, is a known precipitating factor for delirium (114). Therefore, focusing on non-surgical patients, who were not exposed to these risk factors, may have minimized potential biases.

(ii) Our study did not categorize delirium psychomotor subtypes, such as those defined by the Delirium Motor Subtype Scale (DMSS) (115). However, recent suggestions argue that moving away from psychomotor subtype classifications could enable the identification of more specific subphenotypes of delirium (17). This approach, linking precipitating factors to the syndrome, could better facilitate the identification of distinct subphenotypes of patients, which was a key objective of our study.

Conclusion for the first project

CDT, and particularly the derived Anttila Index, have been shown to be independently associated with the development of delirium, prolonged delirium duration, and increased mortality in critically ill patients. As such, elevated levels of CDT and the Anttila Index may serve not only as markers of chronic heavy alcohol consumption but also as potential tools for identifying patients at high risk for ICU delirium. These findings highlight the need for future interventional trials aimed at identifying high-risk patients and implementing strategies to prevent ICU delirium in critical care settings.

Second project- Sex-Specific Differences in Short-Term Mortality After ICU Delirium

This study revealed that women have a notably higher risk of short-term mortality after ICU delirium compared to men. The literature on sex-specific differences in delirium is limited and often contradictory (103). While some studies indicate that male sex increases the risk of ICU delirium, others suggest a higher risk in women (86). The effect of sex on short-term mortality in ICU patients is also unclear, with some research pointing to increased risk-adjusted ICU mortality in women, while others find no significant difference (91,110). Despite these findings, the relationship between sex and outcomes in ICU delirium remains insufficiently studied.

Hence, current guidelines do not explicitly address sex-specific differences in the prevention or management of ICU-delirium, despite the growing recognition of sex differences in critical care literature (41). To the best of our knowledge, our study is the first to specifically assess sex-related differences in short-term mortality among ICU-delirium patients.

These findings herein provide new insights but of course raise important questions:

a.) **Why do women with ICU-delirium experience higher mortality?**

The higher mortality risk observed in women with ICU delirium may be attributed to differences in recovery or deterioration pathways between men and women. Factors such as genetic predisposition, hormonal influences, and immune responses to acute brain dysfunction likely contribute to these differences. Additionally, emerging research suggests that women in the ICU may receive less aggressive treatment despite experiencing greater illness severity (103), and our findings could reflect this treatment gap.

b.) **What are the implications of identifying a mortality difference between male and female patients with delirium?**

From a personalized medicine perspective, these findings emphasize the need to prioritize female patients with ICU delirium in both routine clinical care and future interventional studies, particularly since women have historically been underrepresented in such trials (79). While critical care research has made strides in understanding sex-specific differences in conditions like sepsis and cardiogenic shock

(103), further investigation is crucial to fully understand the mechanisms behind the higher mortality risk in women with ICU delirium.

Strengths and limitations

The strengths of our study include the use of a large, publicly accessible dataset and the provision of detailed methodology and code, which enables the reproduction and extension of our findings. The ample sample size allowed for adjustment across a broad range of covariates, enhancing the robustness of our results. Additionally, by applying propensity scores within a causal inference framework, we aimed to reach the highest possible level of certainty with observational data (111).

However, also when interpreting the data of this second project, several limitations warrant consideration.

We were unable to conduct a subgroup analysis based on delirium subtypes, which may influence short-term mortality and warrants further exploration. Moreover, this study represents a post hoc analysis of data from a single-center observational study, which limits the generalizability of our results. Despite our use of strict propensity score matching, the possibility of residual confounding cannot be ruled out. Additionally, we were not able to assess potential sex-related biases in delirium evaluation, which could have influenced our findings. As such, further replication and validation of these results in diverse cohorts are essential.

Conclusions for the second project

Our findings indicate a higher risk of short-term mortality in female patients after ICU-delirium. These findings underscore the importance of considering sex-specific differences in delirium management and research. Future studies should aim to replicate these results, investigate the underlying mechanisms, and explore how personalized care can address potential differences in the needs of female and male ICU patients with delirium.

Relation between the projects

Gender disparities exist in critical care, and it's particularly interesting that these differences are examined in more detail in some areas of the critical care literature than in others. For instance, we know that following return of spontaneous circulation, women are far less likely

to receive percutaneous coronary intervention in the context of post resuscitation management (116), but we do not know if women are less (or more) likely to receive preventive measures for delirium.

Researchers should therefore be encouraged to explore their datasets for gender and sex-related differences. In the context of personalized critical care medicine, it seems even more important to examine sex differences from the beginning to better tailor treatments to individual patients.

Recent effort led to more journals promoting sex and gender equity in research, with endeavors like the Sex and Gender Equity in Research (SAGER) Guidelines highlighting these initiatives (117).

Encouraged by this movement for greater inclusivity, we analyzed our dataset—specifically the subgroup of delirium-positive patients (n=121)—in an post hoc exploratory analysis. Mainly with the purpose of internal quality assurance, we aimed to assess whether any sex disparities existed, particularly regarding outcomes.

We observed a subtle signal (restricted by the small sample size to be statistically significant), suggesting higher mortality in female patients with and after delirium, even after adjusting for illness severity (**Figure 10**).

(One must note at this point, that illness severity scores themselves often fail to account for sex and gender differences, as many do not incorporate biological sex as a variable (118).)

Figure 10. Adjusted survival probabilities of female and male individuals with delirium in the dataset from the first project (unpublished results)

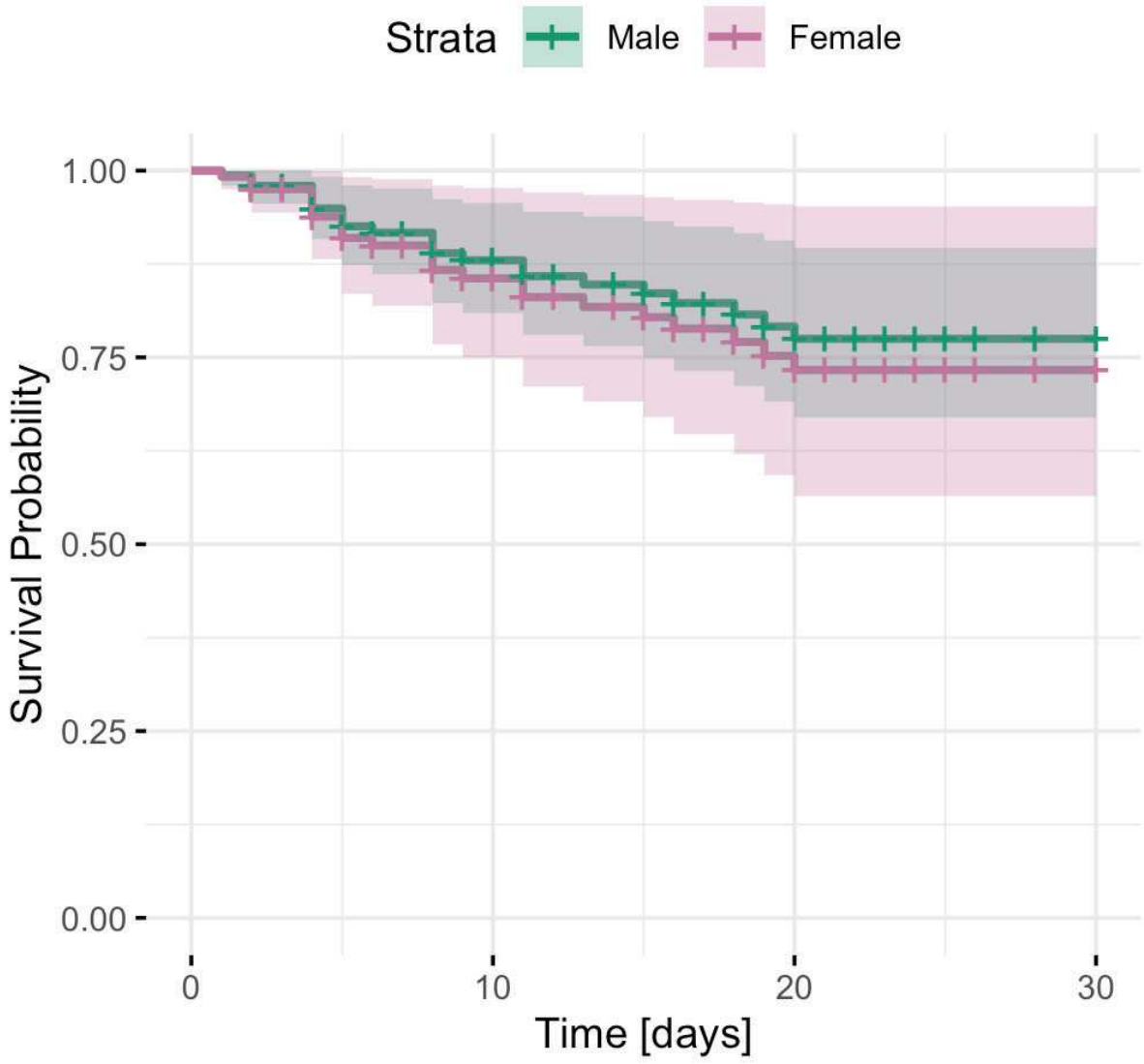


Figure 10. Adjusted survival probabilities of female and male individuals with delirium in the dataset from the first project. SAPSII-adjusted survival probabilities of patients who developed Delirium in the cohort from the first project (n=121) are displayed, with males in green, and females in red. (unpublished data)

This subtle trend made us curious if this was just a result of pure chance, or if this signal was reproducible in a different cohort, capable of detecting smaller effect sizes with more statistical confidence.

This is how the first project led to the second project, whose implications are already discussed above.

Conclusion

Altogether in the first project of this thesis, it could be shown that alcohol consumption related biomarkers CDT and the derived Anttila-Index may be suitable to predict delirium in critically ill patients, with the potential implication of detecting a specific delirium endotype that may benefit from treatment with benzodiazepines, which must be tested in future prospective trials. Moreover, in the second project, we could detect a signal for higher short-term mortality in female patients after ICU-delirium in an extensive and openly available dataset of critically ill patients, providing a highly reproducible analysis and thereby promoting the open science movement. This finding should pave the way for further replication and validation and of utmost importance for explorations of reasons. This thesis should reencourage clinicians as well as scientists to integrate sex and gender related differences in daily clinical routine at the bedside evaluation as well as in research design, as it most likely reflects that female and male patients respond differently to critical illness and current therapies. With the rise of personalized critical care medicine, where the goal is to deliver individually tailored care, sex disparities appear to play a particularly significant role.

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