Advances in Delirium Phenotyping: The Old and The New

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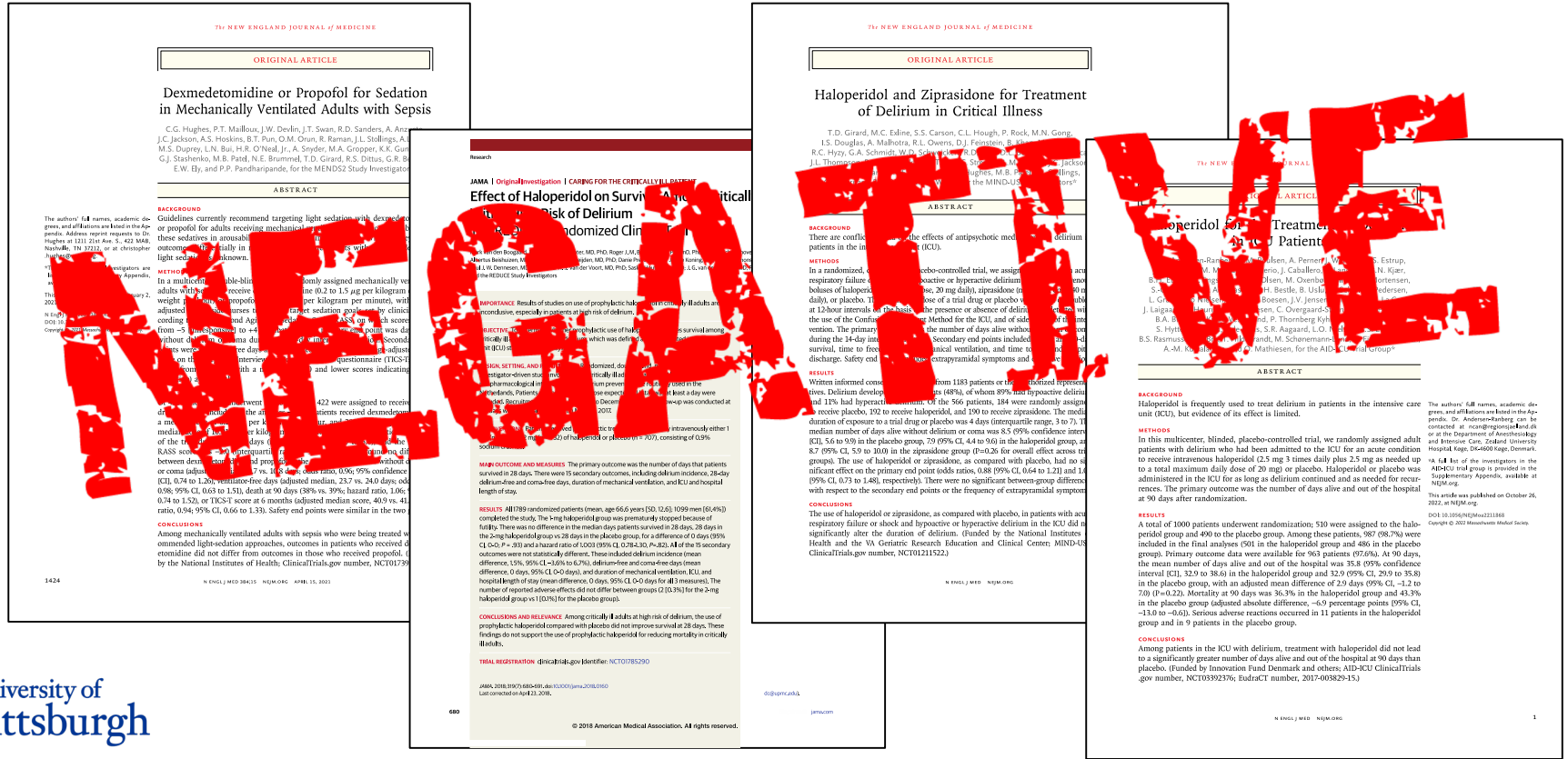
What's Ahead?

1. Pharmacologic Management of Delirium in the ICU
2. Established Approaches in Delirium Heterogeneity
3. New Approaches in Delirium Heterogeneity

Pharmacologic Management of Delirium in the ICU

Clinical Trials to Identify Pharmacologic Treatments for Delirium



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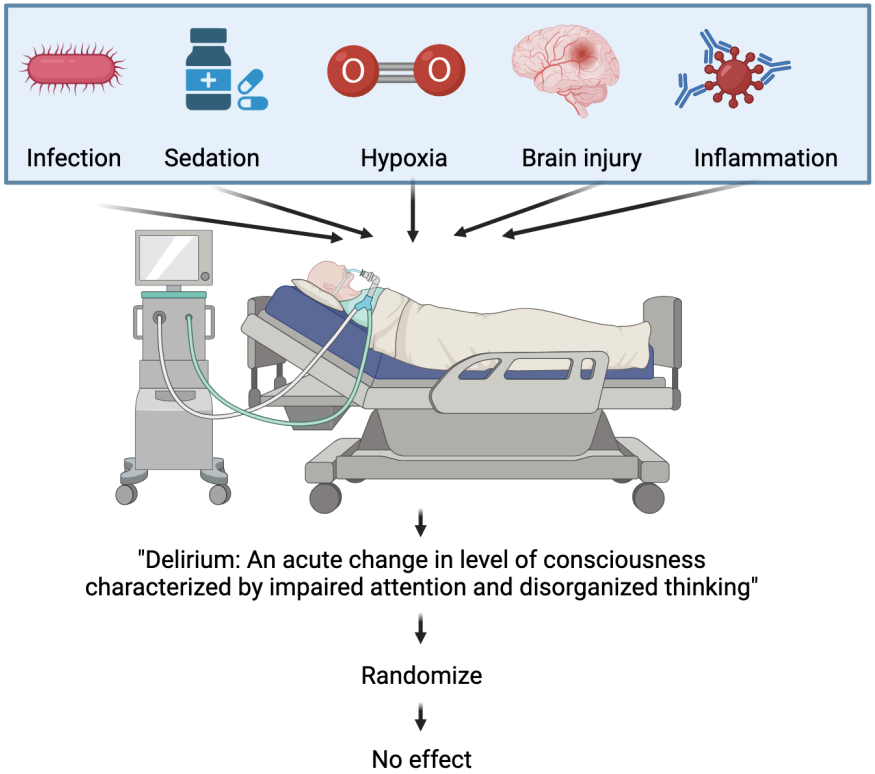
Current Approach to Delirium Clinical Trials



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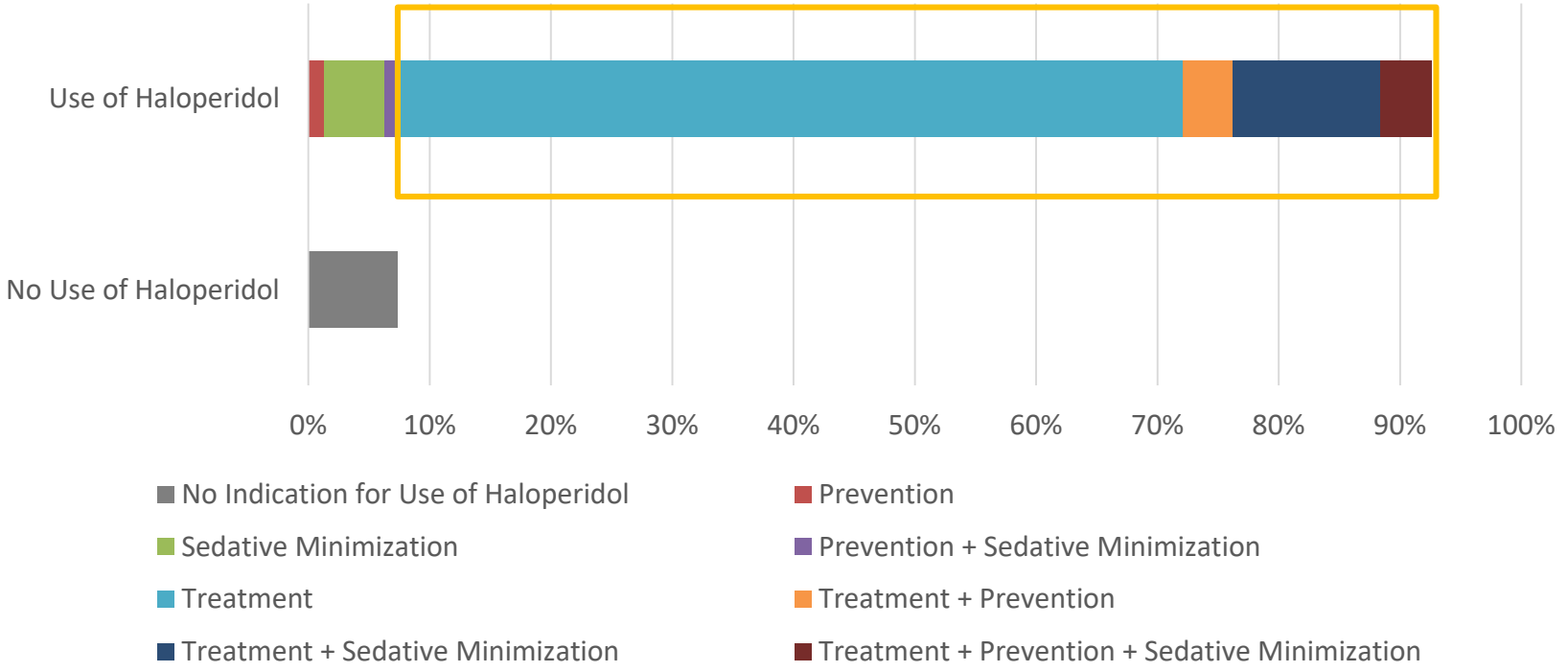
Potter KM, Prendergast NT, Boyd JG. Crit Care Med 2024;52(8):1285-1294.

Clinicians Tend to Use Medications for Delirium Management



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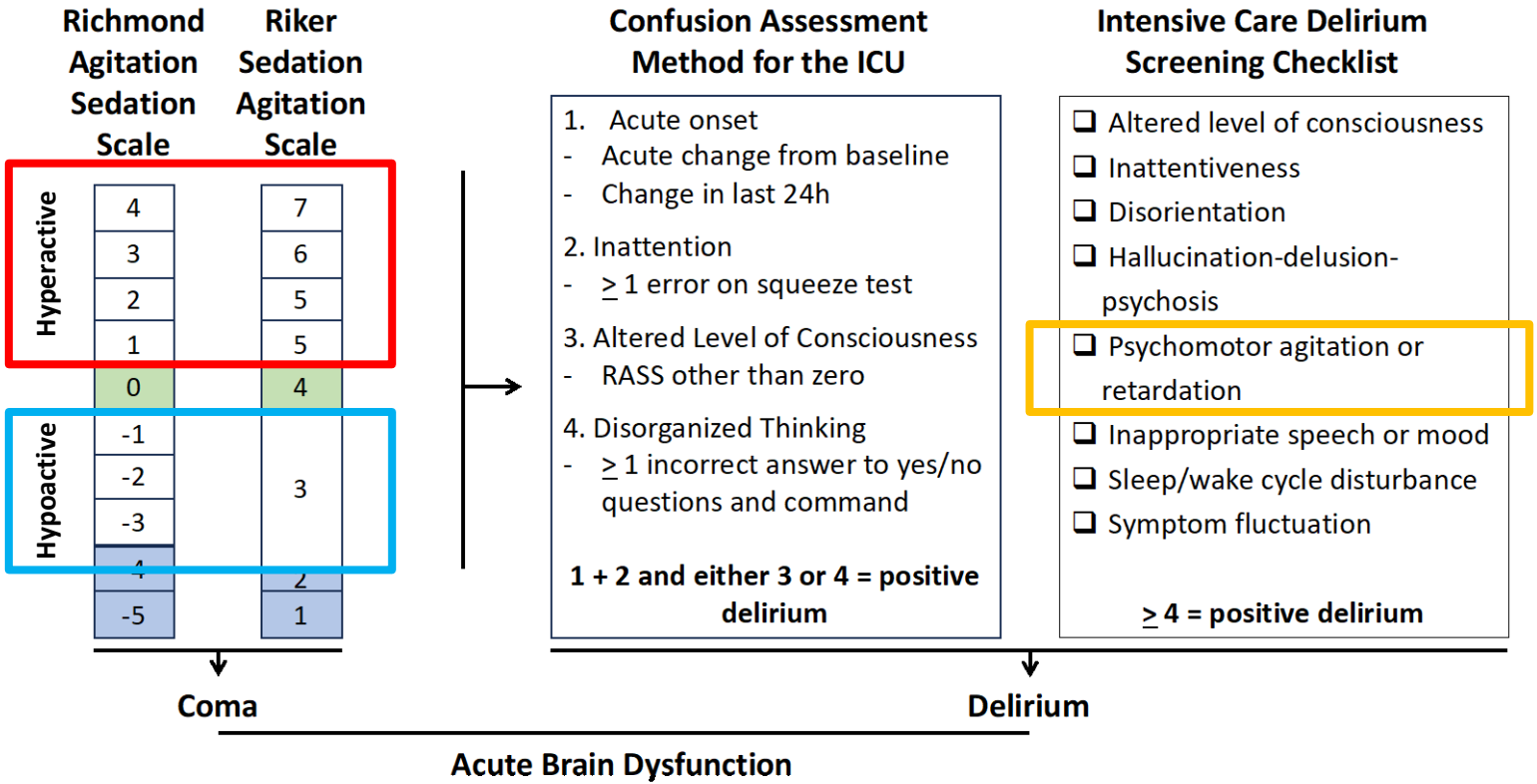
Morandi A et al. Crit Care Med, 2017; 45(11): e1111-e1122

Established Approaches in Delirium Heterogeneity



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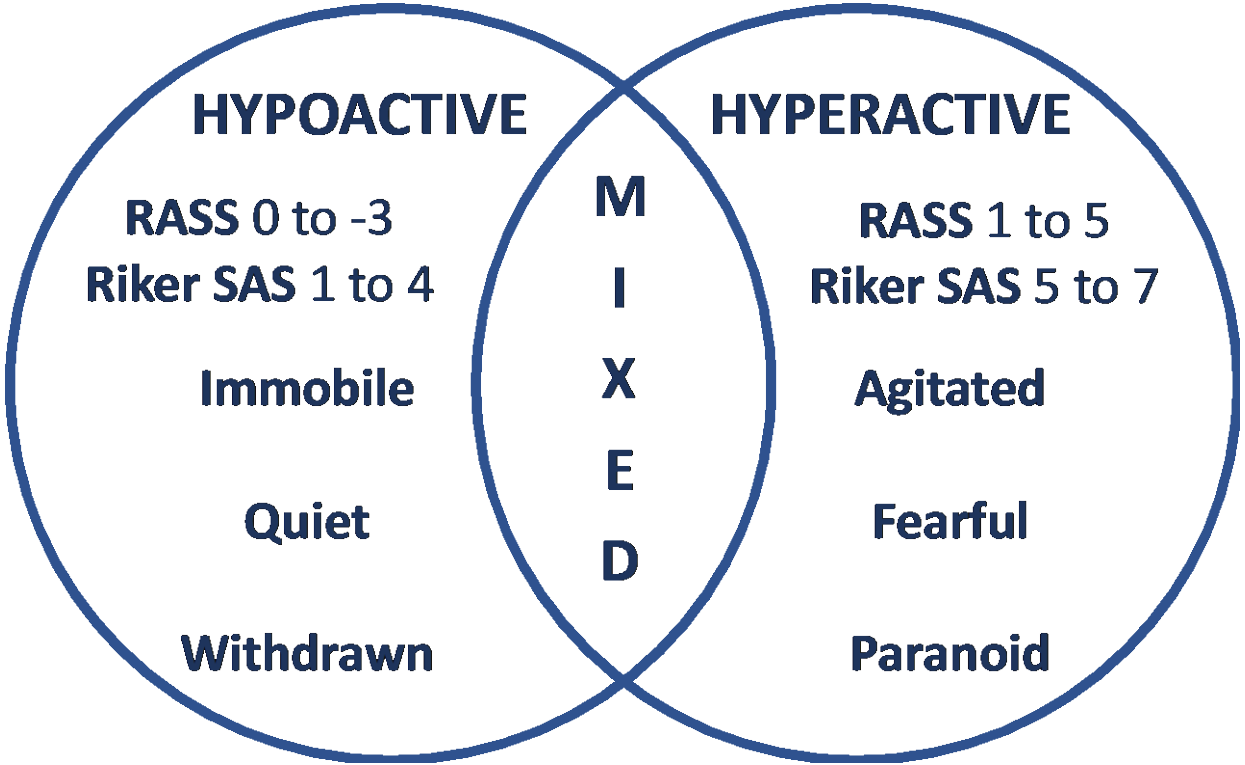
Psychomotor Delirium Subtypes



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Peterson J, et al. J Am Geriatr Soc 2006;54(3):479-84

Psychomotor Delirium Subtypes

Smit *et al. Journal of Intensive Care* (2022) 10:54
https://doi.org/10.1186/s40560-022-00644-1

RESEARCH Open Access

Prognostic significance of delirium subtypes in critically ill medical and surgical patients: a secondary analysis of a prospective multicenter study

Lisa Smit[1*], Eveline J. A. Wiegers[2], Zoran Trogrlic[1], Wim J. R. Rietdijk[3], Diederik Gommers[1], Erwin Ista[4,5] and Mathieu van der Jagt[1]

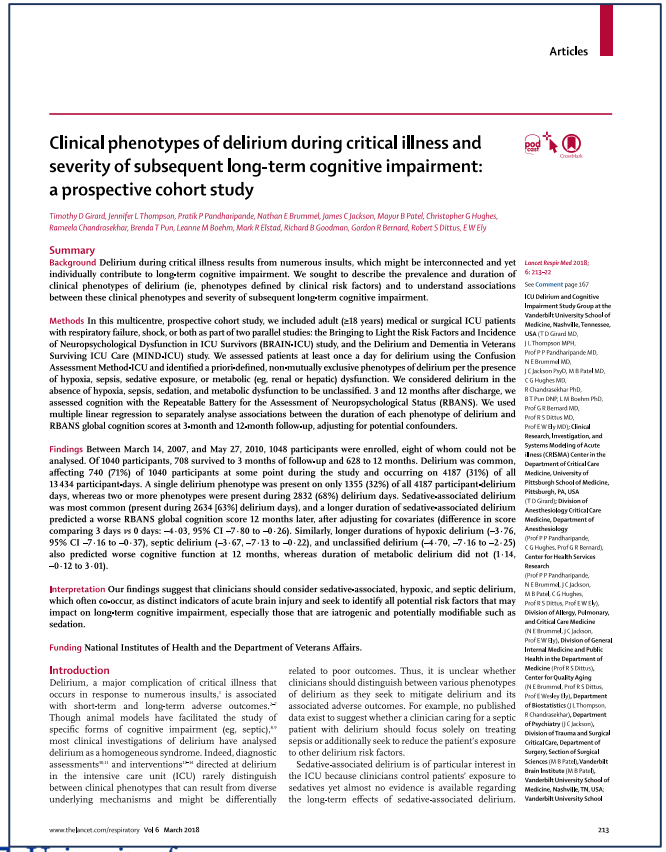
Abstract

Background: The prognostic implication of delirium subtypes in critically ill medical and surgical patients is scarcely investigated. The objective was to determine how delirium subtypes are associated with hospital mortality and other clinical outcomes.

Methods: We performed a secondary analysis on data from a prospective multicenter study aimed at implementation of delirium-oriented measures, conducted between 2012 and 2015 in The Netherlands. We included adults (≥ 18 years) admitted to the medical or surgical intensive care unit (ICU). Exclusion criteria were neurological admission diagnosis, persistent coma or ICU readmissions. Delirium was assessed using the Confusion Assessment Method-ICU or Intensive Care Delirium Screening Checklist, and delirium subtypes (hypoactive, hyperactive, or mixed) were classified using the Richmond Agitation–Sedation Scale. The main outcome was hospital mortality. Secondary outcomes were ICU mortality, ICU length of stay, coma, mechanical ventilation, and use of antipsychotics, sedatives, benzodiazepines and opioids.

Results: Delirium occurred in 381 (24.4%) of 1564 patients (52.5% hypoactive, 39.1% mixed, 7.3% hyperactive). After case-mix adjustment, patients with mixed delirium had higher hospital mortality than non-delirious patients (OR 3.09, 95%CI 1.79–5.33, p < 0.001), whereas hypoactive patients did not (OR 1.34, 95%CI 0.71–2.55, p = 0.37). Similar results

Clinical Risk Factor-Based Delirium Subtypes



Articles

Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: a prospective cohort study

Timothy D Girard, Jennifer L Thompson, Pratik P Pandharipande, Nathan E Brummel, James C Jackson, Mayur B Patel, Christopher G Hughes, Rameela Chandrasekhar, Brenda T Pun, Leanne M Boehm, Mark R Elstad, Richard B Goodman, Gordon R Bernard, Robert S Dittus, E W Ely

Summary

Background Delirium during critical illness results from numerous insults, which might be interconnected and yet individually contribute to long-term cognitive impairment. We sought to describe the prevalence and duration of clinical phenotypes of delirium (ie, phenotypes defined by clinical risk factors) and to understand associations between these clinical phenotypes and severity of subsequent long-term cognitive impairment.

Methods In this multicentre, prospective cohort study, we included adult (≥18 years) medical or surgical ICU patients with respiratory failure, shock, or both as part of two parallel studies: the Bringing to Light the Risk Factors and Incidence of Neuropsychological Dysfunction in ICU Survivors (BRAIN-ICU) study, and the Delirium and Dementia in Veterans Surviving ICU Care (MIND-ICU) study. We assessed patients at least once a day for delirium using the Confusion Assessment Method-ICU and identified a priori-defined, non-mutually exclusive phenotypes of delirium per the presence of hypoxia, sepsis, sedative exposure, or metabolic (eg, renal or hepatic) dysfunction. We considered delirium in the absence of hypoxia, sepsis, sedation, and metabolic dysfunction to be unclassified. 3 and 12 months after discharge, we assessed cognition with the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). We used multiple linear regression to separately analyse associations between the duration of each phenotype of delirium and RBANS global cognition scores at 3-month and 12-month follow-up, adjusting for potential confounders.

Findings Between March 14, 2007, and May 27, 2010, 1048 participants were enrolled, eight of whom could not be analysed. Of 1040 participants, 708 survived to 3 months of follow-up and 628 to 12 months. Delirium was common, affecting 740 (71%) of 1040 participants at some point during the study and occurring on 4187 (31%) of all 13 434 participant-days. A single delirium phenotype was present on only 1355 (32%) of all 4187 participant-delirium days, whereas two or more phenotypes were present during 2832 (68%) delirium days. Sedative-associated delirium was most common (present during 2634 [63%] delirium days), and a longer duration of sedative-associated delirium predicted a worse RBANS global cognition score 12 months later, after adjusting for covariates (difference in score comparing 3 days *vs* 0 days: −4·03, 95% CI −7·80 to −0·26). Similarly, longer durations of hypoxic delirium (−3·76, 95% CI −7·16 to −0·37), septic delirium (−3·67, −7·13 to −0·22), and unclassified delirium (−4·70, −7·16 to −2·25) also predicted worse cognitive function at 12 months, whereas duration of metabolic delirium did not (1·14, −0·12 to 3·01).

Interpretation Our findings suggest that clinicians should consider sedative-associated, hypoxic, and septic delirium, which often co-occur, as distinct indicators of acute brain injury and seek to identify all potential risk factors that may impact on long-term cognitive impairment, especially those that are iatrogenic and potentially modifiable such as sedation.

Funding National Institutes of Health and the Department of Veterans Affairs.

Introduction

Delirium, a major complication of critical illness that occurs in response to numerous insults,[1] is associated with short-term and long-term adverse outcomes.[2–4] Though animal models have facilitated the study of specific forms of cognitive impairment (eg, septic),[5,6] most clinical investigations of delirium have analysed delirium as a homogeneous syndrome. Indeed, diagnostic assessments[7,8] and interventions[9–11] directed at delirium in the intensive care unit (ICU) rarely distinguish between clinical phenotypes that can result from diverse underlying mechanisms and might be differentially related to poor outcomes. Thus, it is unclear whether clinicians should distinguish between various phenotypes of delirium as they seek to mitigate delirium and its associated adverse outcomes. For example, no published data exist to suggest whether a clinician caring for a septic patient with delirium should focus solely on treating sepsis or additionally seek to reduce the patient's exposure to other delirium risk factors.

Sedative-associated delirium is of particular interest in the ICU because clinicians control patients' exposure to sedatives yet almost no evidence is available regarding the long-term effects of sedative-associated delirium.

Lancet Respir Med 2018; 6: 213–22

See Comment page 167

ICU Delirium and Cognitive Impairment Study Group at the Vanderbilt University School of Medicine, Nashville, Tennessee, USA (T D Girard MD, J L Thompson MPH, Prof P P Pandharipande MD, N E Brummel MD, J C Jackson PsyD, M B Patel MD, C G Hughes MD, R Chandrasekhar PhD, B T Pun DNP, L M Boehm PhD, Prof G R Bernard MD, Prof R S Dittus MD, Prof E W Ely MD); **Clinical Research, Investigation, and Systems Modeling of Acute Illness (CRISMA) Center in the Department of Critical Care Medicine, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA** (T D Girard); **Division of Anesthesiology Critical Care Medicine, Department of Anesthesiology** (Prof P P Pandharipande, C G Hughes, Prof G R Bernard), **Center for Health Services Research** (Prof P P Pandharipande, N E Brummel, J C Jackson, M B Patel, C G Hughes, Prof R S Dittus, Prof E W Ely), **Division of Allergy, Pulmonary, and Critical Care Medicine** (N E Brummel, J C Jackson, Prof E W Ely), **Division of General Internal Medicine and Public Health in the Department of Medicine** (Prof R S Dittus), **Center for Quality Aging** (N E Brummel, Prof R S Dittus, Prof E Wesley Ely), **Department of Biostatistics** (J L Thompson, R Chandrasekhar), **Department of Psychiatry** (J C Jackson), **Division of Trauma and Surgical Critical Care, Department of Surgery, Section of Surgical Sciences** (M B Patel), **Vanderbilt Brain Institute** (M B Patel), **Vanderbilt University School of Medicine, Nashville, TN, USA**; **Vanderbilt University School**

Hypoxic

- Hypoxemia (2+ 15-minute intervals where SpO2 < 90%)
- Shock (Lactate > 4.4 mmol or 2+ 15-minute intervals where MAP < 65mmHg)

Septic

- Known or suspected infection ***AND***
- 2+ systemic inflammatory response syndrome (SIRS) criteria

Metabolic

- Blood urea nitrogen > 17.85 mmol/L
- Glucose < 2.5 mmol/L
- INR > 2.5 ***AND*** ALT or AST > 200 U/L
- Sodium < 120 mmol/L or > 160 mmol/L

Sedative-Associated

- Receipt of benzodiazepine ***OR*** propofol ***OR*** opioid ***OR*** dexmedetomidine

Unclassified

- None of the above

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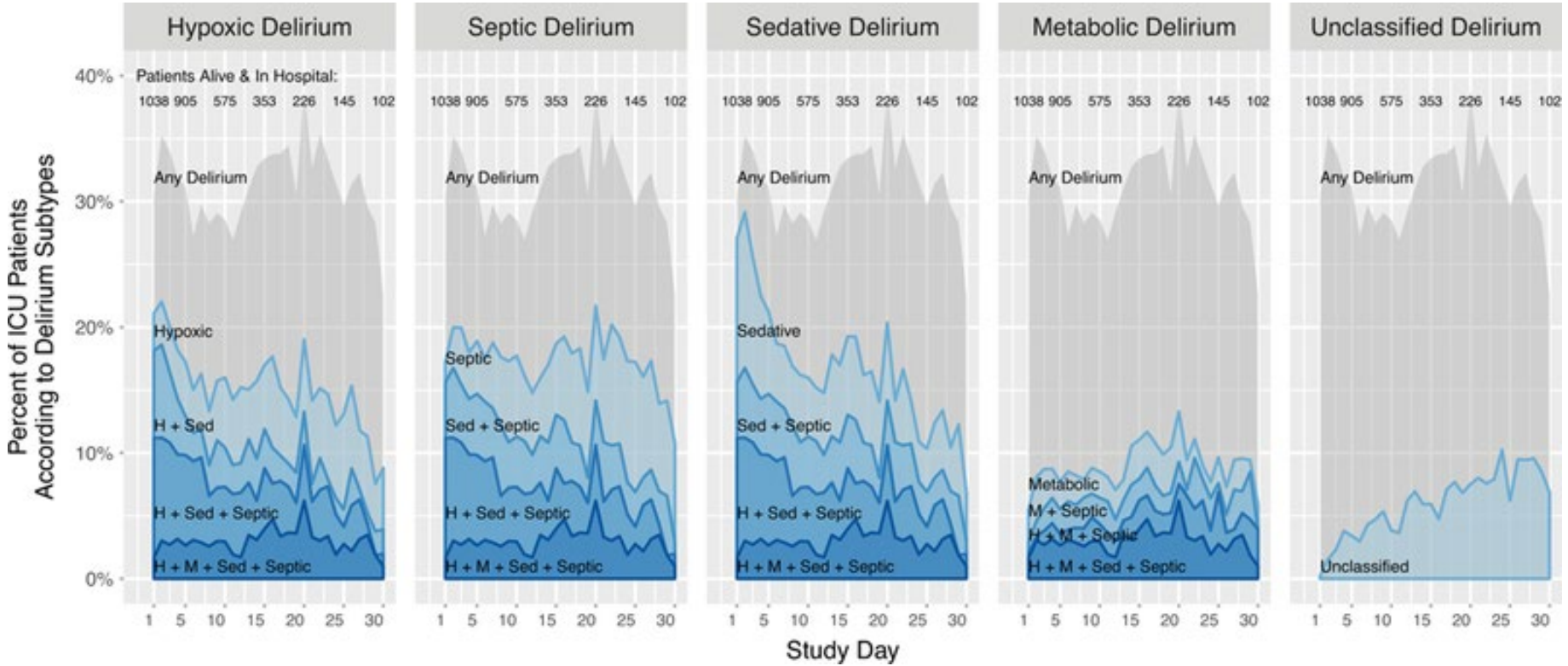
Girard TD, et al. Lancet Respir Med 2018;6:213-222

Prevalence of Risk-Factor Based Delirium Subtypes



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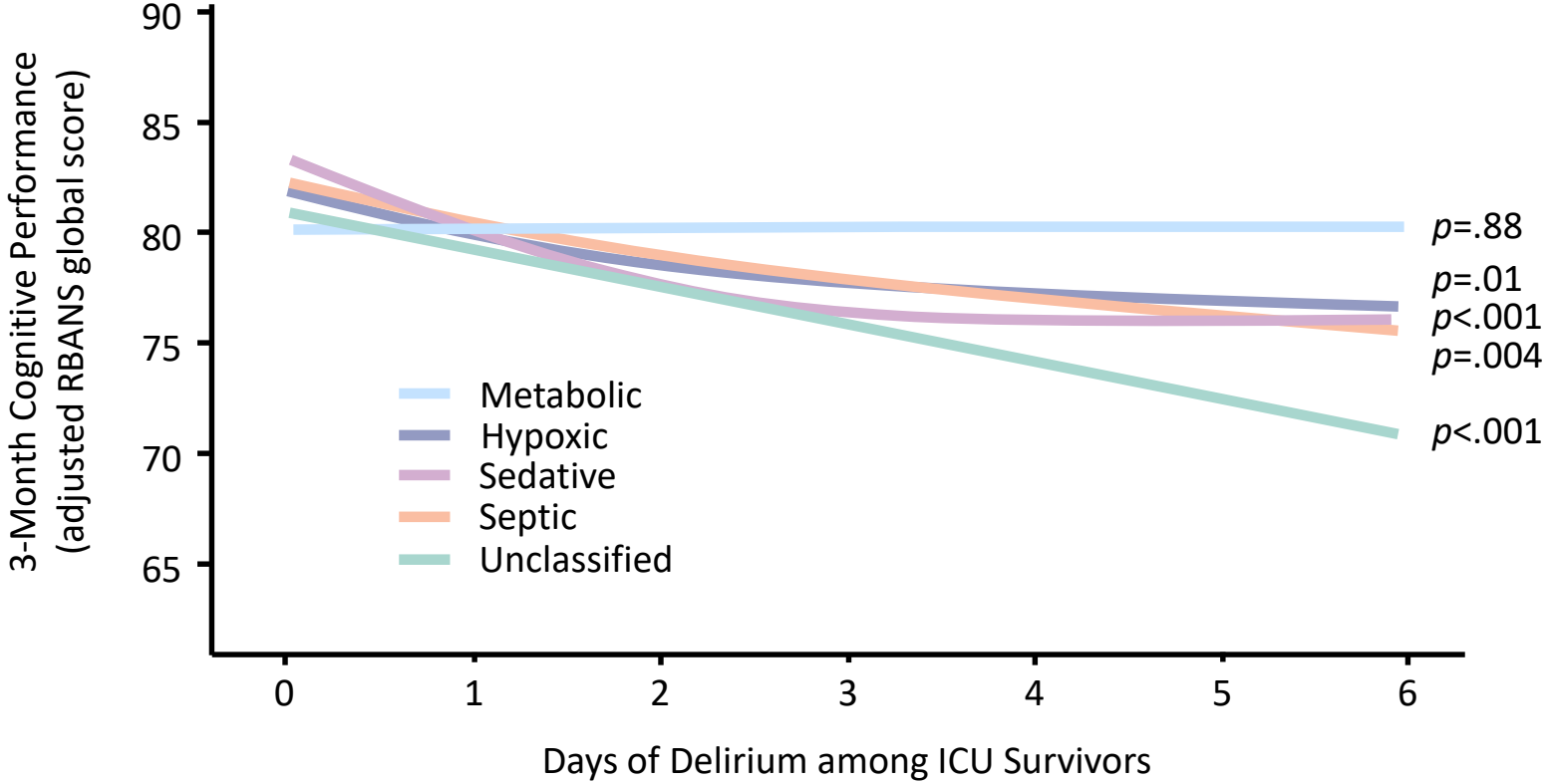
Girard TD, et al. Lancet Respir Med 2018;6:213-222

Risk-Factor Based Delirium Subtypes and 3-Month Cognition



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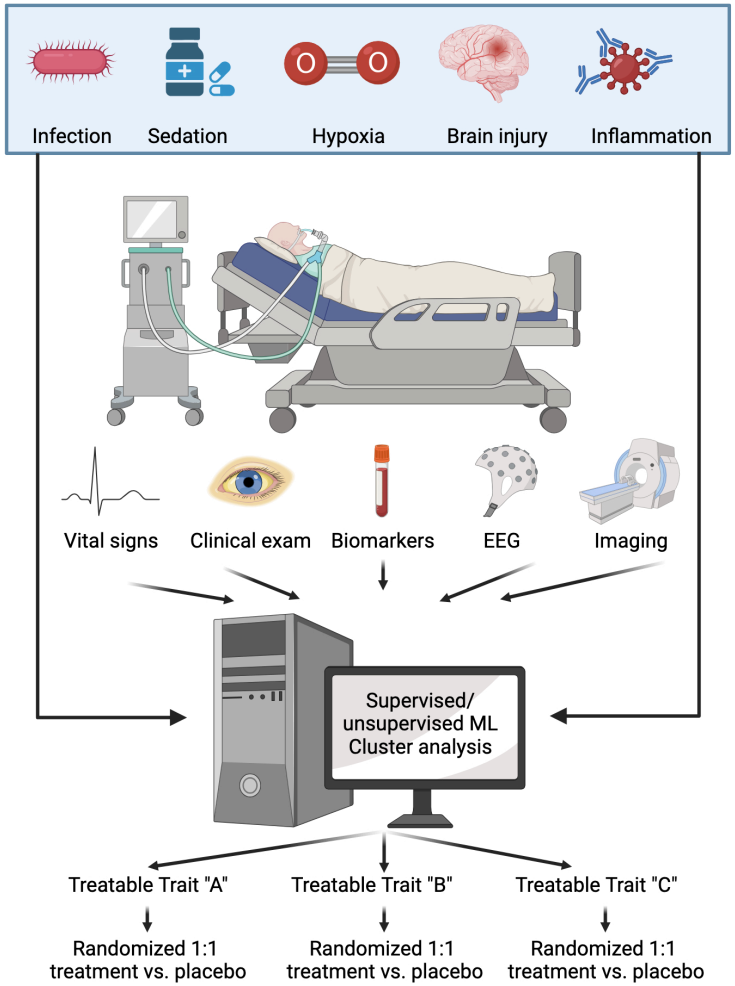
Girard TD, et al. Lancet Respir Med 2018;6:213-222

New Approaches in Delirium Heterogeneity

Potential New Approaches to Trials



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Potter KM, Prendergast NT, Boyd JG. Crit Care Med 2024;52(8):1285-1294.

Articles

Data-derived subtypes of delirium during critical illness

Kelly M. Potter,[a,*] Jason N. Kennedy,[b] Chukwudi Onyemekwu,[b] Niall T. Prendergast,[b] Pratik P. Pandharipande,[c,e] E Wesley Ely,[d,e,f] Christopher Seymour,[g] and Timothy D. Girard[c,e]

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Summary

Background To understand delirium heterogeneity, prior work relied on psychomotor symptoms or risk factors to identify subtypes. Data-driven approaches have used machine learning to identify biologically plausible, treatment-responsive subtypes of other acute illnesses but have not been used to examine delirium.

Methods We conducted a secondary analysis of a large, multicenter prospective cohort study involving adults in medical or surgical ICUs with respiratory failure or shock who experienced delirium per the Confusion Assessment Method for the ICU. We used data collected before delirium diagnosis in an unsupervised latent class model to identify delirium subtypes and then compared demographics, clinical characteristics, and outcomes between subtypes in the final model.

Findings The 731 patients who developed delirium during critical illness had a median age of 63 [IQR, 54–72] years, a median Sequential Organ Failure Assessment score of 8.0 [6.0–11.0] and 613 [83.4%] were mechanically ventilated at delirium identification. A four-class model best fit the data with 50% of patients in subtype (ST) 1, 18% in subtype 2, 17% in subtype 3, and 14% in subtype 4. Subtype 2—which had more shock and kidney impairment—had the highest mortality (33% [ST2] vs. 17% [ST1], 25% [ST3], and 17% [ST4], p = 0.003). Subtype 4—which received more benzodiazepines and opioids—had the longest duration of delirium (6 days [ST4] vs. 3 [ST1], 4 [ST2], and 3 days [ST3], p < 0.001) and coma (4 days [ST4] vs. 2 [ST1], 1 [ST2], and 2 days [ST3], p < 0.001). Each of the four data-derived delirium subtypes was observed within previously identified psychomotor and risk factor-based delirium subtypes. Clinically significant cognitive impairment affected all subtypes at follow-up, but its severity did not differ by subtype (3-month, p = 0.26; 12-month, p = 0.80).

Interpretation The four data-derived delirium subtypes identified in this study should now be validated in independent cohorts, examined for differential treatment effects in trials, and inform mechanistic work evaluating treatment targets.

Funding National Institutes of Health (T32HL007820, R01AG027472).

Keywords: Delirium; Subtypes; Heterogeneity; Latent class analysis

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2024;100: 104942
Published Online 1 January 2024
https://doi.org/10.1016/j.ebiom.2023.104942

Introduction

Delirium is a common and serious syndrome of acute brain dysfunction that affects up to half of critically ill patients.[1] Characterized by inattention, disorganized thinking, altered level of consciousness, and fluctuating symptoms, delirium is associated with numerous adverse outcomes, including prolonged stays,[2] higher mortality,[3] and cognitive impairment that can persist long after critical illness and may never resolve.[4] Despite this, evidence-based treatments for delirium are scarce.

Clinical trials of pharmacologic interventions have used a "one-size-fits-all" approach that treats delirium as

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Data-Derived Subtypes of Delirium

- Identify data-derived delirium subtypes
- Compare with delirium subtypes derived through other methods
- Compare short- and long-term outcomes

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Methods

- Secondary analysis of BRAIN-ICU & MIND-ICU prospective cohort studies

- Latent class analysis
  - Data from first delirium identification (CAM-ICU)
  - Model variables: Baseline, clinical, and treatment characteristics
  - Primary fit evaluation: Bayesian Information Criterion elbow method

- Comparison with:
  - Clinical subtypes
  - Psychomotor subtypes
  - Acuity subtypes

- Unadjusted comparisons of short- and long-term outcomes

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Results

Patient Characteristics

Characteristic	Delirious BRAIN-ICU Cohort (n=731)
Years of age	63.3 (53.8, 72.2)
Race	
White	662 (90.6)
Black or African American	63 (8.6)
Asian	2 (2.7)
Native Hawaiian or Pacific Islander	1 (0.1)
Other race	3 (0.4)
Female	302 (41.3)
BMI	29.0 (24.4, 34.8)
Charlson Comorbidity Index	2 (1, 4)
Years of education	12 (12, 14)
SOFA score	8 (6, 11)
Days of mechanical ventilation	2 (1, 3)

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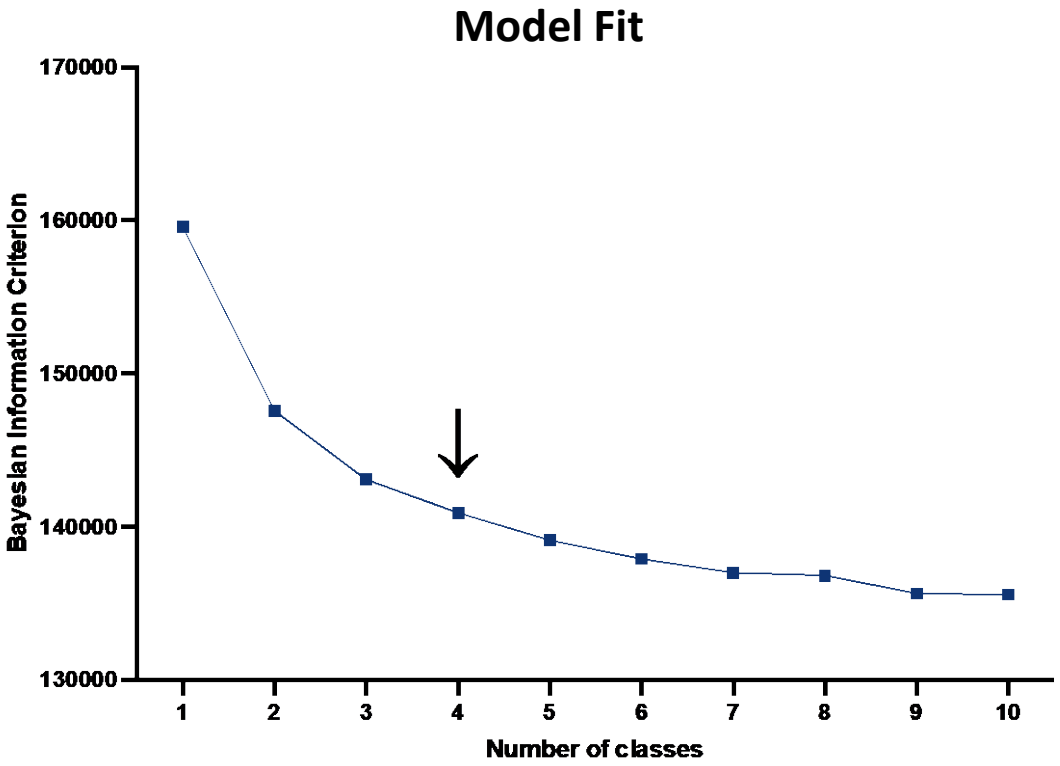
Data are presented as number (percentage) or median (25^{th}, 75^{th} percentile)

Latent Class Analysis: Model Fit

- 1 through 10 hypothesized classes
- Diminishing returns after *k*=4 classes
- Entropy R^2 = 0.97
- Class err = 0.01



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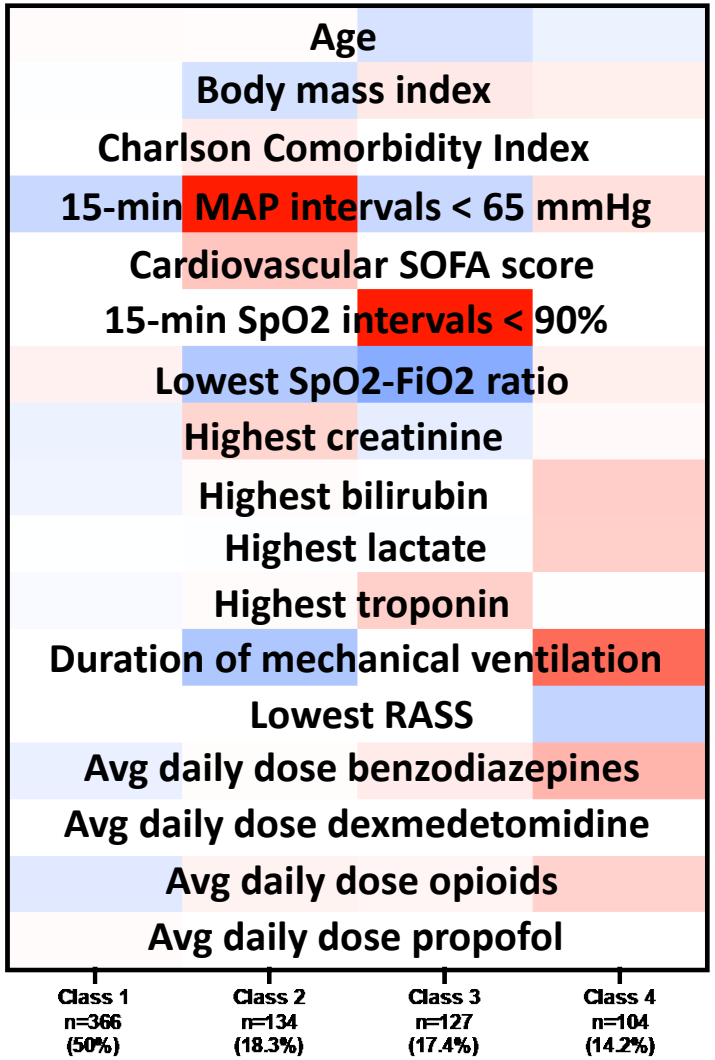
Clinical Profile Among Classes



Class 1:

- More propofol, fewer opioids
- Higher SpO2

Class 2:

- More hypotensive
- Worse kidney impairment

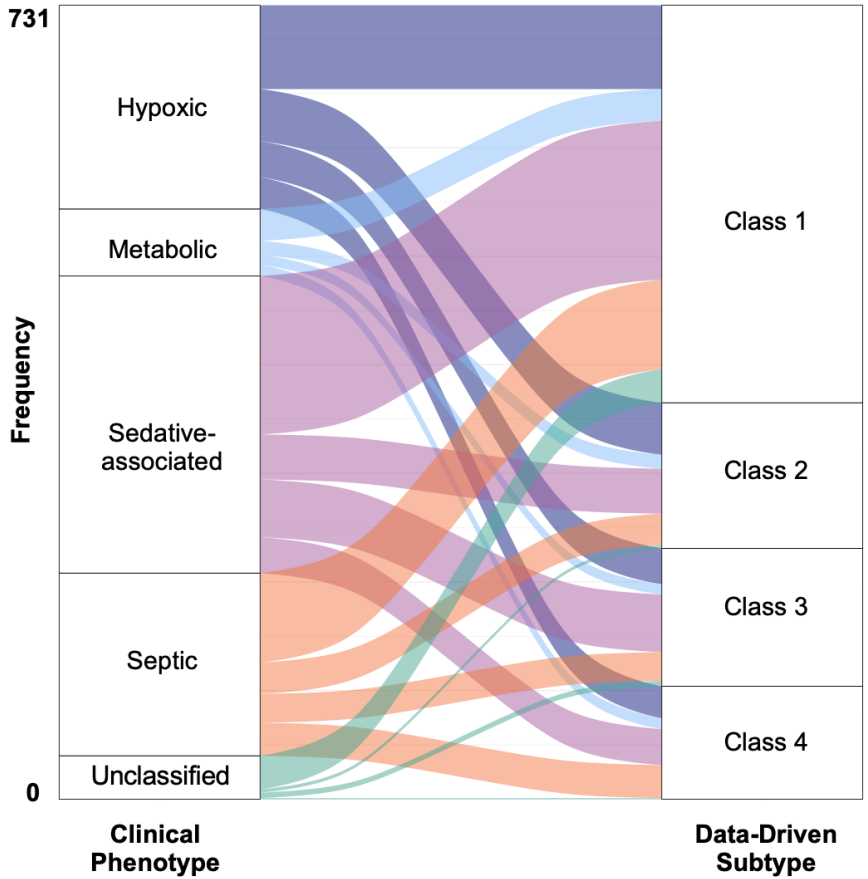
Class 3:

- More hypoxic
- Higher troponin
- Younger, higher BMI

Class 4:

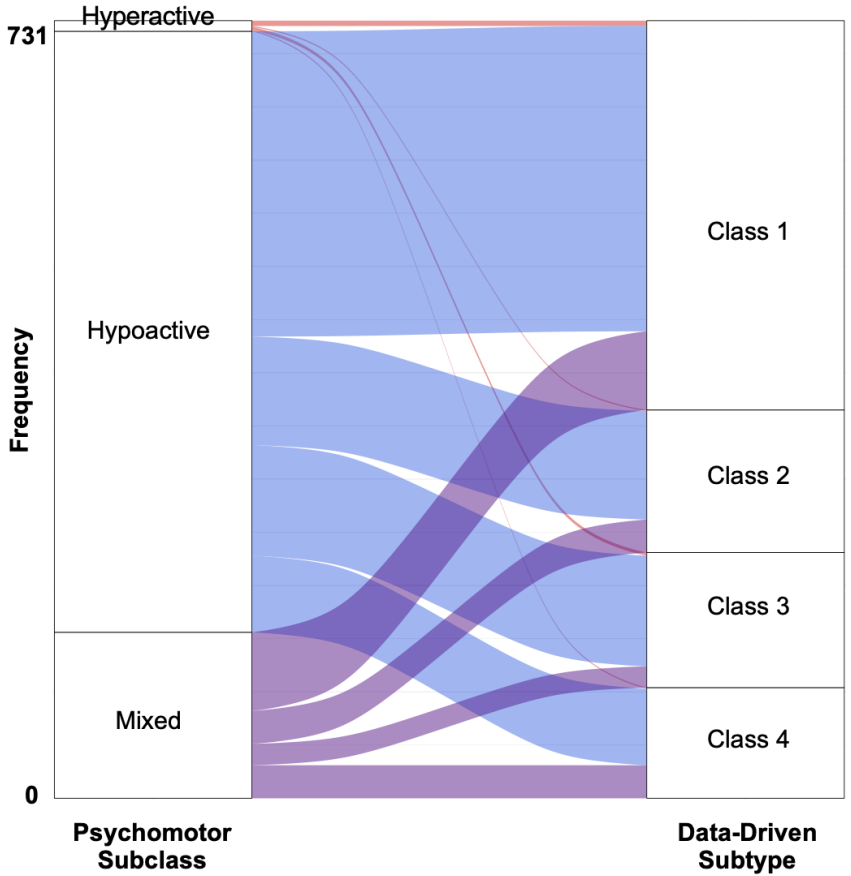
- More ventilator days pre-delirium
- Deeper sedation
- More benzodiazepines, opioids
- Worse liver function, lactate

Comparison with Risk Factor-Based Subtypes



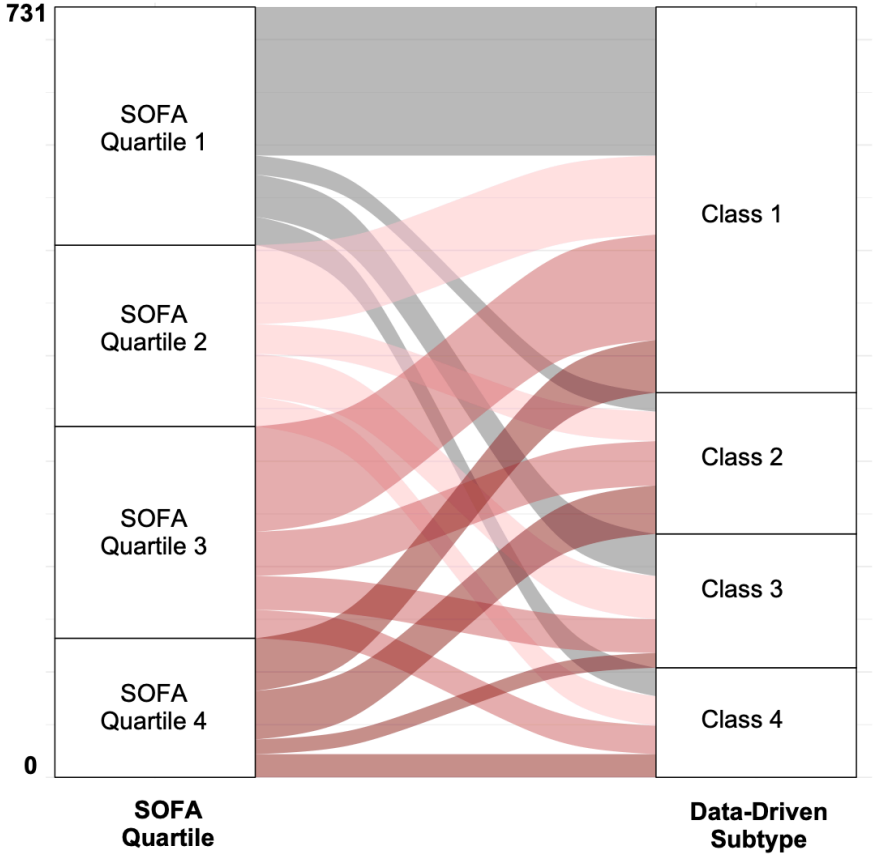
No meaningful representation of risk factor-based delirium subtypes in the data-driven delirium subtypes

Comparison with Psychomotor Subtypes



No association between psychomotor subtypes and data-driven subtypes

Comparison with Acuity Subgroups



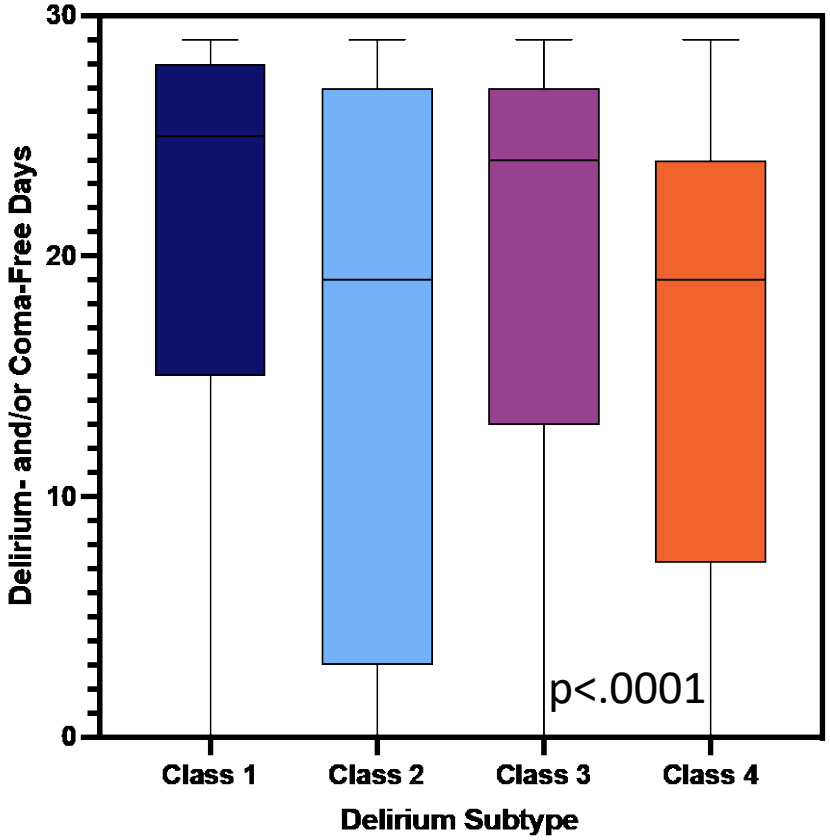
Fewer patients from data-driven Class 2 in SOFA Quartile 1

Patients from all SOFA quartiles in all data-driven subtypes

Hospital Outcomes

Delirium- or Coma-Free Days Among Subtypes

- Class 1: 25 (15-28)
- **Class 2: 19 (3-27)**
- Class 3: 24 (13-27)
- **Class 4: 19 (8-24)**



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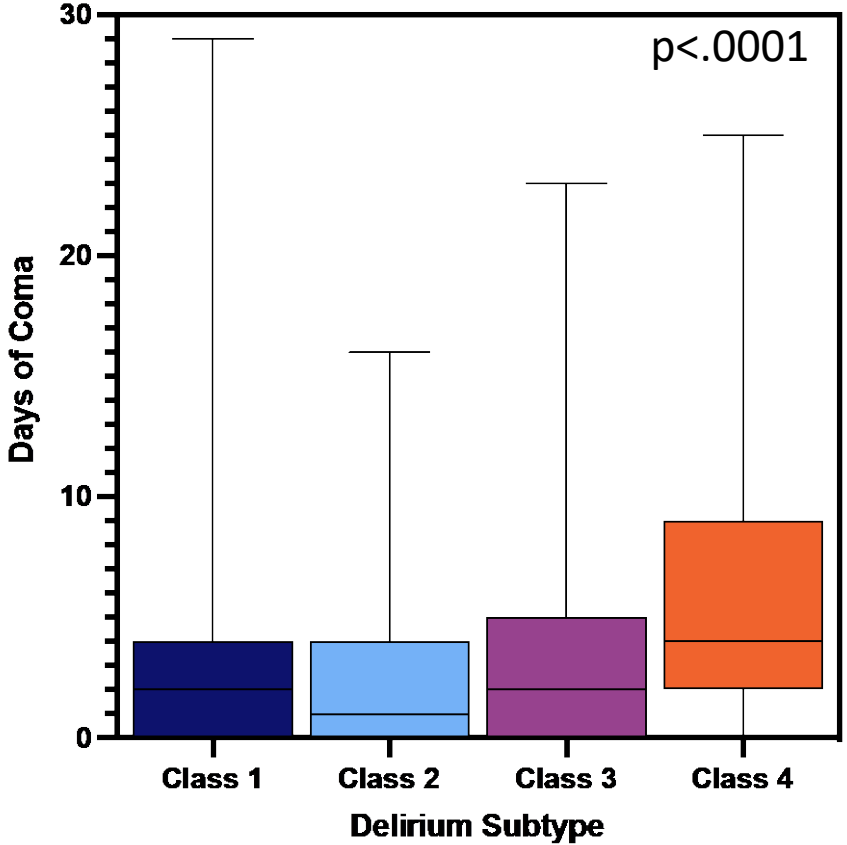
Days of Coma Among Subtypes

- Class 1: 2 (0-4)
- Class 2: 1 (0-4)
- Class 3: 2 (0-5)
- **Class 4: 4 (2-9)**



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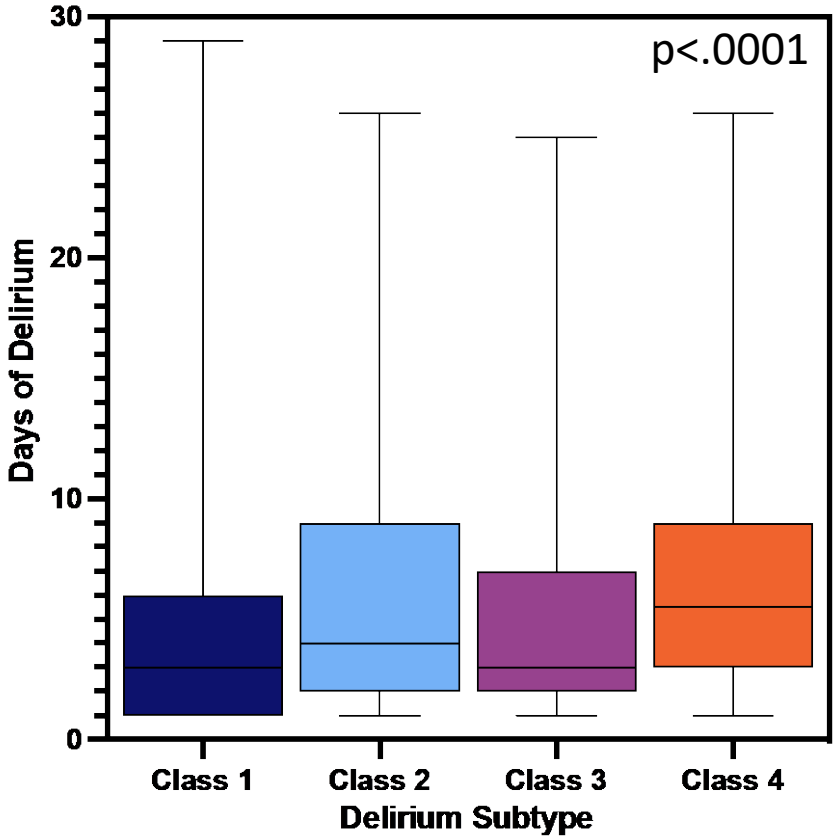
Days of Delirium Among Subtypes

- Class 1: 3 (1-6)
- Class 2: 4 (2-9)
- Class 3: 3 (2-7)
- **Class 4: 6 (3-9)**



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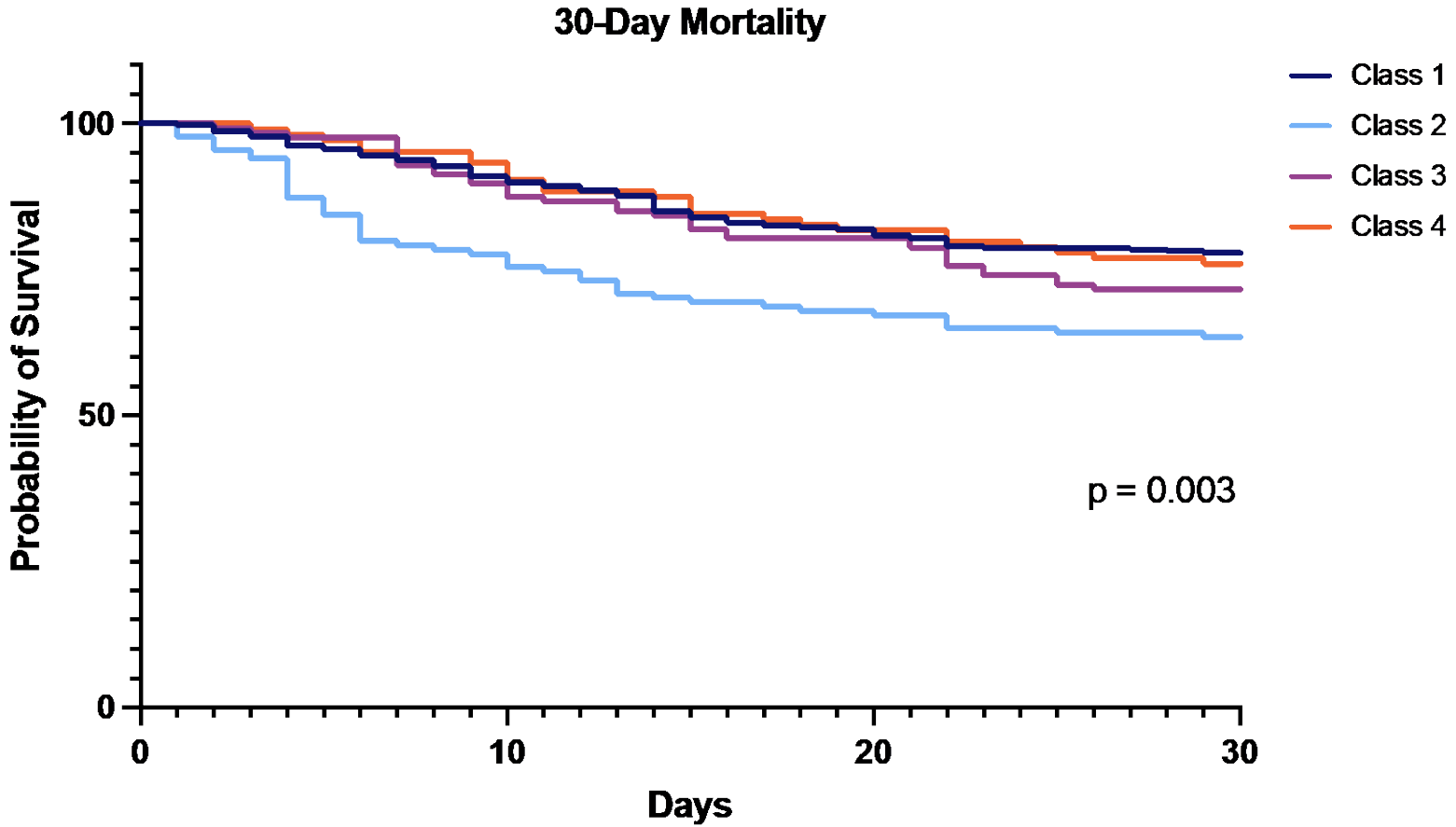
Mortality



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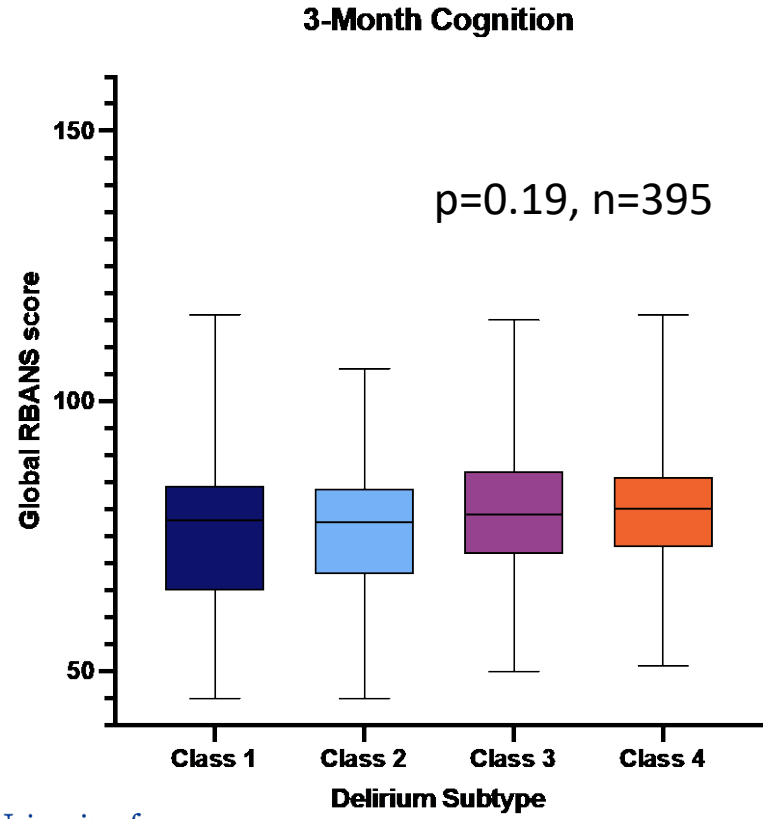
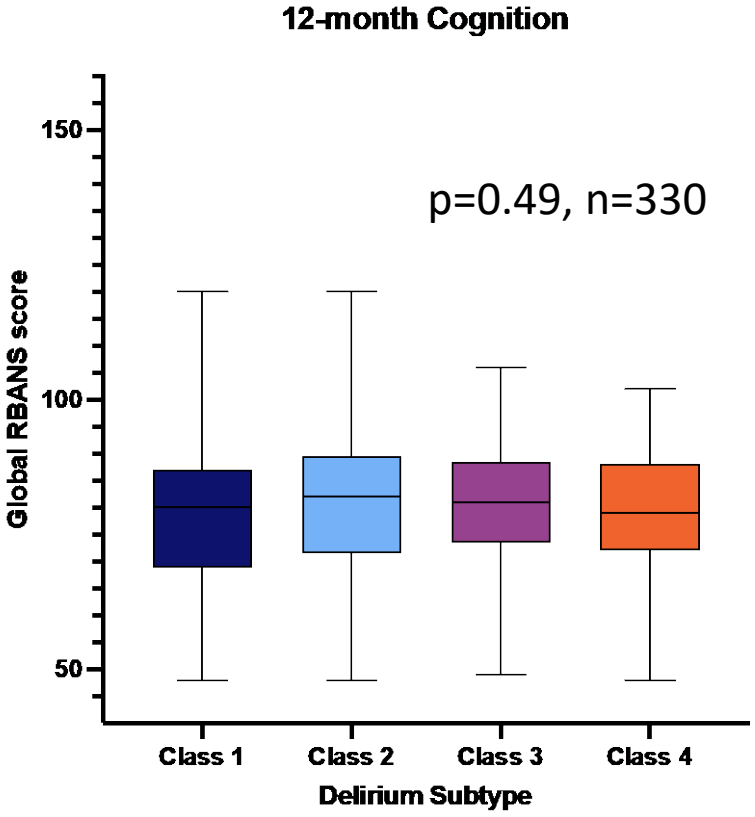
Long-Term Outcomes

Long-Term Outcomes: Cognition





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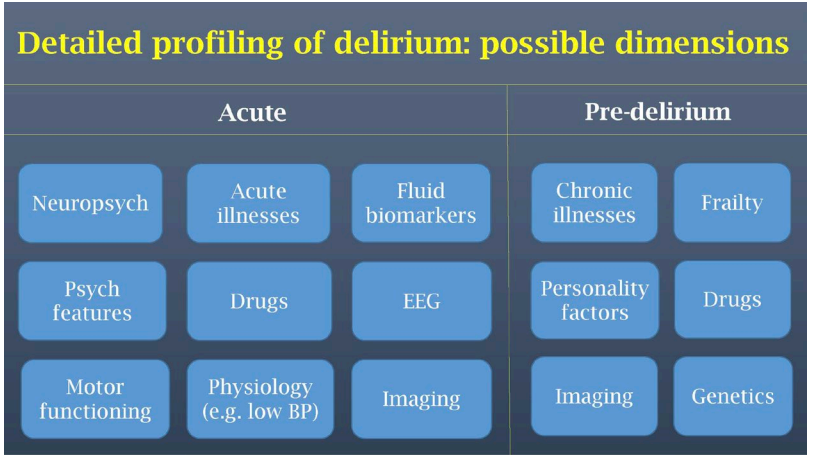
Take Home Message

- We identified four data-driven delirium subtypes that were different from prior subtyping approaches
- Class 2 (hypotensive, kidney impairment) had greatest mortality
- Class 4 (benzodiazepines, liver dysfunction) had longest duration of delirium and coma
- Significant cognitive impairment affected the overall sample, but no statistically significant differences between subtypes

What's Next?

- External validation
- Heterogeneity of treatment effect
- Examine influence of additional domains
- Evaluate trajectories of subtypes
- Prospective identification of delirium subtypes



Maclullich AMJ. International delirium phenotyping meeting.

Acknowledgements

- **Funding:**
  - NIH T32 HL007820 (PI: Jeremy Kahn, MD, MS)
  - NIH 5R01AG027472 (PI: E. Wesley Ely, MD, MPH)

- **Mentor:**
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Thank you!

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