Delirium: The Next Frontier

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HELP

NIDUS

DSM5 CRITERIA FOR DELIRIUM

- Disturbance in attention and awareness (reduced orientation to the environment)
- Disturbance develops acutely and tends to fluctuate
- An additional disturbance in cognition, (e.g., memory deficit, language, visuoperceptual)
- Not better explained by a preexisting dementia
- Not in face of severely reduced level of arousal or coma
- Evidence of an underlying organic etiology or multiple etiologies

Why is delirium important?

- Common problem
- Serious complications
- Often unrecognized
- Complex multifactorial etiology
- Potentially preventable contributor to cognitive impairment

Delirium is common

Delirium Rates

Hospital:	
• Prevalence (on admission)	14-24%
• Incidence (in hospital)	6-56%
Postoperative:	15-53%
Intensive care unit:	70-87%
Nursing home/post-acute care:	20-60%
Palliative care:	up to 80%

Mortality

Hospital mortality:	22-76%
One-year mortality:	35-40%

Ref: Inouye SK, NEJM 2006;354:1157-65; Lancet 2014; 383:911-922; JAMA 2017; 318:1161-1174

Delirium has serious complications

- Delirium associated with:
  - Increased morbidity and mortality
  - Functional and cognitive decline
  - Increased rates of dementia
  - Institutionalization
  - Increased length of stay and healthcare costs
  - Post-traumatic stress disorder
  - Caregiver burden

Patient Experience of Delirium

Patients describe fear, outrage, feeling unsafe, out of control, unprepared.

- “I was afraid, not knowing where I was”
- “I was not able to say what I wanted to say. It was very scary”
- “I was outraged that I should be treated this way with chiming beds and people coming out of walls”

Schmitt EM…Inouye SK. Gerontologist. 2019

Delirium is expensive

Hospital costs (> $8 billion/year)

Post-hospital costs (>$150 billion/year)

- Rehospitalization
- Institutionalization
- Rehabilitation
- Home care
- Caregiver burden

Ref: Leslie DL, et al. Arch Intern Med 2008;168:27-32

Overview of SAGES Study

- NIH-P01AG031720: “Interdisciplinary Study of Delirium and Its Long Term Outcomes”, started in April 2010, ongoing
- SAGES I cohort:
  - 560 patients age > 70 undergoing major scheduled non-cardiac surgical procedures (orthopedic, colectomy, vascular); no dementia at baseline
  - Interviews with complete neuropsychological battery at pre-operative baseline, 1,2,6 months and every 6 months thereafter
  - All received phlebotomy at baseline, immediate post-op, POD2, 1 month; MRI in subset at baseline/1 yr

SAGES…The Story Unfolds

- >90 papers to date
- Will overview a selected handful to tell the story of some interesting learnings from SAGES
- An ongoing story…

SAGES Study: Delirium Severity measure
Why is delirium severity important?

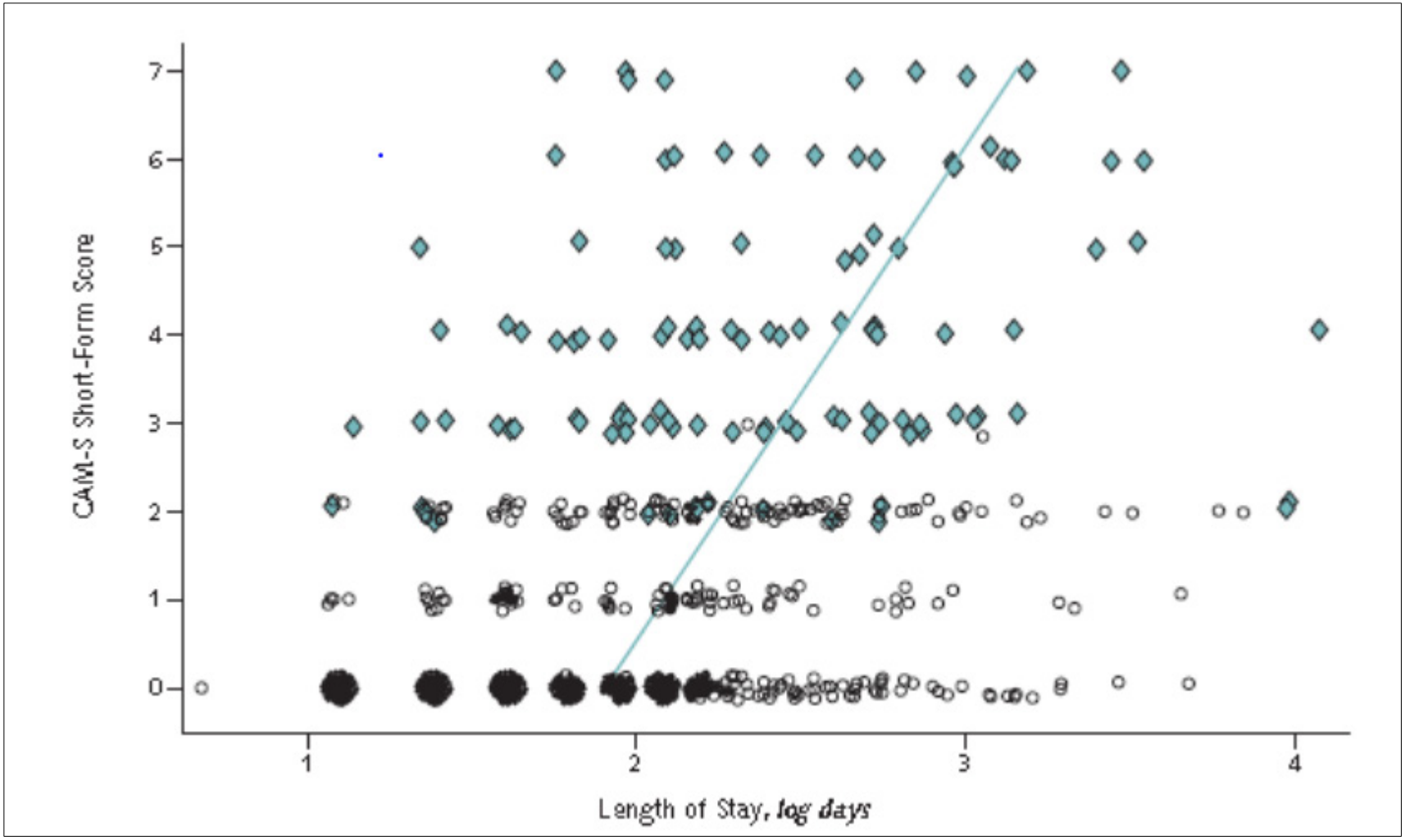
- Provides a continuous measure to track change over time
- Assess response to treatment
- Monitor clinical course and recovery
- Track burden of care & service utilization
- Advance pathophysiologic understanding and mechanisms

CAM-S Severity Scoring

- Simple additive score based on delirium symptoms.
- For 4-item CAM, scored from 0-7.
- For 10-item CAM, scored 0-19.
  - Detailed scoring instructions at: www.hospitalelderlifeprogram.org
- CAM-S score strongly associated with poor clinical outcomes (LOS, costs, placement, functional/cognitive decline, death)

Inouye SK et al. Ann Intern Med. 2014; 160: 526-533

CAM-S Scores and Length of Stay



Inouye SK et al. Ann Intern Med. 2014; 160: 526-533

SAGES: Natural Experiment

- Major scheduled surgery—presents a “natural experiment” to explore delirium
  - Cannot do RCT
- Significance: Allows us to explore some fundamental questions—about delirium and its outcomes
    - What are the bad outcomes?
    - Who is vulnerable?
    - Are there protective factors—can we build resilience?
    - What are the mechanisms/pathophysiology?

Major surgery: What are the bad outcomes?

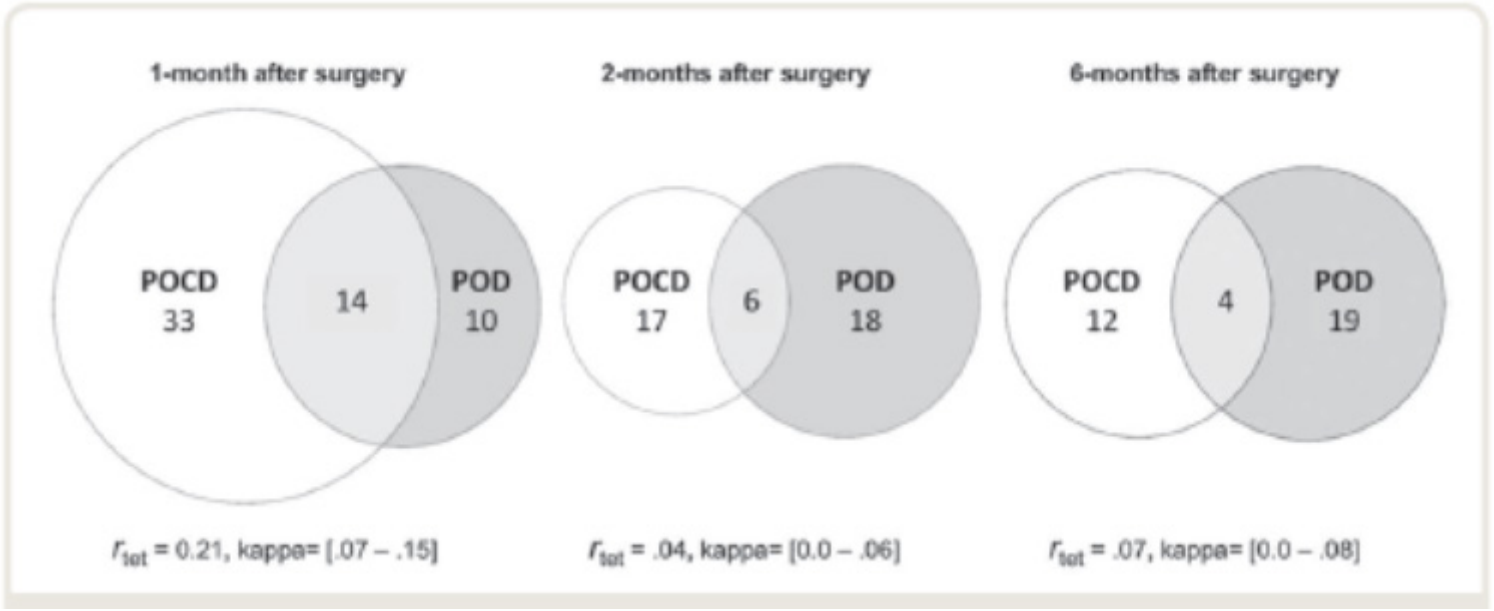
Major Postoperative Outcomes

- Delirium is the most frequent postoperative complication in older adults
- Delirium has a greater effect at the population level than all other major complications (Accordion system).
  - Strong associations with:
    - Increase length of hospital stay
    - New institutional discharge
    - 30-day readmission
    - Any adverse outcome

Gleason LJ. JAMA Surg. 2015; 150: 1134-40

POD ≠ POCD

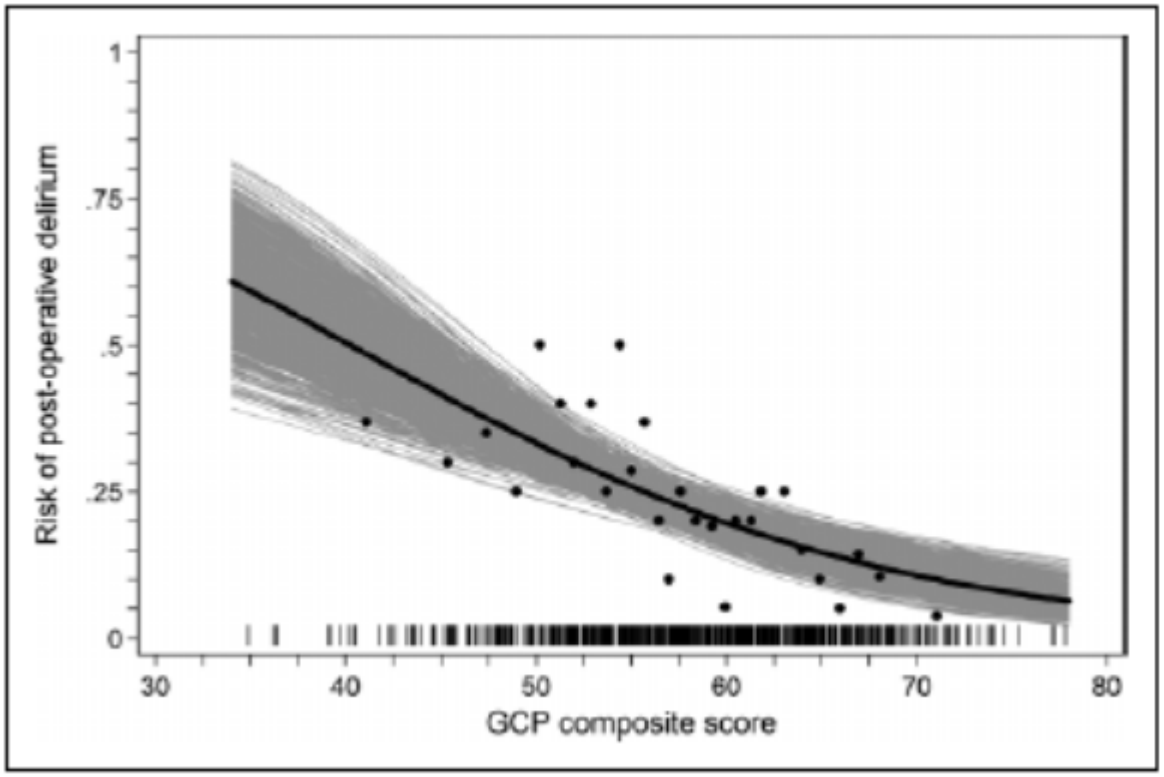
[POD=Postoperative Delirium; POCD=Postoperative Cognitive Decline]



POCD defined by ISPOCD definition (-1.96 SD on 2 tests)
Daiello LA. Anesthesiology. 2019. Epub

Are there protective factors—can we build reserve?

Preoperative Cognitive Performance Dominates Risk for Delirium Among Older Adults



- Risk of delirium is linearly and strongly related to presurgical cognitive performance level, beyond all other risk factors
- Association seen even at levels above the population median, which would be considered unimpaired

Jones RN. J Geriatr Psychiatry Neurol. 2016; 29:320-27

Cognitive and brain reserve and the risk of postoperative delirium

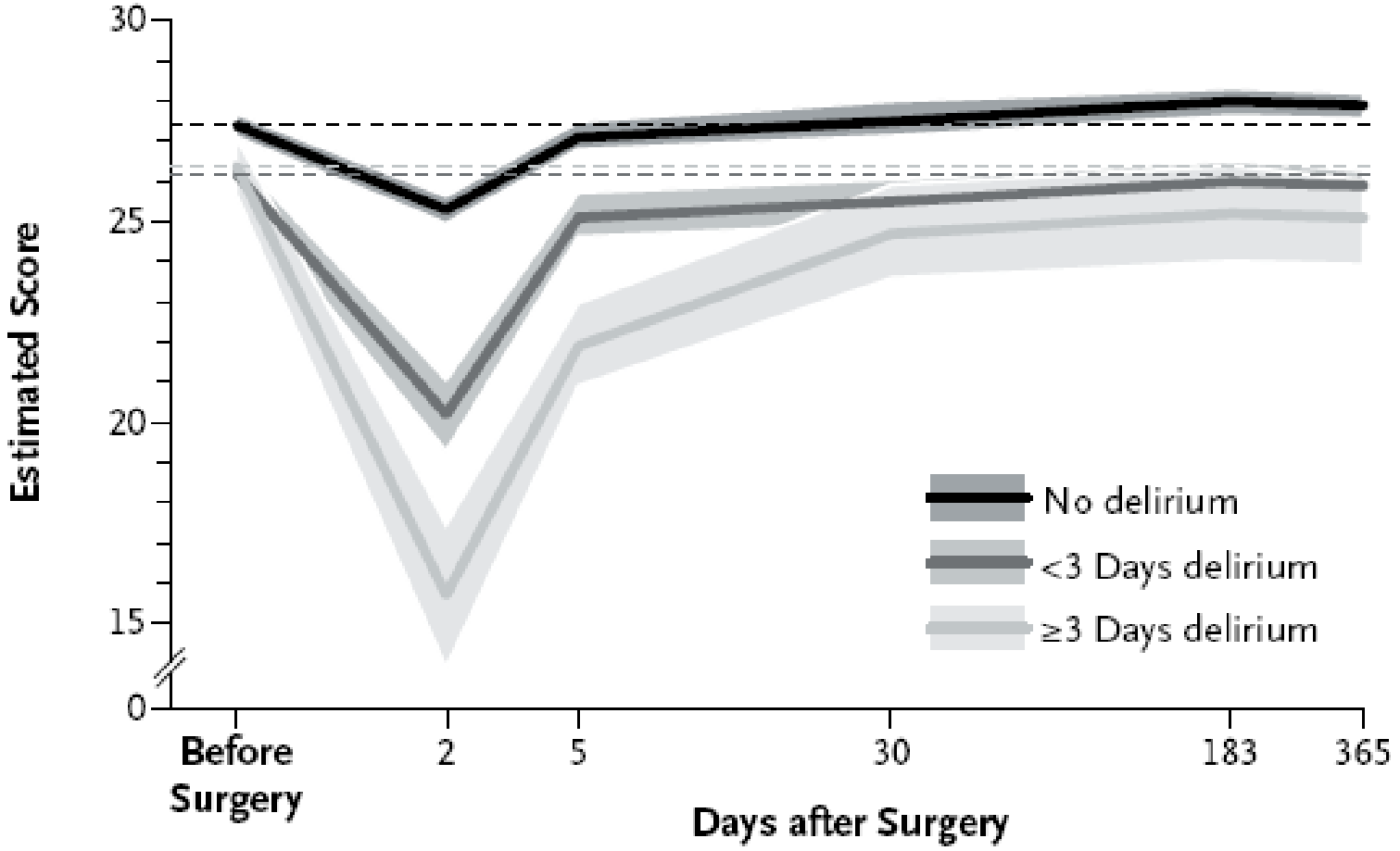
- Examined multiple reserve factors in SAGES
- Only the Wechsler Test of Adult Reading (WTAR), measure of premorbid IQ, was associated with delirium risk.
- Each 0.5 SD increase in WTAR associated with 38% reduction in delirium risk (adjusted risk ratio=0.62, 95% CI 0.45–0.85).
- Effect of WTAR disappears when GCP in model
- Lifelong learning and intelligence associated with cognitive reserve

Saczynski JS. Lancet Psychiatry. 2014; 1:437-43

Does delirium lead to long-term cognitive decline?

Short-Term Impact of Delirium

(N=225 cardiac surgery patients)



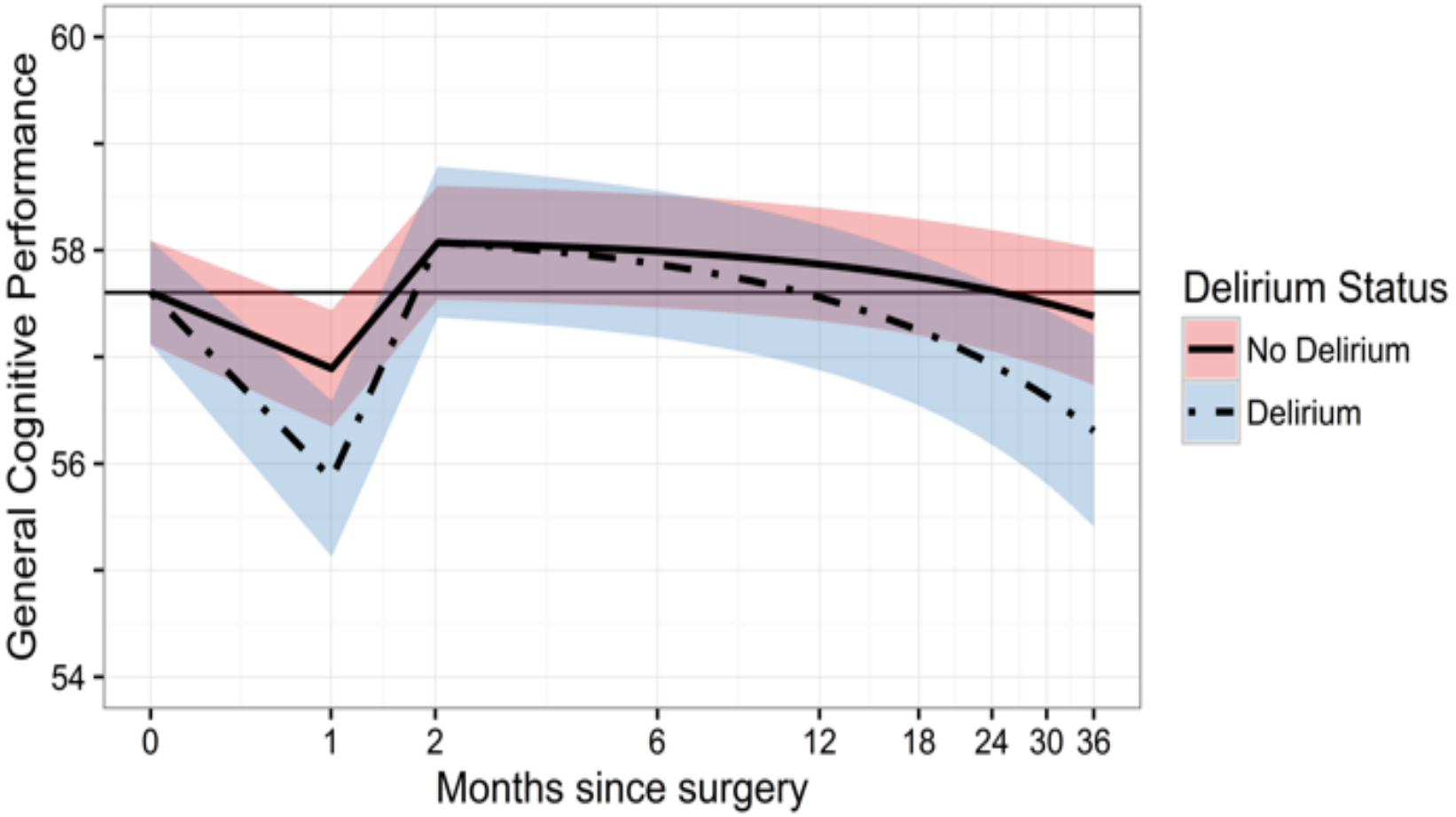
Saczynski JS et al. N Engl J Med. 2012; 367:30-9

Short-Term Impact of Delirium (cont)

- Delirium occurred in 46% patients following cardiac surgery in 225 patients
- Cognitive trajectory characterized by abrupt initial decline followed by gradual recovery over 6 months
- Patients did not get fully back to baseline even at 1 year

Saczynski JS et al. N Engl J Med. 2012; 367:30-9

LONG-TERM COGNITIVE TRAJECTORY AFTER ELECTIVE SURGERY



Inouye SK et al. SAGES Study, Alzheimers Dement. 2016; 12:766-75

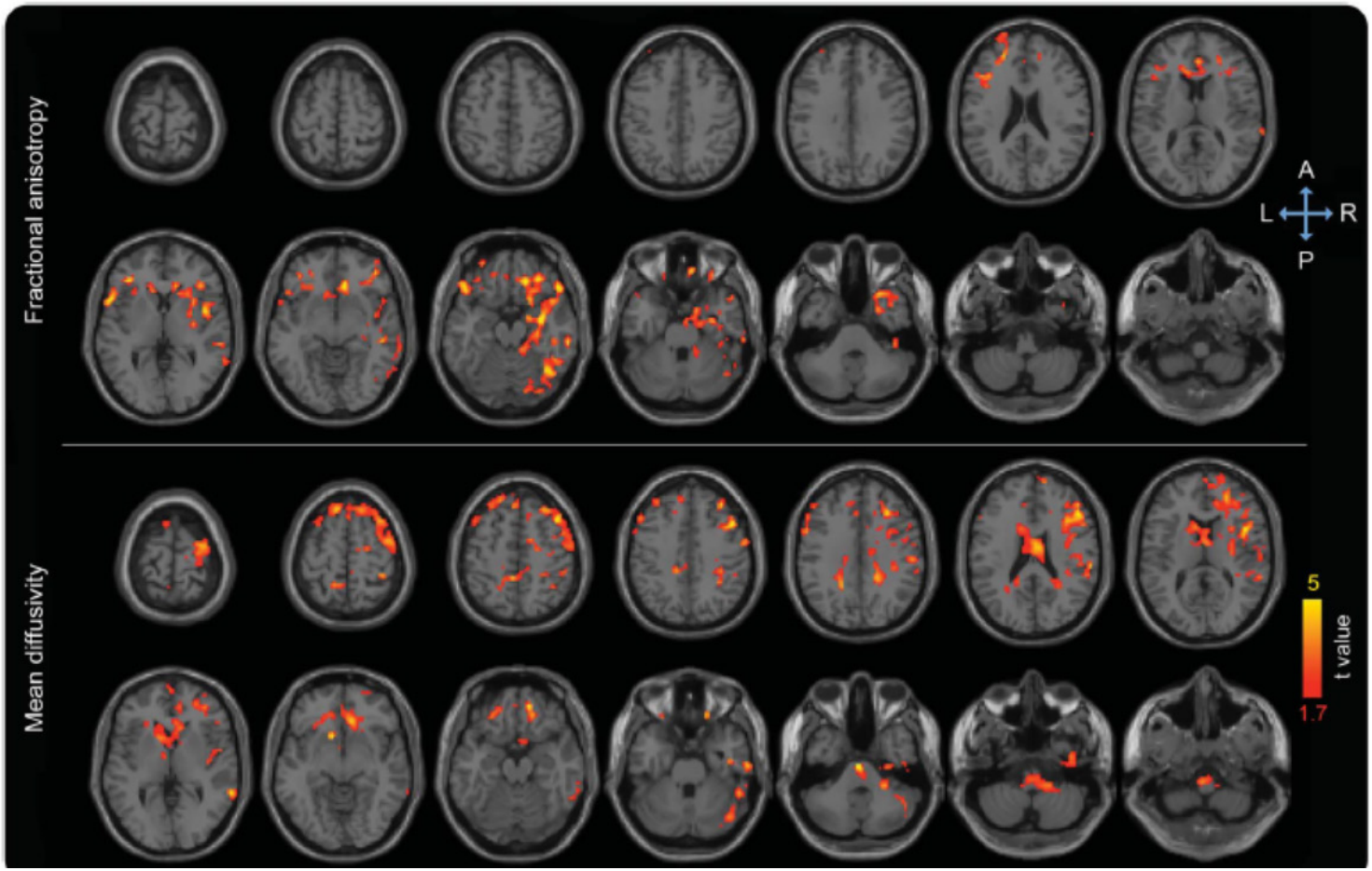
Longer Term Impact: SAGES Study

- Delirium occurred in 24% patients following major elective surgery in 560 patients
- In both groups, acute cognitive decline at 1 month
- Non-delirium group, recovers above baseline at 2 months, then gradual decline out to 36 mos (above baseline)
- Delirium group, recovers above baseline at 2 months, then gradual decline out to 36 months substantially below baseline (equal to MCI).

Inouye SK et al. SAGES Study, Alzheimers Dement. 2016; 12:766-75

DTI Changes at One Year

- At **one-year FU** in SAGES (n=113) , delirium associated with microstructural changes by DTI in frontal, parietal, and temporal white matter (not AD pattern).



Cavallari M. Neurology. 2017; 89: 1020-27

What are the pathophysiologic mechanisms of postoperative delirium?

Importance of Inflammation

- Some inflammation critical for healing
- How much inflammation is too much; when does inflammation become dysfunctional?
- Initial work focused on identifying inflammatory biomarkers in plasma, individually and as a “signature” at sequential timepoints (preop, POD2, 1-month)

SAGES Inflammatory Biomarkers Studies

Study (N)	Cytokine	Marker for Delirium at Timepoint(s)
JGMS 2015 (N=75 pairs)	IL-6, IL-2	POD2
Biopsych 2017 (N=75 pairs)	CRP	PREOP, POD2
JAGS 2017 (N=560)	CRP	PREOP, POD2
JGMS 2019 (N=75 pairs)	• CRP, AZGP1 • CRP, IL-6, IL-2	PREOP POD2
Ann Surg 2019 (N=36)	CH13L1, CRP, IL-6 Plus others by SOMAScan	Change from PREOP to POD2
AJGP 2019 (N=547)	COMT genotype (Val/Val “warriors”) protected against increased risk of delirium associated with high CRP	POD2

Refs: JGMS 2015; 70:1289-95; Biol Psychiatry. 2017; 81:145-53; JAGS 2017; 65(8):e109-e116; JGMS 2018: Epub; Ann Surg 2019:Epub; AJGP 2019; 27:1-8.

SAGES: The Next Frontier

- Biomarker “signature” for delirium
- Relationship of systemic inflammation to neuro-inflammation
- Intervention trials to decrease inflammation and prevent postoperative delirium

Why is addressing delirium important?

- Tremendous clinical impact
- Healthcare costs and policy implications
- Indicator of quality of care for elders
- Helps us understand the brain
- Prevention of cognitive impairment and dementia

Interested in Learning More?

- Delirium prevention-HELP
  - www.hospitalelderlifeprogram.org
- Delirium research-NIDUS (Network for Investigation of Delirium: Unifying Scientists)
  - https://deliriumnetwork.org/
- Contact us:
  - AgingBrainCenter@hsl.harvard.edu
- Follow us: @sharon_inouye @NIDUS_Delirium @ElderLifeProg

NIDUS

Join NIDUS & Connect to Delirium Research

NIDUS is an NIA-funded research network dedicated to advancing the study of delirium through development of research resources, career development opportunities, and dissemination of delirium science.

(NIA grant no. R24AG054259, PI: Inouye)

Advance your delirium research by:

- Registering on the NIDUS website **deliriumnetwork.org** to access our research resources and receive delirium news through our blog and newsletter
- Entering your study in the NIDUS Delirium Research Hub, a database of delirium studies that allows researchers to complete searches and facilitate collaboration
  - Enter here: https://deliriumnetwork.org/delirium-research-hub/
- Applying for a NIDUS Pilot Grant ($50,000 USD) by November 7, 2019
  - Apply here: https://deliriumnetwork.org/pilots/2019-pilot-information/

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