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Hassan Hamadnalla

Henry Ford Health, hhamadn1@hfhs.org

Daniel I. Sessler

Christopher A. Troianos

Jonathan Fang

Eva Rivas

*See next page for additional authors*

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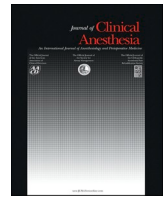
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## Authors

Hassan Hamadnalla, Daniel I. Sessler, Christopher A. Troianos, Jonathan Fang, Eva Rivas, Chao Ma, Edward J. Mascha, and Alparslan Turan



## Original Contribution

## Optimal interval and duration of CAM-ICU assessments for delirium detection after cardiac surgery

Hassan Hamadnalla, MD<sup>a,e</sup>, Daniel I. Sessler, MD<sup>a</sup>, Christopher A. Troianos, MD, FASE, FASA<sup>b</sup>, Jonathan Fang, MD<sup>a</sup>, Eva Rivas, MD<sup>a,f</sup>, Chao Ma, MS<sup>a,c</sup>, Edward J. Mascha, Ph.D<sup>a,c</sup>, Alparslan Turan, MD<sup>a,d,\*</sup>

<sup>a</sup> Department of Outcomes Research, Cleveland Clinic, OH, United States

<sup>b</sup> Anesthesiology Institute, Cleveland Clinic, OH, United States

<sup>c</sup> Department of Quantitative Health Sciences, Cleveland Clinic, OH, United States

<sup>d</sup> Department of General Anesthesiology, Cleveland Clinic, OH, United States

<sup>e</sup> Department of Anesthesiology, Pain Management & Perioperative Medicine, Henry Ford Health System, MI, United States

<sup>f</sup> Department of Anesthesiology, Hospital Clinic de Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Barcelona Spain

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## ABSTRACT

**Study objective:** Our goal was to determine when postoperative delirium first occurs, and to assess evaluation strategies that reliably detect delirium with lowest frequency of testing.

**Design:** This was a retrospective study that used a database from a five-center randomized trial.

**Setting:** Postoperative cardiothoracic ICU and surgical wards.

**Participant:** Adults scheduled for elective coronary artery bypass and/or valve surgery.

**Intervention and measurements:** Postoperative delirium was assessed using CAM-ICU questionnaires twice daily for 5 days or until hospital discharge. Data were analyzed using frequency tables and Kaplan-Meier time-to-event estimators, the latter being used to summarize time to first positive CAM-ICU over POD1–5 for all patients for various evaluation strategies, including all assessments, only morning assessment, and only afternoon assessments. Sensitivity for various strategies were compared using McNemar's test for paired proportions.

**Main results:** A total of 95 of 788 patients (12% [95% CI, 10% to 15%]) had at least 1 episode of delirium within the first 5 postoperative days. Among all patients with delirium, 65% were identified by the end of the first postoperative day. Delirium was detected more often in the mornings (10% of patients) than evenings (7% of patients). Compared to delirium assessments twice daily for five days, we found that twice daily assessments for 4 days detected an estimated 97% (95% CI 91%, 99%) of delirium. Measurements twice daily for three days detected 90% (82%, 95%) of delirium.

**Conclusions:** Postoperative delirium is common, and CAM-ICU assessments twice daily for 4 days, versus 5 days, detects nearly all delirium with 20% fewer assessments. Four days of assessment may usually be sufficient for clinical and research purposes.

## 1. Introduction

Delirium is a serious postoperative complication that has devastating effects on patients and their families and prolongs hospitalization [1]. The consequences of postoperative delirium are long-lived and include reduced functional status, increased risk of falls, memory loss, long-term cognitive dysfunction, and increased mortality [2]. The incidence of delirium after cardiac surgery ranges from 6 to 52% [3,4], and is

associated with prolonged hospitalization [5] and readmission [6].

Delirium usually occurs within the initial postoperative days [7–9] and early recognition is thought to improve prognosis [10]. The Confusion Assessment Method (CAM) was developed by Inouye as a clinician-friendly assessment for delirium. CAM for the ICU (CAM-ICU) has been validated for non-comatose critically ill patients with varying degrees of alertness. It evaluates the same cardinal features of delirium as CAM: (1) altered mental status/fluctuating course; (2) inattention; (3)

\* Corresponding author at: Department of Outcomes Research, Cleveland Clinic, 9500 Euclid Avenue, P-77, Cleveland, OH 44195, United States.

E-mail address: [turana@ccf.org](mailto:turana@ccf.org) (A. Turan).

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altered level of consciousness; and (4) disorganized thinking. Each feature is defined, validated, and objectively assessed by interaction with patients [11].

While the CAM-ICU is well supported for use in clinical practice [12], it remains unknown how often patients should be assessed and for how long. A challenging feature of postoperative delirium is its waxing-and-waning course. Because delirium is inherently fluctuating, multiple assessments are needed for reliable diagnosis. However, it remains unknown whether morning or evening assessments are most likely to detect delirium, and for how long measurements need to continue. The goal of our analysis was to compare once- and twice-daily assessments over various periods to determine which strategies are most efficient in terms of maintaining high sensitivity for delirium detection while reducing the number of assessments required.

## 2. Methods

With Cleveland Clinic Institutional Review Board approval (IRB# 19-337) and waived consent, we conducted a retrospective analysis of data obtained during the DECADE trial (IRB# 12-1379) “Ancillary effects of dexmedetomidine sedation after cardiac surgery” which included CAM-ICU assessments by trained investigators twice daily for five days while patients remained hospitalized (NCT02004613) [13].

Briefly, DECADE was a five-center, double-blind trial in which cardiac surgical patients were randomly assigned to dexmedetomidine for 24 h or placebo. The primary outcomes were postoperative atrial fibrillation (AF) and delirium. Dexmedetomidine infusion was initiated after induction of general anesthesia and before the surgical incision at a rate of 0.1 µg/kg/h. At the end of the bypass, the dose was increased to 0.2 µg/kg/h, and in the postoperative period, dexmedetomidine infusion was continued at a rate of 0.4 µg/kg/h. The reference group was given comparable volumes of saline placebo for each period.

Postoperative delirium was assessed using the Confusion Assessment Method for Intensive Care Unit questionnaire during the ICU and on surgical wards. Delirium assessments were done twice daily for 5 days or until hospital discharge. The morning and evening assessments were made before 10 AM and after 5 PM. The CAM-ICU questionnaire was performed in person by research physicians who trained with the Vanderbilt University CAM-ICU training manual and the supplemental videos.

Before each delirium assessment, the Richmond Agitation and Sedation Scale (RASS) was used to assess consciousness; patients with scores of −4 or −5 were not tested for delirium. CAM-ICU delirium was deemed positive when there was an acute change in mental status from baseline with difficulty focusing attention in combination with altered level of consciousness or disorganized thinking [11]. The major results of the DECADE trial were that 24 h of dexmedetomidine infusion did not alter the incidence of atrial fibrillation and marginally worsened delirium.

### 2.1. Statistical analysis

- Data were analyzed using frequency tables to describe the number (%) of delirium assessments completed each morning and afternoon on postoperative days 1–5, and the proportion of patients with detected delirium at various times and assessment frequencies. Kaplan-Meier time-to-event estimators were used to summarize time to first positive CAM-ICU over postoperative days 1–5 for all patients for various evaluation strategies including all assessments, only morning assessments, and only afternoon assessments.
- McNemar’s test for paired proportions was used to compare morning and evening delirium detection. We used Clopper-Pearson confidence intervals for a binomial proportion to estimate the proportion of postoperative delirium cases detected for each evaluation strategy. SAS statistical software version 9.4 used for all analyses.

## 3. Results

A total of 788 patients were enrolled from April 2013 to September 2018. The average age of enrolled patients was 62 years, and a third were female. About half had combined valve and bypass surgery. Patients who experienced delirium were slightly older more likely to be female, and more likely to have a history of coronary stents inserted than those who did not (Table 1). The median [interquartile range 25–75] assessment times were 20 [18,22] postoperative hours for the first, 27 [25, 29] hours for the second, and 44 [41, 46] hours for the third.

A total of 95 patients (12% [95% CI, 10% to 15%]) had at least 1 episode of delirium within the first 5 postoperative days. Among them, 65% ( $n = 62$ ) had their first positive CAM-ICU on postoperative day 1, 77% ( $n = 73$ ) by end of day 2, 89% ( $n = 85$ ) by end of day 3, and 97% ( $n = 92$ ) by end of day 4 (Table 2, Fig. 1).

We compared the sensitivity of various evaluation strategies for detecting first postoperative delirium compared with twice-daily assessments for 5 days (Table 3). For example, the first delirium for a patient was detected significantly more often in the morning than in the evening. Considering only morning assessments, 79 (10% of 787) patients had at least 1 positive delirium assessment during the initial 5 postoperative days compared to 54 (7%) using only afternoon assessments ( $P < 0.001$ , McNemar’s test).

Sensitivity was an estimated 97% (95% CI 91%, 99%) if assessments were restricted to: 1) every morning for 5 days and every evening for the initial 3 postoperative days; or, 2) morning and evening for 4 days. Both strategies require 20% less effort than twice-daily measurements for 5 days, while still detecting delirium in nearly all delirium observed over 5 days. Similarly, an estimated 90% (95% CI 82%, 95%) of delirium patients would be identified with twice-daily assessments for 3 days which requires only 60% of the effort.

## 4. Discussion

The overall estimated incidence of delirium was 12%, defined as a positive CAM-ICU at any assessment during the initial 5 days. Our incidence was considerably less than the 26 to 52% incidence reported in various small studies [14–17]. One explanation is that delirium risk is

**Table 1**  
Patient characteristics ( $N = 788$ ).

Factor	Any delirium ( $N = 95$ )	No delirium ( $N = 693$ )	ASD
<b>Demographic</b>			
Age – year	66 ± 11	62 ± 12 <sup>a</sup>	0.36
Body mass index (kg/m <sup>2</sup> )	30 ± 8.4	29 ± 12 <sup>a</sup>	0.07
Gender* –female%	38 (40)	203 (29) <sup>a</sup>	0.23
<b>Cardiac history</b>			
Angina –%	29 (31)	169 (25) <sup>a</sup>	0.14
Congestive heart failure –%	10 (11)	48 (6.9) <sup>a</sup>	0.13
Previous MI –%	14 (15)	72 (10) <sup>a</sup>	0.13
Stent placement–%	19 (20)	74 (11) <sup>a</sup>	0.26
Previous cardiac surgery –%	19 (20)	78 (11) <sup>a</sup>	0.24
LVEF %	59 ± 9.3 <sup>b</sup>	60 ± 7.8 <sup>c</sup>	0.14
<b>Surgical information</b>			
Aortic valve –%	29 (31)	234 (34) <sup>b</sup>	0.08
Mitral valve –%	25 (26)	225 (33) <sup>b</sup>	0.14
Tricuspid valve –%	2 (2.1)	34 (5.0) <sup>b</sup>	0.16
Pulmonic valve –%	1 (1.1)	3 (0.44) <sup>b</sup>	0.07
Aorta –%	8 (8.9) <sup>b</sup>	83 (12) <sup>c</sup>	0.07
Cardiac ablation –%	1 (1.1)	2 (0.29) <sup>b</sup>	0.11
Other cardiac procedure –%	12 (13)	63 (9.2) <sup>b</sup>	0.09
<b>Anesthesia maintained with –%</b>			
Propofol infusion	6 (6.3)	27 (3.9) <sup>b</sup>	0.11
Volatile anesthetic	89 (94)	659 (96)	

Summary statistics is presented as mean ± SD,  $N$  (%) as appropriate. ASD = absolute standardized difference.

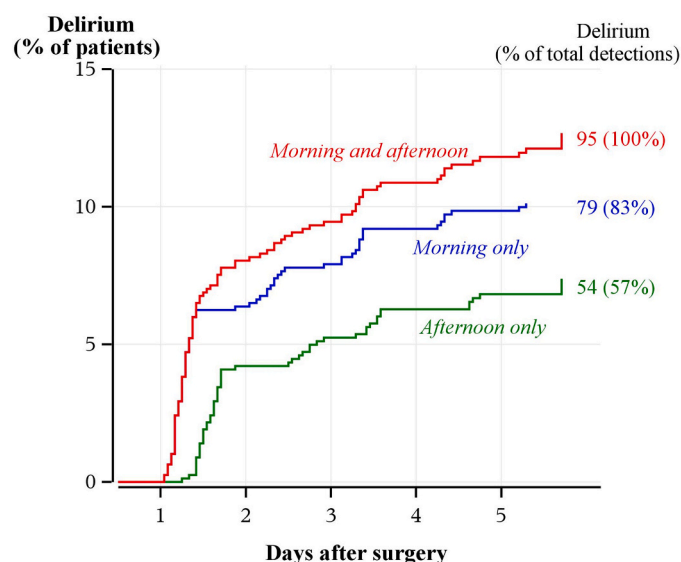
Superscripts a, b and c represent  $N = 1$ –2,  $N = 5$ –7 and  $N = 21$ –22 missing values, respectively.

**Table 2**

First delirium event for patients (n = 95) with any positive delirium during the first 5 postoperative days.

POD	Time	N (%) with initial positive delirium assessment at given time	Cumulative N (%) by given time
1	AM	50 (53)	50 (53)
	PM	12 (13)	62 (65)
2	AM	7 (7.4)	69 (73)
	PM	4 (4.2)	73 (77)
3	AM	8 (8.4)	81 (85)
	PM	4 (4.2)	85 (89)
4	AM	5 (5.3)	90 (95)
	PM	2 (2.1)	92 (97)
5	AM	2 (2.1)	94 (99)
	PM	1 (1.1)	95 (100)
Total		95 (100)	95 (100)

Results presented as N (%).



**Fig. 1.** Kaplan-Meier curves for time to first delirium. (1) Red curve; time to first delirium using all assessments ( $N = 788$ , all patients) (2) Blue curve; time to first delirium using morning assessments only ( $N = 787$ ). (3) Green curve; time to first delirium using afternoon assessments only ( $N = 788$ ). Y-axis reports Kaplan-Meier estimates of percent with delirium. Values to the right report the fraction of the 95 detected delirium cases identified with each strategy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

strongly age-dependent, with risk increasing markedly in patients exceeding 65 years of age [18]. Our patients, averaging just 62 years, were younger than in most previous reports. An additional factor is that we only enrolled patients who had elective surgery where the risk of delirium is lower than for urgent or emergent surgery. And finally, anti-delirium strategies are now routine in critical care units which presumably also reduces risk.

The initial detection of delirium most often occurred on the first postoperative day. By the third day, nearly 90% of the patients who had delirium detected by day 5 were already detected. Our results are consistent with limited previous work in cardiac surgical patients showing that almost two-thirds of the patients who developed delirium did so by the first postoperative day and that new delirium was seldom detected after the fourth day [7–9,19]. In the DEXACET factorial trial [7], for example, delirium was evaluated by CAM-ICU in 121 patients who were randomized to 1 of 4 groups receiving postoperative analgesia with IV acetaminophen or placebo and postoperative sedation with dexmedetomidine or propofol. Delirium was most often detected on the first postoperative day and no new delirium occurred after day 4.

Sauër and colleagues used CAM-ICU to evaluate the effect of statins on delirium [19]. Half of all delirium occurred on the first postoperative day, with an additional 21% being observed during the second postoperative day, and another 20% occurring days 3 to 5, with the caveat that delirium was only assessed while patients remained in the ICU. In a sub-study [9] from the DECS trial [20], delirium was assessed twice daily by research nurses using CAM-ICU during the patients' ICU stay and daily by trained research personnel using the CAM questionnaire after transfer to a medical ward. In contrast to our results, these investigators found that delirium was most common on postoperative days 2 and 3, but also concluded that most delirium occurs within the initial three postoperative days.

As reported by others, delirium was more often detected in the morning before 10 AM than in the evening after 5 PM. Disrupted circadian rhythms consequent to ICU noise and continuous activity may contribute, as might accumulated fatigue during ICU days that start early and provide little opportunity for real rest. Absence of support from family and friends in the evenings may also contribute [21,22].

Delirium probably should be assessed routinely in critical care patients because the incidence is relatively high. Our results suggest that most will be detected by a single daily assessment in the morning, although twice daily assessments will presumably detect some delirium earlier. For research, the question is at least as important because there are real costs associated with each assessment, and any that are missed become protocol deviations. Limiting the number of delirium assessments while retaining high sensitivity would therefore make research less expensive and more practical.

By combining the delirium time course with the observation that delirium is most often detected in the morning, we were able to evaluate alternatives to simply assessing delirium twice daily for five days (Table 3). For example, CAM-ICU assessments twice daily during the initial 4 postoperative days has 97% sensitivity for detecting delirium while requiring 20% less assessments. Moreover, assessing CAM-ICU twice daily for 3 days after surgery requires 40% fewer assessments than twice daily for five days while still detecting 90% of all delirium. At the very least, it is thus reasonable to design studies with no more than four days of delirium assessments, and in some cases, three days may suffice.

A strength of our study is that delirium was assessed prospectively by trained physicians twice daily for five days. Frequent assessments reduce the risk of missing periods of acute-onset inattention, disorganized thinking, or altered level of consciousness. We thus assume most cases of delirium were detected. The underlying trial was a multicenter effort that presumably enhances the generalizability of our conclusions.

All patients in the underlying trial had cardiac surgery. Generally, the incidence of delirium is lower after non-cardiac surgery and the expression pattern may differ. Our results should therefore be extrapolated cautiously to other populations. Surely some patients developed delirium in between assessments or after post-operative day 5, episodes that would have been missed with our protocol. And finally, more than ten research physicians in five sites conducted CAM-ICU assessments over the five-year duration of the underlying trial. While each was fully trained in CAM-ICU administration and interpretation, surely there were inter-individual differences in application and assessment.

In summary, 65% of all delirium detected over 5 days was observed during the initial postoperative day. Delirium was detected more often in the mornings than evenings. Compared to the number of patients detected with delirium using twice-daily measurements for 5 days, sensitivity was 97% when assessments were restricted to: 1) every morning for 5 days and every evening for 3 days; or, 2) twice daily for 4 days. Both strategies require 20% fewer assessments than twice-daily measurements for 5 days, while still detecting nearly all delirium. Similarly, 90% of delirium can be detected with twice-daily assessment for just 3 days which requires only 60% as many assessments.

**Table 3**

Various evaluation strategies for detecting postoperative delirium.

	Day 1	Day 2	Day 3	Day 4	Day 5	Total number of visits for delirium evaluation	Patients with first positive CAM-ICU evaluation (percent of 788)	<sup>a,b</sup> Sensitivity of each strategy to detect delirium (95% CI) <sup>a,b</sup> N = 95 cases
AM	X	X	X	X	X	10	95 (12.1)	100%
PM	X	X	X	X	X			
AM	X	X	X	X	X	8	92 (11.7)	97% (91%, 99%)
PM	X	X	X					
AM	X	X	X	X		8	92 (11.7)	97% (91%, 99%)
PM	X	X	X	X				
AM	X	X	X			6	85 (10.8)	90% (82%, 95%)
PM	X	X	X					
AM	X	X	X	X	X	5	79 (10.0)	83% (74%, 90%)
PM								
AM	X	X	X	X		4	77 (9.8)	81% (72%, 88%)
PM								
AM	X	X	X			3	72 (9.1)	76% (66%, 84%)
PM								
AM						5	54 (6.9)	57% (46%, 67%)
PM	X	X	X	X	X			

<sup>a</sup> Sensitivity of various evaluation strategies for detecting postoperative delirium compared with twice-daily assessments for 5 days. For example, sensitivity would be 97% if assessments were restricted to: 1) every morning for 5 days and every evening for 3 days; or, 2) morning and evening for 4 days. Both strategies require 20% less effort than twice-daily measurements for 5 days, while still detecting nearly all delirium. Similarly, 90% of delirium would be detected with twice-daily assessment for 3 days which requires only 60% of the effort. In contrast, daily evening assessments for 5 days would have a sensitivity of only 57%.

<sup>b</sup> Clopper-Pearson confidence interval for a binomial proportion.

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## Author statement

Hassan Hamadnalla: Conceptualization, Methodology, Validation, Investigation, Resources, Writing - Original Draft, Visualization, Project administration.; Daniel I. Sessler: Conceptualization, Writing - Review & Editing, Visualization, Supervision.; Christopher Troianos: Visualization, Writing - Review & Editing, Supervision.; *Jonathan Fang*: Investigation, Resources.; Eva Rivas: Methodology, Validation, Writing - Original Draft.; Chao Ma: Software, Formal analysis.; Edward J. Mascha: Formal analysis, Visualization, Supervision.; Alparslan Turan: Conceptualization, Methodology, Writing - Review & Editing, Supervision, Project administration.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jclinane.2021.110233>.

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