

## CLINICAL PRACTICE

# Emergence from general anaesthesia and evolution of delirium signs in the post-anaesthesia care unit

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## Abstract

**Background:** Emergence from anaesthesia is often accompanied by signs of delirium, including fluctuating mental status and inattention. The evolution of these signs of delirium requires investigation since delirium in the post-anaesthesia care unit (PACU) may be associated with worse outcomes.

**Methods:** Adult patients emerging from anaesthesia were assessed for agitated emergence in the operating room using the Richmond Agitation-Sedation Scale (RASS). The Confusion Assessment Method for the Intensive Care Unit was then used to evaluate delirium signs at PACU admission and during PACU stay at 30 min, 1 h, and discharge. Signs consistent with delirium were classified as hyperactive vs hypoactive based upon a positive CAM-ICU assessment and the concomitant RASS score. Multivariable logistic regression was utilized to assess potential risk factors for delirium during PACU stay including age, American Society of Anesthesiologists classification, and opioid and benzodiazepine exposure.

**Results:** Among 400 patients enrolled, 19% had agitated emergence. Delirium signs were present at PACU admission, 30 min, 1 h, and PACU discharge in 124 (31%), 59 (15%), 32 (8%), and 15 (4%) patients, respectively. In patients with delirium signs, hypoactive signs were present in 56% at PACU admission and in 92% during PACU stay. Perioperative opioids were associated with delirium signs during PACU stay ( $P=0.02$ ).

**Conclusions:** A significant proportion of patients develop delirium signs in the immediate postoperative period, primarily manifesting with a hypoactive subtype. These signs often persist to PACU discharge, suggesting the need for structured delirium monitoring in the PACU to identify patients potentially at risk for worse outcomes in the postoperative period.

**Key words:** anaesthesia, complications, delirium

Delirium is an acute brain organ dysfunction characterized by changes in level of consciousness, inattention, and disorganized thinking. Delirium can manifest with hyperactive signs (i.e. hyperactive subtype with agitation and restlessness) or with hypoactive signs (i.e. hypoactive subtype with lethargy and inattentiveness).

It is extremely common throughout the hospital, with 60–80% of mechanically ventilated patients and 20–50% of patients with a lower severity of illness developing delirium at some point during their hospital course.<sup>1–3</sup> Studies in surgical patients focusing on delirium in the first few postoperative

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**Editor's key points**

- Limited evidence suggests that early postoperative delirium is associated with worse outcome.
- The authors determined the incidence of emergence agitation and delirium among 400 adult patients.
- On post-anaesthesia care unit admission, 31% of patient had signs of delirium.
- Further studies are needed to confirm an association with adverse outcomes.

days<sup>4–14</sup> have found that this brain organ dysfunction is independently associated with increased length of stay, higher cost of care, prolonged cognitive impairment, and increased mortality, similar to that reported in general hospital patients.<sup>4 15–18</sup> The course of this brain dysfunction in the immediate postoperative period, however, is not well characterized.

Recent data suggest that even early postoperative delirium – at post-anaesthesia care unit (PACU) discharge – may be associated with worse outcomes<sup>14</sup> and that delirium in the PACU is likely predictive of further delirium in the postoperative course.<sup>13</sup> Unfortunately, delirium diagnosis in this period is confounded by the fact that emergence from general anaesthesia often presents with signs similar to delirium with alterations in mental status, inattentiveness, and disorganized thinking. We hypothesized that delirium signs would be most common immediately after general anaesthesia and decrease over time, that signs would persist in a significant number of patients at PACU discharge, that hypoactive features (often underdiagnosed in this setting) would be frequent, and that certain patient and anaesthetic characteristics (e.g. age, drug exposure) would predict increased probability of delirium signs. We, therefore, performed a prospective cohort study of patients undergoing general anaesthesia and assessed them for level of arousal using the Richmond Agitation-Sedation Scale (RASS)<sup>19</sup> and for delirium signs using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)<sup>1</sup> at multiple time points immediately after general anaesthesia.

**Methods****Study design and patient population**

This prospective observational study was approved by the Vanderbilt University Institutional Review Board with waiver of consent due to the non-interventional nature of the study. The principle investigator (EC), experienced in CAM-ICU<sup>1</sup> delirium assessments, first trained five PACU nurse investigators in delirium assessment. We included non-cardiac surgery patients admitted to the PACU at Vanderbilt University Medical Center after general anaesthesia with volatile anaesthetics. These patients were assigned by the charge nurse (in the usual round-robin, rotation fashion) to the PACU nurse investigators, as is standard PACU practice of assigning patients to PACU nurses/beds. Thus, this was a prospective convenience sample study of patients assigned randomly to our five nurse investigators. Exclusion criteria included non-English speaking or deaf patients and those with a history of severe dementia, anoxic brain injury, or neuromuscular disorders as documented in the patient's medical record by his/her treating physicians.

**Data collection**

Data collected included de-identified demographics (age, gender, race, American Society of Anesthesiologists [ASA] classification),

health history (comorbid diseases, chronic alcohol or illicit drug use, and smoking status), details of anaesthetic course (length of anaesthetic exposure, inhaled agent used, induction agent and dose, and lowest intraoperative vital signs [temperature, oxygen saturation, systolic and diastolic blood pressure]), perioperative medications (benzodiazepines, opioids, ketamine), PACU vital signs (lowest temperature, oxygen saturation, systolic and diastolic blood pressure), blood product administration, Aldrete scores,<sup>20</sup> and verbal pain scores.

**Assessments and definitions**

A multidisciplinary focus group of anaesthesiologists, intensivists, and nurses (including but not restricted to the authors) determined face valid definitions for agitated emergence and PACU delirium signs based on review of literature and expert opinion. Agitated emergence was defined as agitation after discontinuation of the inhaled anesthetic based on RASS score of +1 to +4 as reported by in-room anaesthesia providers. Patients were assessed for delirium signs using the CAM-ICU performed by the trained nurse investigators at PACU admission, at 30 min, at 1 h, and at discharge from the PACU. The CAM-ICU has been validated against the *Diagnostic and Statistical Manual of Mental Disorders-IV*<sup>21</sup> in both ventilated and non-ventilated verbal patients<sup>1 22–24</sup> and can be rapidly and accurately performed by bedside nurses. The CAM-ICU has a higher specificity than sensitivity for delirium when used in the PACU<sup>25</sup>; thus, we expected fewer false positives than false negatives, thereby taking a conservative approach to the determination of the incidence of delirium signs in our cohort. Delirium signs were defined as being present if patients were CAM-ICU positive at any time point. Hyperactive delirium signs were defined as a RASS score of +1 to +4 (i.e. agitated patient) accompanying a positive CAM-ICU. Hypoactive delirium signs were defined as a RASS score of –3 to 0 (i.e. somnolent or calm patient) accompanying a positive CAM-ICU. Postoperative delirium (not assessed in this study) was defined as delirium that continued beyond the PACU or occurred in the hospital ward or the ICU.

**Statistical analysis**

Descriptive data are presented as medians (with interquartile ranges [IQR]) and percentages where applicable. We used a multivariable logistic regression model to study the associations of perioperative risk factors with the occurrence of delirium signs during PACU stay (dependent variable). For the regression model alone, having PACU delirium signs was classified as a positive CAM-ICU at 30 min, at 1 h, or at PACU discharge (thus excluding the assessment upon arrival to the PACU for this was considered continuation of emergence from general anaesthesia). The following a priori defined risk factors were assessed: age, ASA classification, opioid exposure (fentanyl equivalents), and benzodiazepine exposure (midazolam equivalents). A sensitivity analysis was performed adjusting for anaesthetic duration in addition to these above mentioned risk factors, as a recent study demonstrated surgical duration to be associated with postoperative delirium.<sup>14</sup> In the statistical model, opioid doses were transformed using their cube root to reduce the influence of extreme outliers, and continuous variables were modelled using restricted cubic splines to allow for nonlinear associations. Benzodiazepine exposure was categorized into three categories (0, 0.5–2, and >2 mg) owing to sparseness of data.

Per standard recommendations, each degree of freedom for our multivariable model required 10 cases of delirium in order to reliably fit the model. Thus, a multivariable model with a

complexity of 7 degrees of freedom would require at least 70 patients with delirium.<sup>26</sup> We anticipated our PACU delirium signs rate to be approximately 20% in this cohort of general surgical patients, thus our study had a planned enrollment of 400 subjects into the cohort to be able to evaluate the risk factors of interest. Because missing data rarely occur entirely randomly, excluding such patients may have biased our results.<sup>27</sup> Thus, we used multiple imputation to account for missing variables at time of modelling, which occurred in 9 patients (2.3%). We calculated optimization to assess potential overfitting. Smaller optimization is indicative of less overfitting, and optimization <0.20 indicates a model with good predictive ability (lack of overfitting). Optimization in our PACU delirium model was 0.14, confirming that the model was not overfit. We used R software version 3.0.1 ([www.r-project.org](http://www.r-project.org)) for all statistical analyses. We used REDCap, a secure online database, supported in part by a National Institutes of Health grant (UL1 TR000445 from NCATS/NIH).

## Results

Between December 2010 and February 2012, 400 patients were enrolled in this convenience sample prospective cohort. Patient, anaesthesia, and surgery characteristics are presented in Table 1. Median (interquartile [IQR]) age was 57 (44, 67) years, ASA classification was 3 (2, 3), anaesthetic duration was 140 (87, 207) min, and 55% of the cohort was male.

Agitated emergence was present in 75 (19%) patients (Table 2). Of these 75 patients, 45 (60%) were also CAM-ICU positive at PACU admission, with 25 (33%), 12 (16%), and six (8%) continuing to be CAM-ICU positive at 30 min, at 1 h, and at PACU discharge, respectively. Thus, 30 patients (8%) had agitated emergence only without subsequent delirium signs.

Overall, 124 (31%) patients had delirium signs (positive CAM-ICU) at PACU admission, 56% of whom had hypoactive features based upon concomitant RASS score (Table 2). At PACU admission, median Aldrete scores were 8 (7, 8) in patients with concurrent delirium signs vs 8 (8, 9) in patients without signs. Median verbal pain scores at PACU admission in patients with vs without concurrent delirium signs were 0 (0, 2) vs 0 (0, 3).

Excluding the CAM-ICU evaluation at PACU admission, delirium signs were present during PACU stay in 65 (16%) patients overall and in 59 (15%), 32 (8%), and 15 (4%) patients at 30 min, at 1 h, and at PACU discharge, respectively (Table 2). Of these 65 patients with delirium signs during PACU stay, 92% had hypoactive features. At PACU discharge, median Aldrete scores were 9 (8, 9.8) in patients with concurrent delirium signs vs 10 (9, 10) in patients without signs. Median verbal pain scores at PACU discharge in patients with vs without concurrent delirium signs were 1 (0, 3.5) vs 0 (0, 2).

In our multivariable regression model, we found total perioperative opioid administration (fentanyl equivalents) to be independently associated with delirium signs during PACU stay ( $P=0.02$ , Table 3) after adjusting for relevant covariates. This association was nonlinear and is demonstrated in Fig. 1. The additional risk factors studied, including age, ASA classification, and benzodiazepine exposure, did not have significant associations with delirium signs during PACU stay in this cohort. Sensitivity analysis demonstrated that anaesthetic duration was also independently associated with delirium signs during PACU stay ( $P<0.001$ ).

## Discussion

In this study, 19% of patients had agitated emergence from general anaesthesia. Furthermore using a structured delirium

**Table 1** Description of Baseline Characteristics. \*Median (interquartile range) unless specified. †Total preoperative, intraoperative, and post-anaesthesia care unit administration. Abbreviations: ASA, American Society of Anesthesiologists; PACU, post-anaesthesia care unit

Variable*	n=400
Age (years)	57 (44, 67)
Sex ratio (M/F)	220/180
ASA Classification	3 (2, 3)
1	4%
2	44%
3	49%
4	3%
Comorbid Disease (% of patients)	
Malignancy	33%
Diabetes	17%
Cardiovascular Disease	13%
Congestive Heart Failure	4%
Liver Disease	3%
Mild Dementia	1%
Surgical Operation (% of patients)	
Urology	24%
General Surgery	22%
Orthopedic	19%
Neurosurgery	7%
Vascular	5%
Other	23%
Anaesthetic Duration (minutes)	140 (87, 207)
Inhalation Agent (% of patients)	
Sevoflurane	53%
Desflurane	35%
Isoflurane	12%
Benzodiazepines (midazolam equivalents, mg)†	2 (0, 2)
Opioids (fentanyl equivalents, µg)†	383 (200, 554)
Aldrete Score	
PACU admission	8 (8, 8)
PACU discharge	10 (9, 10)
Verbal Pain Score	
PACU admission	0 (0, 3)
PACU discharge	0 (0, 2)

**Table 2** Emergence and PACU Delirium Signs. Abbreviations: CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; PACU, post-anaesthesia care unit. Delirium assessments were performed at PACU admission, at 30 minutes, at 1 hour, and at PACU discharge using CAM-ICU.<sup>1</sup> Hypoactive delirium was defined as a Richmond Agitation-Sedation Scale<sup>19</sup> score of -3 to 0 accompanying a positive CAM-ICU. Hyperactive delirium was defined as a Richmond Agitation-Sedation Scale score of +1 to +4 accompanying a positive CAM-ICU

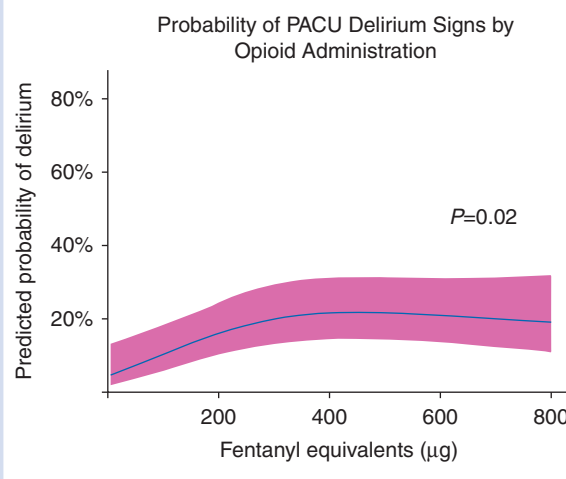
Outcome	n=400
Agitated Emergence	75 (19%)
Delirium signs at PACU admission (N)	124 (31%)
Hypoactive Subtype	56%
Hyperactive Subtype	44%
Delirium signs during PACU stay (N)	65 (16%)
Hypoactive Subtype	92%
Hyperactive Subtype	8%
CAM-ICU positive at 30 min (N)	59 (15%)
CAM-ICU positive at 1 h (N)	32 (8%)
CAM-ICU positive at PACU discharge (N)	15 (4%)

**Table 3** Risk factors for delirium signs during PACU Stay. \*Total preoperative, intraoperative, and post-anaesthesia care unit administration. †Nonlinear association. Abbreviations: ASA, American Society of Anesthesiologists; PACU, post-anaesthesia care unit. Multivariable logistic regression was used to study the association of potential risk factors with signs of delirium during PACU stay, defined as a positive Confusion Assessment Method for the Intensive Care Unit<sup>†</sup> at 30 min, at 1 h, or at discharge from the PACU. Perioperative opioid administration was significantly associated with delirium signs during PACU stay. The additional risk factors studied did not have significant associations with delirium signs during PACU stay. Given the nonlinear associations between opioid administration and delirium signs, a single odds ratio cannot represent the relationship and hence is not presented (see Fig. 1)

Variable, n=65	P-value
Age (yrs)	0.12
ASA Classification	0.20
Benzodiazepines (midazolam equivalents, mg)*	0.24
Opioids (fentanyl equivalents, µg)*	0.02 <sup>†</sup>

assessment tool at multiple time points immediately following general anaesthesia, we found a high incidence of delirium signs at arrival to the PACU and then continuing during the PACU stay, with a significant proportion of these patients manifesting signs consistent with hypoactive delirium. While the percentage of patients with delirium signs decreased over the PACU stay, 4% of patients still had persistent signs of delirium at PACU discharge despite meeting discharge criteria, indicating that these patients would not have been detected without delirium screening. Given that the volume of major surgery is greater than 230 million cases per year worldwide<sup>28</sup> and that PACU delirium is likely predictive of postoperative delirium,<sup>13</sup> this represents a substantial number of patients who leave the PACU with altered brain function and at risk for persistent delirium and its associated complications in the postoperative period. Of the risk factors studied, perioperative opioid administration was independently associated with delirium signs during PACU stay.

Studies evaluating patterns of abnormal emergence from general anaesthesia have focused on emergence delirium with reported prevalence rates of approximately 5%.<sup>29–30</sup> In our study, 19% of our patients emerged from general anaesthesia with agitation (as measured by a sedation-agitation scale), while 31% of our patients had signs consistent with delirium (measured with a highly specific delirium monitoring instrument) at admission to the PACU. Whether these delirium-like signs on PACU arrival are manifestations of delirium or are just “normal” emergence from general anaesthesia can be debated. Conversely, while there are no standard definitions of when emergence from an anaesthetic is considered complete, it is important to note that delirium signs persisted in about one-tenth of our patients 1 h after arriving in the PACU and in 4% of patients at PACU discharge, when they had met their Aldrete score<sup>20</sup> for readiness for discharge. Attention needs to be focused on early diagnosis and management of such patients, as recent data have shown that delirium at PACU discharge predicts postoperative delirium and potentially a decline in cognitive function and increased institutionalization after hospital discharge.<sup>13–14</sup> Furthermore, these patients with delirium signs at PACU discharge may have a form of persistent delirium, as opposed to rapidly reversible sedative-related delirium, portending worse outcomes.<sup>31</sup>



**Fig 1** Probability of PACU Delirium Signs by Opioid Administration. Total preoperative, intraoperative, and post-anaesthesia care unit (PACU) opioid administration was independently associated with delirium signs during PACU stay, defined as a positive Confusion Assessment Method for the ICU<sup>†</sup> at 30 min, at 1 h, or at discharge from the PACU. The solid line demonstrates the predicted probability of developing PACU delirium signs according to fentanyl equivalents received, with the pink ribbon indicating the 95% confidence interval. This association was most meaningful when examined between the 5th (50 µg fentanyl) and 50th (383 µg fentanyl) percentiles of opioid administration (common dose ranges for opioids in patients undergoing general anaesthesia) in our cohort, such that a patient receiving opioids equivalent to 383 µg fentanyl would have over 6 times the adjusted odds of developing delirium signs during PACU stay than a patient receiving 50 µg fentanyl (odds ratio [OR] 6.2, 95% CI 1.7, 22.1). Alternatively, when comparing the 50th to the 95th percentiles of opioid administration within our cohort, a patient receiving 383 µg fentanyl would have similar adjusted odds of developing delirium signs during PACU stay than a patient receiving 850 µg fentanyl (OR 0.88, 95% CI 0.45, 1.71). The lack of association at the higher doses could reflect a ceiling effect of the role of opioids in contributing to delirium signs or be a manifestation of fewer patients receiving such large doses.

Our incidence of delirium signs was lower than the 45% reported in a recent cohort by Neufeld and colleagues<sup>14–25</sup> which examined postoperative delirium in 91 patients >70 yr old by performing neuropsychiatric evaluations *after* patients had completed recovery from anaesthesia (Aldrete score<sup>20</sup> ≥9 and at least 45 min of elapsed PACU time). The elderly patient population studied was likely at higher risk for developing delirium signs than our population, whose median age was 57 yr old. In addition, the CAM-ICU has a higher specificity than sensitivity for delirium in low severity of illness patients, especially in the PACU<sup>25–32</sup>; thus, we likely *underdiagnosed* delirium signs in our cohort. While neuropsychiatric evaluations by specifically trained personnel using the *Diagnostic and Statistical Manual of Mental Disorders*<sup>21</sup> are generally held as the reference standard, they are time- and resource-intensive. We chose the CAM-ICU over the CAM<sup>33</sup> secondary to its ease of use and practicality for assessment in the PACU setting (e.g. rapid patient turnover, frequent physiologic changes, occasional nonverbal patient), given the CAM-ICU can be performed by trained nursing staff at the bedside in less than 2 min. Furthermore, in promoting delirium screening in the PACU, a concise tool such as the CAM-ICU or brief CAM (bCAM)<sup>34</sup> is more likely to be adopted and utilized on a daily basis.

We found opioid administration to be associated with delirium signs during PACU stay after adjusting for covariates such as age,

ASA classification, and duration of anaesthesia. In our cohort, pain scores at both PACU admission and PACU discharge were overall low and clinically comparable in patients with vs without concurrent delirium, suggesting pain was an unlikely cause of delirium in our cohort. One may assume that higher opioid doses contributed to additional sedation, thus potentially contributing to hypoactive delirium features, but the association between opioid administration and delirium signs was most meaningful at lower opioid doses (Fig. 1). The lack of association at higher doses could reflect a ceiling effect of the role of opioids in contributing to delirium signs. Prior studies have not shown a consistent association of opioid analgesia with perioperative delirium, with some suggesting increased risk<sup>2, 35–37</sup> and others suggesting either no association<sup>38</sup> or a reduction in delirium rates.<sup>7</sup> Thus while it is important to achieve adequate pain control in the perioperative setting, it is also imperative to recognize that overzealous administration of these medications may contribute to delirium signs.

Previously reported risk factors of postoperative delirium (in hospital wards or ICUs) seem to be predominantly related to the preoperative medical conditions, severity of surgical insult, and sedative and analgesic drug exposure.<sup>35, 36, 39–45</sup> While both young and old age have been associated with emergence delirium,<sup>30</sup> our cohort had a median age of 57 yr, with only a few patients <40 or >65 yr old, potentially negating the impact of age on delirium signs in our study. Additionally, 93% of our cohort had an ASA classification of 2 or 3, making it difficult to study any significant differences based on ASA classification. We did not assess the relationship of surgical insult with delirium signs, and we did not find any relationship between benzodiazepine use and delirium signs as previously reported,<sup>29, 30, 36, 46</sup> possibly reflecting the low dose and usage of benzodiazepines currently in our practice (96% of patients received 0–2 mg of midazolam).

This study has both strengths and limitations. We were able to detect signs of delirium in patients immediately after general anaesthesia, including both hyperactive and hypoactive features, with a structured delirium assessment tool. Though this was a single academic center study, our large cohort size with a wide range of non-cardiac surgical operations should be applicable to a broader patient population. Our incidence of PACU delirium signs was lower than predicted, limiting our regression model and increasing the potential for hidden confounders. A larger cohort would have enabled us to study additional factors (e.g. postoperative nausea and vomiting, use of regional nerve blockade) while also increasing our power to detect associations that might be significant. We did conduct a sensitivity analysis that demonstrated a significant association between increased anaesthetic duration and increased risk of delirium in the PACU; however, this result needs to be interpreted with caution as this model was potentially overfit. Although neither delirium assessments nor cognitive status evaluations were performed preoperatively, all patients met the criteria for consenting adults preoperatively. Without specific testing, however, we do not know if any of the patients with delirium signs postoperatively were delirious prior to general anesthetic exposure or had evidence of mild cognitive impairment, both of which could have increased their risk for postoperative delirium signs. We did, however, exclude patients with known severe dementia or other neurocognitive disease or who were unable to sign their informed consent for surgery.

We used the RASS to assess for agitated emergence since performance of CAM-ICU assessments at emergence from general anaesthesia is not clinically feasible, and we did not perform pain score evaluations on patients at the time of emergence. While agitated emergence may be secondary to pain, the majority

of patients with agitated emergence based upon RASS in our study were also CAM-ICU positive at admission to the PACU. Furthermore, there were no differences in pain scores in patients with vs without delirium signs at PACU admission. Thus, they possessed signs of brain dysfunction such as inattention or disorganized thinking, suggesting the hyperactive features upon emergence were not due to pain in the majority of these patients. This is in agreement with recent data that demonstrate moderate sensitivity and high specificity of abnormal RASS measurements for delirium.<sup>47, 48</sup> Delirium assessments were completed by the same bedside nurse investigators who were also providing bedside care, a common and practical approach used in other hospital settings, but also a potential source of bias since the delirium assessments were not blinded. Finally, we did not evaluate the patients for delirium after they were discharged from the PACU or assess hospital or long-term outcomes. Therefore, we cannot comment on the continued trajectory of delirium signs further in the postoperative period and the effects they may have on patient outcomes.

## Conclusions

In conclusion, in this prospective observational study of patients undergoing general anaesthesia, we found delirium signs in the immediate postoperative period to be common, with the incidence highest upon arrival to the PACU and decreasing during the PACU stay, though some patients had persistent delirium signs at discharge from the PACU. Hypoactive features were common and far more prevalent during PACU stay compared to hyperactive features. Routine delirium monitoring in the PACU may therefore be important, since delirium at discharge from the PACU is likely associated with worse outcomes. Additional research is needed to assess if the mortality or morbidity associated with delirium in hospitalized and critical care patients is applicable to patients with delirium signs in the immediate postoperative period.

## Authors' contributions

E.B.C.: study design, data collection, data analysis, manuscript preparation. P.P.P, A.J.G, A.K.S, E.W.E, C.G.H.: study design, data analysis, manuscript preparation. C.M.T, C.A.L, J.M.W, D.M.N.: data collection, manuscript preparation.

## Declaration of interest

No conflicts of interest.

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