Delirium after Cardiac Surgery: A Pilot Study from a Single Tertiary Referral Center

Abstract

Background: Advances in cardiac surgery has shifted paradigm of management to perioperative psychological illnesses. Delirium is a state of altered consciousness with easy distraction of thoughts. The pathophysiology of this complication is not clear, but identification of risk factors is important for positive postoperative outcomes. The goal of the present study was to prospectively identify the incidence, motoric subtypes, and risk factors associated with development of delirium in cardiac surgical patients admitted to postoperative cardiac intensive care, using a validated delirium monitoring instrument. **Materials and Methods:** This is a prospective, observational study. This study included 120 patients of age 18–80 years, admitted to undergo cardiac surgery after applying inclusion and exclusion criteria. Specific preoperative, intraoperative, and postoperative data for possible risk factors were obtained. Once in a day, assessment of delirium was done. Continuous variables were measured as mean ± standard deviation, whereas categorical variables were described as proportions. Differences between groups were analyzed using Student's t-test, Mann–Whitney U-test, or Chi-square test. Variables with a $P < 0.1$ were then used to develop a predictive model using stepwise logistic regression with bootstrapping. **Results:** Delirium was seen in 17.5% patients. The majority of cases were of hypoactive delirium type (85.72%). Multiple risk factors were found to be associated with delirium, and when logistic regression with bootstrapping applied to these risk factors, five independent variables were detected. History of hypertension (relative risk [RR] =6.7857, $P = 0.0003$), carotid artery disease (RR = 4.5000, $P < 0.0001$) in the form of stroke or hemorrhage, noninvasive ventilation (NIV) use (RR = 5.0446, $P < 0.0001$), Intensive Care Unit (ICU) stay more than 10 days (RR = 3.1630, $P = 0.0021$), and poor postoperative pain control (RR = 2.4958, $P = 0.0063$) was associated with postcardiac surgical delirium. **Conclusions:** Patients who developed delirium had systemic disease in the form of hypertension and cerebrovascular disease. Delirium was seen in patients who had higher postoperative pain scores, longer ICU stay, and NIV use. This study can be used to develop a predictive tool for diagnosing postcardiac surgical delirium.

Keywords: *Delirium, Intensive Care Unit, postcardiac surgery delirium*

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Introduction

Delirium is defined as an "acute disturbance in consciousness along with impaired thought processing and easy distraction."[1] Patients' ability to receive information, store, recall, and judge is disturbed.[2] Inattention is characteristic finding in delirium. Importance of identifying and treating delirium has gained importance very late. Early recognition of delirium and its prevention is important since delirium correlates with increased length of hospital stay, increased morbidity and mortality, and impaired cognitive and functional recovery.[3,4] With particular reference to the postoperative cardiac surgery, delirium can persist even after discharge from cardiac Intensive Care Unit (ICU) in the form of functional disability which may have significant impact on patient's quality of life. Patients developing postoperative delirium may have postoperative respiratory insufficiency and have high prevalence of sternum instability and need revision surgery for sternum.[4]

There is increasing interest in developing India, specific data with regard to the complications after cardiac surgery and methods of predicting them in diverse group of patients.[5] The goal of the present study was to prospectively study the prevalence, motoric subtypes, and risk factors associated with the development of delirium in cardiac surgical patients admitted to the postoperative cardiac ICU, using a

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validated delirium monitoring instrument. This study was designed to be a derivation cohort for a larger study in designing a model that can predict the development of delirium after cardiac surgery. The risk factors so identified will then be tested at a later date in a validation cohort in a larger patient population. The identification of such risk factors we believe will then help us target modifiable risk factors involved in the development of postcardiac surgery delirium in our practice.

Aims and objectives

The aim of this study was to assess the perioperative factors that predispose to cause delirium in postoperative cardiac surgery patients in our ICU and to develop a risk model for the same that can be tested in a larger validation cohort.

Materials and Methods

After obtaining approval from the Institute Ethics Committee, all consenting serial adult patients (18–80 years), 120 in number who underwent elective or emergency surgery for coronary artery disease, valve replacement/repair, and other open heart surgeries were enrolled in this study. Exclusion criteria include patients with preexisting delirium on screening at preoperative evaluation on the confusion assessment method (CAM), those on mechanical ventilation, those with deafness, and those refusing consent.

Specific preoperative data such as history of substance abuse, stroke, renal dysfunction, and other medical disorders were obtained. Anesthesia management was done as per the standard institutional protocol. The choice of monitors, placement of pulmonary artery catheters, choice of anesthesia induction agents, and maintenance of anesthesia were left to the discretion of the attending team. Data were obtained on each of these facets as per the questionnaire enclosed. Precardiopulmonary bypass and postbypass the anesthesia provider had attempted to keep mean arterial pressures within ± 20% of baseline or a mean arterial pressure >60 mmHg; the choice of vasopressors, inotropes, and vasodilators was left to the attending anesthetist. α-stat pH management was used. Surgery was performed during mild hypothermia to normothermia (32°C–36°C). Patients were shifted to ICU after the procedure for mechanical ventilation. Titrated doses of propofol/midazolam and bolus doses of morphine were used in the postoperative period. Patients were weaned from mechanical ventilation at the discretion of the ICU physician.

Data collection

Baseline demographics and information regarding preadmission risk factors for delirium were obtained at admission. Intraoperative data such as cardiopulmonary bypass (CPB) time, aortic cross-clamp time, and inotrope use were obtained. Postoperatively, total amount of midazolam, bolus doses of morphine, and the total time on mechanical ventilation and other variables were noted. Daily Richmond Agitation–Sedation Scale (RASS) scoring was done and scores with −4 and 5 were deemed as comatose and not assessable. Those with RASS scores −3 and more were evaluated using the CAM-ICU. The CAM-ICU scores were obtained on the day of extubation, patients were scored for maximum of 5 days or till ICU discharge, and any change in these scores was recorded. All the critical perioperative events and ICU course were noted. Delirium assessment was performed by anesthesia resident/consultant, following rounds each day. We have used the RASS scale in CAM-ICU to define motoric subtypes of delirium. Patients with CAM-ICU positive and RASS scores positive (+1 to + 4) for every evaluation were considered as having hyperactive delirium; in these patients, delirium manifested in the form of restlessness, agitation, and pulling of devices. Those with CAM-ICU positive and RASS scores negative (0–−3) with every evaluation were considered as having hypoactive delirium; this manifested as lethargy, somnolence, and inattention. In addition to these data, EuroSCORE and sequential organ functional assessment scoring were also enumerated.

Statistical analysis

Continuous variables were profiled as mean ± standard deviation (SD), whereas categorical variables were described as proportions in the groups with and without delirium. Differences between groups were analyzed using Student's *t*-test, Mann–Whitney U-test, or Chi-square test as applicable. Variables with a $P < 0.1$ were then used to develop a predictive model for postcardiac surgical delirium using stepwise logistic regression with bootstrapping.

Observations and Results

One hundred and twenty patients who underwent elective or emergency cardiac surgery and were subsequently admitted to cardiac surgical ICU were enrolled into this study. All subjects were screened for delirium using the CAM-ICU test once daily, and all those who tested positive were thereafter designated as cases and the other subjects were deemed controls.

Among 120 patients, 21 patients (17.5%) were found to have delirium and 99 patients (82.5%) were delirium free. Hyperactive type of delirium was seen in 3 patients (14.28%) while the remaining 18 patients (85.72%) had hypoactive delirium. One mortality happened in hyperactive delirium group.

Demographic data

The Chi-square test was used for evaluation of age, sex, and education status; Yates correction was used for marital status. Of those with delirium, 8 patients (38.1%) were below the age of 60 years while the remaining 13 cases (61.9%) were older than 60 years. Thus, age >60 years was a

significant predictor of delirium ($P = 0.002$). Patients' gender ($P = 0.460$), marital status ($P = 0.144$), and education status ($P = 0.601$) were not significantly different between cases and controls [Table 1].

Preoperative factors

The diagnosis at presentation was not a significant predictor of delirium. A total of 9 cases (42.9%) had valvular disease,

11 cases (52.4%) suffered from coronary artery disease, and one patient with delirium had presented for surgical closure of an atrial septal defect [Table 2].

Among the preoperative factors, a history of hypertension, diabetes, preoperative renal dysfunction, New York Heart Association Class (NYHA) 3 or 4 and a history of carotid artery disease are found to be statistically significant ($P < 0.05$) on univariate analysis to be associated with delirium. A history of drug abuse, alcohol intake, thyroid disease, previous cardiac surgery, history of stroke, vascular disease, and depression was insignificantly associated with the diagnosis of delirium. Left ventricular ejection fraction <30%, preoperative atrial fibrillation, cardiogenic shock, presence of severe pulmonary artery hypertension, emergency nature of surgery, and premedication with benzodiazepines were not significantly associated with delirium. The additive EuroSCORE was not significantly associated with delirium. Seventeen patients (81.0%) among the cases had EuroSCORE 1–5 and 4 patients (19.0%) had EuroSCORE 6–10.

Intraoperative factors

Categorical intraoperative factors were evaluated using Chi-square or Yates correction of Chi-square test. Continuous variables were evaluated using mean, SD, and

Table 1: Demographic characteristics

	Group		*P*
	Control, *n* (%)	Case, *n* (%)	
Age (years)			
≤60	73 (73.7)	8 (38.1)	0.002
>60	26 (26.3)	13 (61.9)	
Gender			
Male	65 (65.7)	12 (57.1)	0.460
Female	34 (34.3)	9 (42.9)	
Education			
High school and below	58 (58.6)	11 (52.4)	0.601
Above high school	41 (41.4)	10 (47.6)	
Marital status			
Unmarried	14 (14.1)	0	0.144**
Married	85 (85.9)	21 (100.0)	

**Yate's corrected Chi-square test

Table 2: Preoperative factors

	Group		*P*
	Controls (*n*=99), *n* (%)	Cases (*n*=21), *n* (%)	
Diagnosis			
Valvular heart disease	44 (44.4)	9 (42.9)	0.894
Coronary artery disease	36 (36.4)	11 (52.4)	0.172
Acyanotic congenital heart disease	10 (10.1)	1 (4.8)	0.723**
Congenital cyanotic heart disease	2 (2.0)	0	0.778**
Vascular surgery	7 (7.1)	0	0.457**
Drug abuse	2 (2.0)	1 (4.8)	1.000**
Alcoholic	12 (12.1)	4 (19.0)	0.621**
HTN	27 (27.3)	15 (71.4)	<0.0001
Diabetes	15 (15.2)	8 (38.1)	0.034**
Thyroid disease	4 (4)	0	0.789**
History of cardiac surgery	9 (9.1)	2 (9.5)	1.000**
History of stroke	5 (5.1)	2 (9.5)	0.778**
Vascular disease	4 (4.0)	1 (4.8)	1.000**
Depression	1 (1.0)	0	1.000**
Renal dysfunction	3 (3.0)	4 (19.0)	0.020**
LVEF<30%	8 (8.1)	0	0.386**
Atrial fibrillation	17 (17.2)	1 (4.8)	0.267**
Emergency surgery	7 (7.1)	1 (4.8)	1.000**
Cardiogenic shock	2 (2)	0	1.000**
Severe PAH%	8 (8.1)	1 (4.8)	0.945**
NYHA 3 or 4	36 (36.4)	14 (66.7)	0.011
Premedication	88 (88.9)	18 (85.7)	0.970**
Carotid artery disease	5 (5.1)	7 (33.3)	<0.0001

**Yate's corrected Chi-square test. LVEF: Left ventricular ejection fraction, PAH: Pulmonary artery hypertension, NYHA: New York Heart Association, HTN: Hypertension

t-test for normally distributed data. The choice of induction agents used (thiopentone, ketamine, and midazolam) was not significantly associated with delirium; however, the use of propofol ($P = 0.015$) as induction agent was associated with delirium. Total patients induced with propofol in control group were 98 (99%) and for cases 18 (85.7%). There was no association between delirium and intraoperative blood transfusion, temperature >36°C, temperature <28°C, phenylephrine use for more than five min, and use of propofol or isoflurane as the maintenance agent [Table 3].

There was no significant association between CPB time and aortic cross-clamp time with postoperative delirium. Intraoperative use of morphine and fentanyl was not significantly associated with delirium. In 94 patients, mean morphine used in control group was 30.85 ± 29.768 and in cases of 19 was 30.85 ± 29.768. Mean use of fentanyl in 99 patients of control group was 300.81 ± 133.880 and in 20 patients of cases was 300.81 ± 133.880.

Postoperative factors

Postoperative factors such as reoperation, postoperative atrial fibrillation, fresh frozen plasma or platelet transfusion, cardiogenic shock, postoperative infection, bilirubin >2 mg/dL, use of atropine, Na^+ >140 mEq, PaO_2 <70 mmHg, prolonged hypotension, and sleep deprivation were not significantly related to delirium. Delirium was significantly associated with postoperative

blood transfusion, intra-aortic balloon pump (IABP) use, hematocrit <30, postoperative pain, creatinine >2 mg/dL, and noninvasive ventilation (NIV) use. Postoperative blood transfusion was seen in 16 cases (76.2%). IABP use was present in 2 of controls (2.0%) and 3 among cases (14.3%). Hematocrit <30 was seen in 15 cases (71.4%) and raised levels of creatinine (>2 mg/dL) was seen in 6 cases (28.6%). NIV use was present in 14 patients (14.1%) among control group and 9 patients (42.9%) among cases. Postoperative chest drain volumes were not significantly associated with delirium [Table 4]. Duration of mechanical ventilation was not significantly associated with delirium. With respect to stay in ICU, there was a significant association with patients staying from days 1 to 5 and stay >10 days but no association with duration of ICU stay if this lasted between 6 and 10 days.

There were no significant differences between cases and controls in the amounts of midazolam and morphine administered in ICU. Mean midazolam use among 44 controls was 10.18 ± 12.348 mg and among 15 cases was 10.18 ± 12.348 mg. Morphine among 98 patients of control group was given with median and interquartile range (IQR) of 27 (15.0–42.50) and that of 21 cases was 32 (16.5–45.0). Sequential organ failure assessment score and numerical rating scores for pain differed significantly between cases and controls. Median and IQR for pain score in the control group with 99 patients were 2 (2.0–3.0), and for the 21 cases, it was 3 (2.0–4.0).

Logistic regression analysis with bootstrapping

We applied logistic regression analysis with bootstrapping to the variables which were significant on univariate analysis. Those with $P \leq 0.1$ were included in logistic regression. After applying logistic regression, history of hypertension, carotid disease, ICU stay more than 10 days, NIV use, and pain scale are found to be independent risk factors for delirium. As our sample size was small and this was a pilot study, we have applied bootstrapping analysis. We have applied bootstrapping to same variables those were applied for logistic regression. We used bootstrap samples of 1000 with random number generator using a Mersenne twister. After applying bootstrapping, there was no change in number of variables which were significant. The relative risk of each of these variables is presented in Table 5.

Discussion

The last century has seen tremendous improvement in the perioperative care domain in terms of gross outcomes such as mortality and serious morbidity, particularly for elective care.[6] However, as this classic anesthesia treatise points out, there are rapidly emerging challenges such as care of aging patients in an ever extending spectrum of surgical complexity. There is therefore increased focus in evolving protocols and standards of care for this vulnerable

Table 3: Intraoperative factors

	Group		*P*
	Controls (*n*=99), *n* (%)	Cases (*n*=21), *n* (%)	
Induction agent			
Propofol	98 (99.0)	18 (85.7)	0.015**
Midazolam	1 (1.0)	1 (4.8)	0.778**
Thiopentone	0	1 (4.8)	0.390**
Ketamine	0	1 (4.8)	0.390**
Blood transfusion	42 (42.4)	11 (52.4)	0.404
Temperature (°C)			
<28	5 (5.1)	1 (4.8)	1.000**
>36	46 (46.5)	9 (42.9)	0.763
Phenylephrine use (min)			
>5	21 (21.2)	7 (33.3)	0.363**
CPB time (min)			
≤60	6 (6.1)	1 (4.8)	0.778**
61-120	25 (25.3)	4 (19.0)	0.546
>120	68 (68.7)	16 (76.2)	0.495
Aortic clamp time (min)			
≤60	13 (13.1)	2 (9.5)	0.927**
61-120	55 (55.6)	13 (61.9)	0.593
>120	31 (31.3)	6 (28.6)	0.804

**Yate's corrected Chi-square test. CPB: Cardiopulmonary bypass

Table 4: Postoperative factors

	Group		P
	Controls (*n*=99), *n* (%)	Cases (*n*=21), *n* (%)	
Reoperation	3 (3.0)	0	0.969**
Postoperative atrial fibrillation	24 (24.2)	3 (14.3)	0.481**
Postoperative blood transfusion	51 (51.5)	16 (76.2)	0.039
FFP/platelet transfusion	37 (37.4)	10 (47.6)	0.382
Postoperative cardiogenic shock	4 (4.0)	2 (9.5)	0.620**
IABP use	2 (2.0)	3 (14.3)	0.051**
Postoperative infection	2 (2.0)	1 (4.8)	1.000**
Hematocrit <30	44 (44.4)	15 (71.4)	0.025
Creatinine >2 mg/dL	5 (5.1)	6 (28.6)	0.003**
Bilirubin >2 mg/dL	6 (6.1)	2 (9.5)	0.923**
Atropine use	1 (1.0)	1 (4.8)	0.778**
Postoperative pain	17 (17.2)	9 (75)	0.0212**
Sodium >140 mEq	30 (30.3)	10 (47.6)	0.126
PaO$_2$ <70 mmHg	7 (7.1)	0	0.457**
NIV used	14 (14.1)	9 (42.9)	0.006**
Prolonged hypotension	33 (33.3)	8 (38.1)	0.676
Sleep deprivation	10 (10.1)	3 (14.3)	0.862**
Postoperative drain (ml)			
≤500	80 (80.8)	16 (76.2)	0.857**
501-1000	14 (14.1)	4 (19.0)	0.813**
>1000	5 (5.1)	1 (4.8)	0.619**
Mechanical ventilation time			
<12 h	19 (19.2)	3 (14.3)	0.828**
12-24 h	68 (68.7)	12 (57.1)	0.310
25-48 h	7 (7.1)	2 (9.5)	0.945**
49-72 h	2 (2.0)	1 (4.8)	0.969**
>3 days	3 (3.0)	3 (14.3)	0.110**
ICU stay (days)			
1-5	71 (71.7)	8 (38.1)	0.003
6-10	26 (26.3)	8 (38.1)	0.275
>10	2 (2.0)	5 (23.8)	0.0008**

**Yate's corrected Chi-square test. NIV: Noninvasive ventilation, ICU: Intensive Care Unit, IABP: Intra-aortic balloon pump, FFP: Fresh frozen plasma

Table 5: Logistic regression analysis with bootstrapping: Relative risk for variables associated with delirium

Risk factors	RR with CI	P value
History of HTN	6.7857 (2.4067-19.1327)	0.0003
Carotid artery disease	4.5000 (2.2713-8.9157)	<0.0001
ICU stay >10 days	5.0446 (2.6272-9.6864)	<0.0001
NIV use	3.1630 (1.5166-6.5970)	0.0021
Postoperative pain	2.4958 (1.2944-4.8123)	0.0063

HTN: Hypertension, ICU: Intensive Care Unit, NIV: Noninvasive ventilation, CI: Confidence interval, RR: Relative risk

group of patients. Delirium in the postoperative period and in intensive care is an area of active research since it is estimated to have huge public health importance given the large occurrence and equivocal results from pharmacological prevention.[7] This complication of in-hospital care is also not innocuous as it is associated with multiple adverse outcomes some as serious as death and others such as increased length of stay in intensive

care and in hospital.[8] There is also a huge divergence in the risk factors for delirium and the actual incidence across populations.[9] There is also apprehension that in specialized intensive care, the incidence of this complication is higher.[10] This study was motivated to generate epidemiologic data regarding this complication in our health system; in line with the development of risk models, this is designed to be a derivation cohort to give us a point estimate of the occurrence of delirium and the possible risk profile of patients who suffer this complication.

We found an incidence of 17.5% in our cohort of 120 patients. The CAM-ICU was used on a daily basis for the first 5 postoperative days or till ICU discharge as typical assessments of this condition are currently performed.[11] This incidence is either comparable or much lower than that of other cardiovascular surgical ICUs.[11,12] The divergence in estimates of occurrence is in our using an unselected population whereas selecting only geriatric patients would have led to higher estimated incidence. We

also did not use a translated assessment instrument unlike other groups;[13] further, the CAM-ICU has always shown a higher occurrence of delirium in validation studies but not so in daily practice[14] where other instruments might yield a higher sensitivity but at the cost of lower specificity.[15]

In parallel with the global literature on the subject, age was a weighty factor on univariate analysis, but this association was not sustained later on multivariate logistic regression. Like ICU delirium elsewhere, most patients were hypoactive rather than hyperactive sustaining the methodology of regular and systematic examination to avoid a missed diagnosis. A host of other variables was found to be significantly associated with delirium on univariate analysis; some of these factors such as higher severity of illness (as reflected by higher NYHA class of dyspnea) or renal dysfunction were shown in other studies as well.[16] However, our cohort did not replicate older literature in showing that higher values of EuroSCORE, the use of midazolam, emergency nature of surgery impacted the course of delirium.[3]

Our study therefore shows that in our population, we may indeed have a distinct set of factors different from other cardiac surgical ICUs. However, the sample size of our study is clearly a limitation in making conclusive remarks about any of these risk factors. Bootstrapping is a common statistical tool that draws strength from the idiom that "bootstrapping is to the sample what sample is to the population;" it can significantly improve the predictive value of variables from a relatively small population. Although distinct variables were shown to be associated with delirium on univariate analysis, only five variables are seen to be associated with delirium in this derivation cohort. These variables are history of hypertension, carotid disease, ICU stay more than 10 days, NIV use, and pain scale are found to be independent risk factors for delirium. Patients with a history of cerebrovascular disease had higher incidence of delirium 7 (33.3%) than without delirium 5 (5.1%). In our study, it was found as an independent risk factor for delirium. A study by Bucerius *et al.*[16] found a history of carotid artery disease strongly predicted delirium. This increased risk can be explained by the presence of atherosclerotic plaques in the carotid arteries.[17] Risk of cerebral embolization increases in generalized atherosclerotic disease, particularly during intraoperative manipulation and cannulation of aorta.[18] A recent study found decreased oxygen saturation suggesting decreased cerebral perfusion preoperatively using cerebral oximetry as a risk factor for postoperative delirium.[19] Although Bucerius *et al.*[16] found increased risk is seen in patients with atrial fibrillation suggesting cause of microembolization, in our study we did not find any significance of atrial fibrillation with delirium. ICU stay was longer in patients with delirium in our study. Among patients with delirium, 23.8% stayed for more than

10 days and 61.9% were stayed more than 5 days in ICU, whereas in the control group, only 28.3% stayed more than 5 days. Other studies gave this association of longer ICU stay with prolonged ventilation with delirium.[20] We could not demonstrate these associations in our final analysis, but this will need confirmation in a larger validation cohort.

In our study, we found association of higher pain score on numeric rating scale (NRS) with delirium. In a study conducted by Lynch *et al.*,[21] higher postoperative rest pain score was seen associated with delirium, but not pain with movement. The mean resting pain score in their study was 3.8 ± 3.8 (our study median NRS value was 3). A study by Smulter *et al.*[22] also found this association. In contrast, Marcantonio *et al.*[23] reported that pain is not associated with risk of postoperative delirium. The drugs used to alleviate pain, particularly opioids, are known to cause both delirium and postoperative cognitive dysfunction.[24] This paradoxical association highlights the balance between adequate pain control, analgesic choice, and delirium reduction.

Our study found significant association ($P = 0.006$) of NIV with delirium. To the best of our knowledge, this was the first prospective study where NIV use after cardiac surgery is related with delirium. A meta-analysis by Charlesworth *et al.*[25] concluded association of delirium with NIV failure based on three previous studies. This study was based on medical illness with acute respiratory failure, not of cardiac cause. Use of NIV in ICU is for patients with hypoxia and with hypercarbia in the process of weaning after extubation. This might be associated with delirium because cerebral hypoxia is one of the important causes for delirium and hypercarbia is associated with drowsiness and hypoventilation.

As with all derivation cohorts, the exact occurrence of delirium and its associated precipitating and predisposing factors will need further validation in a bigger sample. Our study has limited sample size to draw conclusions; however, our pilot study lays the groundwork for refining the epidemiology of postcardiac surgery delirium in our country.

Summary and Conclusions

Our study was designed to be a derivation cohort for postcardiac surgery delirium in adult patients presenting to a tertiary referral center. This study shows that while the occurrence of delirium is 17.5%, five factors predict the occurrence of delirium when a comprehensive list of preoperative, intraprocedural, and postoperative data is collated although a host of other factors figures in the univariate analysis. This will need further corroboration in a larger cohort of patients.

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Conflicts of interest

There are no conflicts of interest.

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