Original Article

Factors Associated with Delirium after Cardiac Surgery: A Prospective Cohort Study

Lina Maria Ordóñez-Velasco, Edgar Hernández-Leiva[1]

Intensivist at Cardiovascular Intensive Care Unit. Instituto de Cardiología – Fundación Cardioinfantil, [1]Department of Cardiology, Head of the Cardiac Surgical Intensive Care Unit, Instituto de Cardiología – Fundación Cardioinfantil, Colombia

ABSTRACT

Background: Delirium is a frequent complication after cardiac surgery and is associated with a higher incidence of morbidity and mortality and a prolonged hospital stay. However, knowledge of the variables involved in its occurrence is still limited; therefore, in this study, we evaluated the perioperative risk factors independently associated with this complication.

Methods: This study was conducted in a referral tertiary care university hospital with a cardiovascular focus. A total of 311 consecutive adult patients undergoing any type of cardiac surgery were evaluated. The subjects were examined at regular intervals in the postoperative period using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) tool.

Results: The incidence of postoperative delirium (PD) was 10%. Among the 18 pre-, intra- and postoperative variables evaluated, the logistic regression analysis showed that low education level, history of diabetes or stroke, type of surgery, prolonged extracorporeal circulation, or red blood cell transfusion in the intra- or postoperative period were independently associated with delirium after cardiac surgery. An increased body mass index was identified as a protective factor.

Conclusions: The aforementioned risk factors are significantly and independently associated with the presentation of PD. Because some of these factors can be treated or avoided, the results of this study are highly relevant to reduce the risk of this complication and improve the care of patients undergoing cardiac surgery.

Keywords: Body mass index, cardiopulmonary bypass, cerebral near infrared spectroscopy, intensive care unit, postoperative delirium

Address for correspondence: Dr. Edgar Hernández Leiva, Calle 163 A # 13B-60, Bogotá DC, Cundinamarca, Colombia.
E-mail: edgarhernandez@cardioinfantil.org

Submitted: 02-Mar-2020 **Revised:** 30-May-2020 **Accepted:** 26-Jun-2020 **Published:** 19-Apr-2021

INTRODUCTION

Postoperative delirium (PD) is the most frequent neuropsychological complication after cardiac surgery, with a reported prevalence of between 25% and 50%.[1] Clinically, it manifests as an acute and fluctuating change in cognition with characteristics of inattention, disorganized thinking, and altered consciousness.[2] PD has been found to be consistently related to increased mortality, prolonged hospital stay, higher costs, and other complications such as infection and stroke.[3]

Multiple causal factors have been reported, including pre-existing conditions, surgical-anesthetic management, and postoperative care. However, despite its frequency, the pathophysiology of PD remains poorly understood, and its management is a clinical challenge, even today,

Access this article online	
Quick Response Code:	Website: www.annals.in
	DOI: 10.4103/aca.ACA_43_20

How to cite this article: Ordoñez-Velasco LM, Hernández-Leiva E. Factors associated with delirium after cardiac surgery: A prospective cohort study. Ann Card Anaesth 2021;24:183-9.

because few therapeutic tools are available. Therefore, a very important goal in postoperative management is to reduce the incidence of PD by identifying and treating modifiable risk factors. The main objective of this study was to identify independent risk factors associated with the onset of PD.

METHODS

The study was conducted in a referral tertiary care university hospital with a cardiovascular focus.

Design

A prospective analytical study of a concurrent cohort was conducted, consecutively including all adult patients undergoing any type of cardiac surgery. Patients admitted to the intensive care unit (ICU) before surgery or with a diagnosis of delirium or psychiatric illness before surgery were not included. Another exclusion criterion was a history of taking any type of antipsychotic medication in the last month. Aspects such as preoperative evaluation, premedication, and anesthetic and surgical techniques were performed according to institutional protocols; no changes were made for the participants. Before beginning the study, a nurse specialized in intensive care was trained to detect PD using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), which was previously translated into Spanish and validated in our setting [Appendix 1].[4] After surgery, patients were immediately transferred to the ICU. Once mechanical ventilation was weaned or the patient was considered able to communicate, the PD evaluation was started using the CAM-ICU scale. The scale was applied every 8 h to each patient during the ICU stay or until the seventh day after surgery (whichever occurred first). The evaluator was not part of the group of researchers and did not have access to any other study information.

Risk factors

Three groups of exposure variables were defined according to the time relative to the surgical procedure [Table 1]. The outcome, PD, was defined as a positive result on the CAM-ICU scale in at least 1 measurement.

Ethical aspects

The recommendations of good clinical practice, the principles of the Declaration of Helsinki and international regulations for observational studies were followed. According to the national regulation—resolution 008430 of 1993 of the Ministry of Health—this study was classified as research with minimum risk. The study was presented to and approved for execution by the institutional Clinical Research Ethics Committee and, due to its characteristics, exempt from having to obtain informed consent. Confidentiality was ensured through the assignment of codes not linked to the identification of subjects.

Sample size

Due to the high number of variables expected to be included in the analysis and the variability reported in the literature with respect to the importance of each variable in its independent association with the outcome, the sample size was estimated by several methods. In the end, the method described by Perduzzi[5] was adopted; the method considers at least 10 events per variable but includes each of the dummy variables and the dichotomous outcome variable. Therefore, after generating 7 dummy variables (education level: 4 strata; type of surgical procedure: 3 strata) and including the delirium variable, a sample size of 270 was obtained. After adjusting by 15% for the possibility of incomplete patient data, a final sample size of 311 subjects was calculated.

Statistical analysis

The categorical variables are presented as ratios or percentages, and the continuous variables are presented as the mean and standard deviation or median and interquartile range according to the variable. For comparisons of continuous variables, the Mann–Whitney test or Student's *t*-test were used depending on the distribution of the data (evaluated by the Shapiro–Wilk test). Categorical variables were compared using the Chi-squared test. For the adjusted analysis of the data, a logistic regression model was constructed by stepwise selection, with PD as the dependent variable and the pre-, intra- and postoperative variables (described in Table 1) as independent variables. The criterion for the addition or removal of a variable in the model was a bivariate probability of $P < 0.15$ (variables with a possible association). The goodness-of-fit of the model was evaluated using the Hosmer–Lemeshow method; its ability to discriminate between participants who developed PD or not was estimated by ROC curve analysis. All tests were performed using STATA 13.0 (StataCorp LLC., TX 77845, USA). For all evaluations, $P < 0.05$ were considered significant.

RESULTS

During a period of 9 months, 554 patients were admitted to the post-cardiac surgery ICU. After applying the selection criteria, a total of 311 patients were enrolled [Figure 1], and 31 (10%) of them were diagnosed with PD. Patient characteristics and the results of the bivariate analysis are

Table 1: Exposure variables

Preoperative	Intraoperative	Postoperative
Age	Type of surgery (elective or emergency)	Maximum lactate value in the first 24 h
Sex	Surgical procedure performed:	Transfusion of red blood cells
	Myocardial revascularization	
	Single valve surgery	
	Combined surgery (2 or more procedures in the same intervention)	
	Atrial septal defect closure	
	Atrial myxoma resection	
	Transcatheter aortic valve implantation (TAVI)	
Education level (none, primary, secondary, higher)	Duration of extracorporeal circulation	Surgical reoperation in the first 48 h
Hypertension	Duration of aortic clamping	
Diabetes		
Atrial fibrillation		
Cerebrovascular disease, including transient ischemic attack		
Body mass index		
Urea nitrogen level		
Creatinine level		
Hemoglobin value		
EuroSCORE II		

provided in Table 2, differentiated into 2 groups according to whether the outcome was presented. Patients with PD were older, had a lower education level, and had a higher frequency of comorbidities (higher EuroSCORE II and higher prevalence of hypertension, diabetes, history of atrial fibrillation, stroke and impaired renal function). Regarding the surgical procedure, the group with PD was more frequently subjected to combined procedures and with longer durations of extracorporeal circulation and aortic clamping. In the postoperative period, patients with PD had higher arterial lactate levels, a higher frequency of red blood cell transfusion, and a higher need for early reintervention due to bleeding or tamponade.

The multivariate logistic regression analysis identified the following variables as independently and significantly associated with the onset of PD: older age, low education level, history of diabetes, history of stroke, type of surgery (higher incidence in combined procedures), prolonged extracorporeal circulation and red blood cell transfusion in the intra- or postoperative period. Increased body mass index was found to be a protective factor. The model obtained is shown in Figure 2. The Hosmer–Lemeshow test showed a proportion of 93.2% of patients ($Chi^2 = 0.94$) who were correctly classified (See the receiver operating characteristic curve in Additional File ACA_43_20I7850).

DISCUSSION

In this unselected population of postoperative cardiac surgery patients, an incidence of PD of 10% was found. In the literature, this complication has been reported in

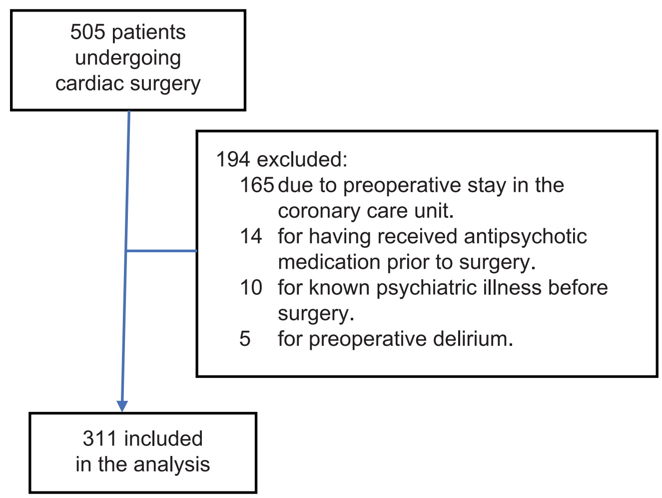

Figure 1: Flowchart of study participants

3–70% of patients.[6] Several factors should be explored to explain this important variability, such as the characteristics of the study patients (age, comorbidities, and complexity of cardiac surgery, among others), the evaluation methodology, and the instrument used to recognize PD.[7] Our patients were monitored several times a day to detect PD using the CAM-ICU scale, a standardized and validated tool that allows an accurate evaluation of the primary components of delirium: level of consciousness, inattention, disorganized thinking, and fluctuating course.[8] The relatively low incidence of delirium in our population may be related to unmeasured factors, such as the characteristics of each postoperative unit (design, light and environmental noise, among others), family visitation schedule and patient preparation before surgery, or to population differences in the various geographical locations

Table 2: Bivariate analysis

Variable	Delirium (-)	Delirium (+)	*P*
n (%)	280 (90)	31 (10)	
Age in years, median (p25-p75)	64 (54-72)	71 (62-76)	0.001
Sex, *n* (%)	183 (65)	20 (64.5)	0.92
Educational level, *n* (%)			
No educational level	22 (7.9)	8 (25.8)	0.001
History of arterial hypertension, *n* (%)	162 (57.9)	25 (80.6)	0.01
History of diabetes, *n* (%)	55 (19.6)	12 (38.7)	0.01
History of atrial fibrillation, *n* (%)	38 (13.6)	6 (19.3)	0.41
History of stroke/TIA, *n* (%)	10 (3.6)	7 (22.6)	0.0005
IMC kg/m^2, median (p25-p75)	25.9 (23.5-29)	24.2 (23.2-27.9)	0.08
BUN mg/dL, median (p25-p75)	18 (14-22)	21 (15-25)	0.03
Creatinine mg/dL, median (p25-p75)	0.9 (0.8-1.1)	1.1 (0.9-1.2)	0.01
Hemoglobin g/dL, median (p25-p75)	14.8 (13.3-16.1)	13.3 (11.3-15)	0.001
EuroSCORE II, median (p25-p75)	1.8 (1-3.5)	3.7 (2.2-7.8)	<0.0001
Type of surgery, *n* (%)			
Elective	213 (76)	24 (77.4)	0.87
Emergency	67 (24)	7 (22.6)	
Procedure, *n* (%)			
CABG	104 (37)	10 (32.3)	0.59
Single valve surgery	97 (34.6)	6 (19.3)	0.09
2 or more procedures in the same intervention (Mixed)	52 (18.6)	13 (41.9)	0.002
IAC/Myxoma	13 (4.6)	1 (3.2)	0.72
TAVI	14 (5)	1 (3.2)	0.66
CPB duration min, median (p25-p75)	103 (82-133)	139 (106-168)	0.001
Clamping duration min, median (p25-p75)	85 (64-116)	112 (85-133)	0.003
Postoperative lactate maximum 24 h mmol/dL, median (p25-p75)	2 (1.5-2.5)	2.4 (1.9-3.5)	0.01
Perioperative transfusion of RBC, *n* (%)	76 (27)	22 (71)	<0.0001
Reintervention, *n* (%)	12 (4.3)	7 (22.6)	<0.0001

p25-p75: 25th to 75th percentile. TIA: Transient ischemic attack. BMI: Body mass index. BUN: Blood urea nitrogen. IAC: Interauricular communication. TAVI: Transcatheter aortic valve implantation. CPB: Cardiopulmonary bypass. RBC: Red blood cells

worldwide. Very few analyses have reported data specifically on patients in Latin America.[9]

We found several risk factors that were independently associated with the onset of PD: advanced age is one of the most uniformly reported factors.[10,11] In our population, we found that the median age of patients with PD was 7 years older than that of those without PD (P = 0.001). There are several hypotheses to explain the increased incidence of PD in elderly patients. Rudolph *et al.*, in a population of subjects undergoing coronary artery bypass graft (CABG), evaluated whether the burden of arteriosclerosis in the ascending aorta or in the carotid arteries was a predictor of PD, finding that an age ≥70 years implied a relative risk (RR) of 3.6 (95% CI: 1.2–10.5) for the onset of PD. After adjusting for age and other covariates, the burden of arteriosclerotic plaques in the assessed anatomical location was significantly associated with PD.[12] In a randomized controlled trial, Lei *et al.* described that lower preoperative regional cerebral oxygen saturation (≤50%) may be associated with an increase in the rate of PD.[13] This information is very important given that previous studies have shown that cerebral near infrared spectroscopy (NIRS) measurements show changes with age reflecting the deterioration of cerebral hemodynamics in advanced age.[13,14] In support of this hypothesis, Chan and Aneman recently described an association between the deterioration of cerebrovascular self-regulation, estimated by NIRS, and early onset of PD after cardiac surgery.[15] However, a greater arteriosclerotic burden and vascular dysfunction are not the only factors that seem to affect the genesis of PD. There is current evidence suggesting that PD results from a complex interrelation between multiple predisposing baseline conditions and perioperative precipitating factors. In a systematic review by Hollinger *et al.*, 196 studies were analyzed, identifying a total of 123 risk factors for PD.

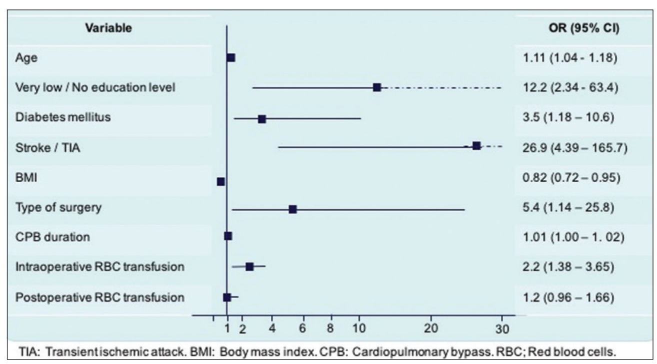

Figure 2: Multivariate analysis. Factors associated with postoperative delirium

Of these, 8 were mentioned in at least 10 studies (age, type of heart disease, personality traits, history of cerebrovascular or peripheral vascular disease, metabolic syndrome, diabetes, preoperative cognitive decline, and type and duration of surgery).[16] This enormous number of risk factors highlights the complexity of PD pathogenesis. The pathophysiological hypotheses with greater plausibility are related to dysfunction in neurotransmitters or possible stress-related disruptions in serum cortisol levels. These alterations may be present with or without a combination of associated psychiatric factors.[16,17] In turn, inflammatory markers (C-reactive protein, IL-6, procalcitonin) are significantly elevated in the cardiac surgery postoperative period as a result of trauma.[18] Microglial cells are activated by peripheral inflammatory responses and are capable of producing neuroactive cytokines and other signals that contribute to neuropsychiatric changes after surgery. It is very likely that the interaction between cholinergic transmission and neuroinflammation plays a key role in the development of delirium.[19]

A very low education level (illiteracy/incomplete primary education) was identified in our study as one of the factors most strongly related with the onset of PD: odds ratio (OR) 12.2 (95% CI: 2.3–63.4). This finding has been described in a few previous studies. Galanakis *et al.* found that a low education level was a well-defined risk factor for delirium (OR: 3.6, 95% CI 1.1–11.2).[20] Folks *et al.* found that the occupation and education levels of patients who showed postoperative cognitive dysfunction were significantly lower than those of controls.[21] However, the pathway through which this phenomenon intervenes in the pathogenesis of PD has not yet been defined. Jones *et al.* proposed the concept of brain reserve to explain individual differences in the risk of delirium.[22] This is a generic term that refers to passive and active processes in the brain that modify an individual's risk for the expression of clinical signs and symptoms associated with brain injury or neurological disease. The key concept in brain reserve models is that there are differences in the amount of damage the brain can endure before reaching a critical threshold for clinical expression. The differences would be caused by structural characteristics such as brain volume and synaptic density.[22]

Cerebrovascular disease is one of the most commonly identified risk factors in previous studies. In fact, a history of a clinical neurological event is part of several predictive scores. An example is the work by Rudolph *et al.*;[23] in that study, in a cohort of 122 patients, the authors validated a simple model with good predictive ability consisting of 4 preoperative characteristics (Mini Mental State Examination, Geriatric Depression Scale, previous stroke/transient ischemic attack and abnormal albumin level). It has already been mentioned that PD is related to more advanced carotid, aortic, and intracerebral atherosclerosis, which increases the risk of cerebral hypoperfusion. Decreased cerebral blood flow, together with factors such as perioperative hypotension or hypoxemia, puts brain oxygenation at risk and may facilitate the development of postoperative cerebral dysfunction.

Diabetes as well as several of the risk factors identified in this study are potentially associated with atherosclerosis of the central nervous system (history of stroke, cognitive decline, and old age). Therefore, the higher burden of atherosclerosis observed in patients with diabetes may be associated with a combination of risk factors that predispose patients to delirium.

We found that more complex surgical procedures (combined surgeries: CABG along with valve surgery, double valve replacement or similar) had a higher incidence of PD than did single procedures. Cardiopulmonary bypass (CPB) could play an important role; several studies have found an independent association between the duration of CPB and PD.[16,24] In a study by O'Neal,[25] the use of CPB and its duration were significantly associated with an increased risk of delirium in patients undergoing CABG. In another study of 215 patients with PD, it was found that valve repair or replacement is associated with a higher incidence of PD than is coronary surgery; it was not possible to determine whether valve surgery itself could lead to a higher incidence of delirium due to an increase in the rate of cerebral embolism or whether this finding reflects different characteristics of the study population (older age or duration of CPB). One of the important contributions of that study was the development of a model for the prediction of PD with a sensitivity of 71% and specificity of 76%, which resulted from a combination of age, Mini Mental State Examination score, Charlson comorbidity index, and CPB time.[17]

It has been demonstrated that brain embolic events lead to neuronal-specific enolase release, a marker that has been found to be elevated in patients with delirium.[26] A recent meta-analysis showed that silent brain infarcts are very common in cardiac surgery, especially when involving the aortic valve. Although there is significant variability in the postoperative frequency of silent brain infarcts with respect to the type of surgical procedure, the transcatheter aortic valve implantation (TAVI) and aortic valve replacement groups reported the highest incidences, 74% and 58%, respectively. This is consistent with the suspicion that silent brain infarcts are due in part to microemboli as a result of direct disruption of the atherosclerotic plaque in the ascending aorta.[27] An increase in the levels of proximal thoracic aortic atheroma has been found to be associated with higher incidences of intraoperative cerebral embolism, a finding that has also been evident in transcranial Doppler studies.[28]

Our results confirm that the transfusion of one or more red blood cell units in the intra- and postoperative period is associated with the onset of PD. Katznelson *et al.* found that transfusions greater than 5 red blood cell units were associated with a 3-fold increased risk of PD.[29] Similarly, Stransky *et al.* reported that each unit of red blood cell transfused was associated with an 18% increase in the onset of PD.[30] The explanation for this association is complex; blood transfusions may reflect the greater technical difficulty of surgery with an increased inflammatory response, leading to multiorgan dysfunction and delirium. However, microvascular alterations and microparticle side effects induced by transfusions have recently been demonstrated;[31] their role in the etiopathogenesis of PD has not yet been determined.

One of the most interesting findings of our study is that being overweight or obese seems to have a protective effect against the onset of PD. Although the nature of this association is not clear, it has been described that mortality in cardiac surgery is lower in patients who are overweight or obese. This finding was corroborated in a meta-analysis of more than 500,000 patients conducted by Mariscalco.[32] Mashour identified that a body mass index (BMI) of 35–40 kg/m² resulted in a lower incidence of perioperative stroke after noncardiac surgery.[33] Lei also identified that being overweight or obese seemed to confer protection against PD.[13] Similarly, we have shown that a higher BMI is a protective factor for PD; the explanation could be related to a subclinical nutritional deficit state among subjects who presented this outcome. This relationship has been studied in patients hospitalized in nursing homes, finding that lower body mass and body fat were related to the onset of delirium.[34] The authors propose that given that many drugs are transported to their effector sites linked to plasma proteins, having low levels of albumin or total protein could alter pharmacological actions and increase the risk of delirium. An alternative hypothesis has to do with the differential immunity characteristics in overweight subjects; experimental studies have found changes in the function of T cells, characterized by slow proliferation and decreased ability to produce chemical messages to communicate with other immune cells;[35] it has already been described that inflammatory mediators could play an important role in the onset of PD.

This study has limitations, especially related to the fact that a large number of risk factors for PD are described in the literature. However, the relationship with many of these factors has been inconsistent between the different publications. This discrepancy could be a result of the retrospective design of some studies. On the other hand, many prospective series include a small number of participants, with insufficient statistical power to select patients with PD and detect the implicated risk factors. Other studies have methodological limitations; for example, the diagnostic criteria, tools used, length of time evaluated, or experience of the evaluator are not defined.[36]

Most importantly, despite having identified multiple risk factors for PD, its incidence does not appear to be decreasing.[37] Thus, further research efforts are justified.

It should be noted that due to the large number of analyzed variables, we did not include intraoperative hemodynamic aspects, nor every medication administered to the patients, in the analysis. With regard to the latter, the literature reports indicate a vast number of medications potentially related to the onset of PD: statins, diuretics, beta blockers, inotropes, benzodiazepines, barbiturates, opioids, metoclopramide, dimenhydrinate, antiarrhythmics, and multiple antihypertensives, among many others.[16] Attempting to include these medications in the multivariate model would lead to a substantial increase in sample size, which is not feasible in this phase of our line of research. Finally, since the primary objective of this study was to determine the variables associated with the onset of PD, we make no reference to the progression or duration of this cognitive disorder.

Our study has important strengths, one of which is the prospective analysis of multiple potential predictors of delirium after different types of cardiac surgery in a significant number of patients. The study included 18 pre-, intra- and postoperative variables and was performed using a rigorous methodology with standardized definitions and a widely accepted diagnostic tool (CAM-ICU).

CONCLUSIONS

With the aging of the population and increased number of cardiac surgeries performed annually, PD in cardiac surgery has become a major clinical and epidemiological problem. Our results are highly relevant because the preoperative identification of risk factors is the basis of prevention.

Financial support and sponsorship

This study was funded by a grant from Fundación Cardioinfantil. It is a high-complexity cardiac private hospital of Bogotá, Colombia.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Martin B-J, Arora RC. Delirium and cardiac surgery: Progress - and more questions. Critical Care 2013;17:140.
2. American Psychiatric A, American Psychiatric Association DSMTF. Diagnostic and Statistical Manual of Mental Disorders: DSM-5. Washington, D.C.: American Psychiatric Association; 2013.
3. Martin B-J, Buth K, Arora R, Baskett R. Delirium as a predictor of sepsis in post-coronary artery bypass grafting patients: A retrospective cohort study. Crit Care 2010;14:R171.
4. Tobar E, Romero C, Galleguillos T, Fuentes P, Cornejo R, Lira MT, *et al.* Método para la evaluación de la confusión en la unidad de cuidados intensivos para el diagnóstico de delirio: Adaptación cultural y validación de la versión en idioma español. Med Intensiva 2010;34:4-13.
5. Perduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49:1373-9.
6. McPherson JA, Wagner CE, Boehm LM, Hall JD, Jonhson DC, Miller DR, *et al.* Delirium in the cardiovascular ICU: Exploring modifiable risk factors. Crit Care Med 2013;41:405-13.
7. Devlin JW, Fong JJ, Fraser GL, Riker RR. Delirium assessment in the critically ill. Intensive Care Med 2007;33:929-40.
8. Gusmao-Flores D, Salluh JI, Chalhub RA, Quarantini LC. The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: A systematic review and meta-analysis of clinical studies. Crit Care 2012;16:R115.
9. Dotti S, Montes de Oca O, Bigalli D, Gutiérrez F, Russo N, Pouso M. Prospective analysis of cumulative incidence of delirium in the postoperative period of cardiac surgery. Rev Urug Cardiol 2017;32.
10. Koftis K, Szylinska A, Listewnik M, Strzelbicka M, Brykcznski M, Rotter I, *et al.* Early delirium after cardiac surgery: An analysis of incidence and risk factors in elderly (≥65 years) and very elderly (≥80 years) patients. Clin Interv Aging 2018;13:1061-70.
11. O'Neal JB, Shaw AD. Predicting, preventing, and identifying delirium after cardiac surgery. Perioper Med (Lond) 2016;26:5-7.
12. Rudolph JL, Babikian VL, Birjiniuk V, Crittenden MD, Treanor PR, Pochay VE, *et al.* Atherosclerosis is associated with delirium after coronary artery bypass graft surgery. J Am Geriatr Soc 2005;53:462-6.
13. Lei L, Katznelson R, Fedorko L, Carroll J, Poonawala H, Machina M, *et al.* Cerebral oximetry and postoperative delirium after cardiac surgery: A randomised, controlled trial. Anaesthesia 2017;72:1456-66.
14. Safonova LP, Michalos A, Wolf U, Wolf M, Hueber DM, Choi JH, *et al.* Age-correlated changes in cerebral hemodynamics assessed by near-infrared spectroscopy. Arch Gerontol Geriatr 2004;39:207-25.
15. Chan B, Aneman A. A prospective, observational study of cerebrovascular autoregulation and its association with delirium following cardiac surgery. Anaesthesia 2018. doi: 10.1111/anae.14457.
16. Hollinger A, Siegemund M, Goettel N, Steiner LA. Postoperative delirium in cardiac surgery: An unavoidable menace? J Cardiothorac Vasc Anesth 2015;29:1677-87.
17. Guenther U, Theuerkauf N, Frommann I, Brimmers K, Malik R, Stori S, *et al.* Predisposing and precipitating factors of delirium after cardiac surgery: A prospective observational cohort study. Ann Surg 2013;257:1160-7.
18. Liu X. Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): A meta-analysis of observational studies. PLoS One 2018;13:e0195659.
19. Van Gool WA, Van de Beek D, Eikelenboom P. Systemic infection and delirium: When cytokines and acetylcholine collide. Lancet 2010;375:773-5.
20. Galanakis P, Bickel H, Gradinger R, Von Gumppenberg S, Förstl H. Acute confusional state in the elderly following hip surgery: Incidence, risk factors and complications. Int J Geriatr Psychiatry 2001;16:349-55.
21. Folks DG, Freeman AM, Sokol RS, Govier AV, Reves JG, Baker DM. Cognitive dysfunction after coronary artery bypass surgery: A case-controlled study. South Med J 1988;81:202-6.
22. Jones RN, Yang FM, Zhang Y, Kiely DK, Marcantonio ER, Inouye SK. Does educational attainment contribute to risk for delirium? A potential role for cognitive reserve. J Gerontol A Biol Sci Med Sci 2006;61:1307-11.
23. Rudolph JL. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. Circulation 2009;119:229-36.
24. Sanson G, Khlopenyuk Y, Milocco S, Sartori M, Dreas L, Fabiani A. Delirium after cardiac surgery. Incidence, phenotypes, predisposing and precipitating risk factors, and effects. Heart Lung 2018. doi: 10.1016/j.hrtlng.2018.04.005.
25. O´Neal JB. Risk factors for delirium after cardiac surgery: An historical cohort study outlining the influence of cardiopulmonary bypass. Can J Anaesth 2017;64:1129-37.
26. Herrmann M, Ebert AD, Tober D, Hann J, Huth C. A contrastive analysis of release patterns of biochemical markers of brain damage after coronary artery bypass grafting and valve replacement and their association with the neuro- behavioral outcome after cardiac surgery. Eur J Cardiothorac Surg 1999;16:513-8.
27. Indja B, Woldendorp K, Vallely MP, Grieve SM, Phil D. Silent brain infarcts following cardiac procedures: A systematic review and meta-analysis. J Am Heart Assoc 2019;8:e010920.
28. Djaiani G, Fedorko L, Borger M, Mikulis D, Carroll J, Cheng D, *et al.* Mild to moderate atheromatous disease of the thoracic aorta and new ischemic brain lesions after conventional coronary artery bypass graft surgery. Stroke 2004;35:e356-8.
29. Katznelson R, Djaiani GN, Borger MA, Friedman Z, Abbey SE, Fedorko L, *et al.* Preoperative use of statins is associated with reduced early delirium rates after cardiac surgery. Anesthesiology 2009;110:67-73.
30. Stransky M, Schmidt C, Ganslmeier P, Grossmann E, Haneya A, Moritz S, *et al.* Hypoactive delirium after cardiac surgery as an independent risk factor for prolonged mechanical ventilation. J Cardiothorac Vasc Anesth 2011;25:968-74.
31. Hariri G, Bourcier S, Marjanovic Z, Joffre J, Lemarié J, Lavillegrand JR, *et al.* Exploring the microvascular impact of red blood cell transfusion in intensive care unit patients. Critical Care 2019;23:292.
32. Mariscalco G, Wozniak MJ, Dawson AG, Serraino GF, Porter R, Nath M, *et al.* Body mass index and mortality among adults undergoing cardiac surgery. A nationwide study with a systematic review and meta-analysis. Circulation 2017;135:850-63.
33. Mashour GA, Shanks AM, Kheterpal S. Perioperative stroke and associated mortality after noncardiac, nonneurologic surgery. Anesthesiology 2011;114:1289-96.
34. Kulp KR, Cacchione PZ. Nutritional status and delirium in long-term care elders. Appl Nurs Res 2008;21:66-74.
35. Wang Z, Aguilar E, Luna J, Dunai C, Khuat LT, Le C, *et al.* Paradoxical effects of obesity on T cell function during tumor progression and PD-1 checkpoint blockade. Nat Med 2019;25:141-51.
36. Kazmierski J, Kowman M, Banach M, Fendler W, Okonski P, Banys A, *et al.* Incidence and predictors of delirium after cardiac surgery: Results from The IPDACS Study. J Psychosom Res 2010;69:179-85.
37. Zagaria MA. Delirium risk following cardiac surgery. US Pharm 2020;45:8-12.