

Perioperative Neurocognitive Disorder After Cardiac Surgery – A Narrative Study of a Retrospective Casuistic

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ABSTRACT

Introduction: Delirium is one of the most serious and common neuropsychological complications in the immediate postoperative period of cardiac surgery, always resulting in negative consequences, prolonged hospitalization, and increased early and late morbidity and mortality.

Methods: An active search for acute cognitive dysfunction was performed in the electronic medical records written by the multidisciplinary team about the immediate postoperative period of 262 consecutive adult patients undergoing cardiac surgery with cardiopulmonary bypass operated on in 2019 at the Instituto do Coração of Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo. To maintain randomness, data were collected from 25 patients per month for a total of 10 months.

Results: Seventy-three patients (27.9%) presented symptoms of delirium or

perioperative neurocognitive disorder in the postoperative period, with a median time of four days. The most frequent symptoms were changes in cognition (25.6%), attention (25.2%), and agitation (24.8%). Patients with delirium had a longer intensive care unit stay (median seven days vs. three days, $P < 0.001$), longer mechanical ventilation (median 977 vs. 535, $P < 0.001$), longer hospital stay (median 20 days vs. 13 days, $P < 0.001$), and higher incidence of hospital death (22.2% vs. 3.2%, $P < 0.001$).

Conclusion: The incidence of delirium immediately after cardiac surgery was high, around 27.9%, which is consistent with values found in the literature. The occurrence of delirium was highly associated with worse outcomes, such as longer hospital stays and mortality.

Keywords: Cardiopulmonary Bypass. Cardiac Surgical Procedures. Delirium. Postoperative Period. Cognitive Dysfunction. Incidence.

Abbreviations, Acronyms & Symbols

ACD	= Acute cognitive dysfunction	ICU	= Intensive care unit
AH	= Arterial hypertension	LVEF	= Left ventricular ejection fraction
AMI	= Acute myocardial infarction	MRI	= Myocardial revascularization
CABG	= Coronary artery bypass grafting	NYHA	= New York Heart Association
CAM-ICU	= Confusion assessment method for the intensive care unit	OR	= Odds ratio
CI	= Confidence interval	P ₂₅	= 25 th percentile
CKD	= Chronic kidney disease	P ₇₅	= 75 th percentile
CPB	= Cardiopulmonary bypass	SD	= Standard deviation
CRD	= Chronic renal disease	SIFH	= Systems integration failure hypothesis
DM	= Diabetes mellitus	TAVI	= Transcatheter aortic valve implantation

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INTRODUCTION

Delirium or perioperative neurocognitive disorder in adult patients is an acute neurobehavioral syndrome secondary to changes in organic homeostasis. Delirium is relatively common in medical hospitalizations, with an incidence between 10 and 31%. It often causes admission to the intensive care unit (ICU), reportedly in up to 87% of cases. In patients hospitalized after noncardiac surgeries, postoperative delirium can affect 4.7 to 74% of patients. After cardiac surgery with cardiopulmonary bypass, 13 to 32% of patients have postoperative delirium. Five phenotypes can be observed in affected patients: (1) subclinical, with a diagnosis that goes unnoticed without a detailed neuropsychiatric exam; (2) hypoactive, characteristic of a depressive condition, with difficulty in communicating verbally; (3) hyperactive, with exuberance of symptoms and the need for physical restraint and antipsychotic medication most of the time; (4) mixed, with alternating hypoactivity and psychic arousal; and (5) prolonged or persistent mental alteration^[1].

Regarding the clinical conditions, this acute cognitive dysfunction or delirium presents with a fluctuating level of consciousness and attention and may also affect memory, thinking, perception, mood, and sleep. The symptoms are varied, such as disorientation in time and space, changes in psychomotricity, aggression, agitation, memory changes, and even hallucinations^[2].

The pathophysiology is still uncertain, but it is believed to involve a state of inflammation in the central nervous system, which may cause increased apoptosis of neurons, inhibit neurogenesis, and reduce synaptic plasticity. Altered neurotransmitter function or availability has also been implicated in the pathogenesis of delirium, as well as neuroendocrine mechanisms and oxidative stress. All these hypotheses on the pathophysiology of delirium are complementary rather than competing^[1].

The consequences of cognitive impairment include higher rates of morbidity and mortality, worsening of the prognosis, longer hospital stay, and an eventual lowering of the level of consciousness^[3]. Added to these factors is the fact that neuroinflammation can persist for a long time and progress to a condition of permanently impaired cognition, evolving to dementia with social and intellectual limitations.

These cognitive changes that occur after anesthesia and surgery, particularly in the elderly, have been recognized for decades. This state of acute change in mental status and level of consciousness after surgery is generically called delusion or postoperative cognitive dysfunction. This state of intellectual decline often persists after the effect of anesthetics and analgesics used in the postoperative period ends. However, due to the variety of diagnoses and different nomenclatures for the same situation, a working group elaborated a consensus to align the terminology used in cognitive classifications for the general population to those observed after surgery and anesthesia. This consensus recommends the term "perioperative neurocognitive disorders" to cover all terms that identify acute cognitive disorders. This includes intellectual or cognitive decline observed in the perioperative period, described as *neurocognitive disorder*, and any form of postsurgical acute event, widely known as *postoperative delirium*, and finally the late cognitive decline diagnosed from 30 days after the procedure to 12 months, called *delayed neurocognitive recovery*^[4].

The main objective of this study was to retrospectively measure the incidence of delirium in patients undergoing cardiac or basal vessel

surgery, as well as the association of this event with age, sex, type of surgery, personal history, and clinical outcomes.

METHODS

This project was approved by the Institutional Ethics Committee under number 4863687 of 07/23/2021. The incidence of cognitive dysfunction was retrospectively investigated in the electronic medical records of patients over 18 years of age who underwent cardiac and thoracic aorta surgery during 2019 at the Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo. The patients were randomly selected for collection, 25 for each month of the year, totaling 262 who were eligible out of a population of 300, and the information recorded in the institutional electronic medical record was transcribed into an Excel spreadsheet for statistical analysis (Figure 1).

The medical records included surgery reports, evolution of the condition, and prescriptions of the multiprofessional team of the surgical ICU and laboratory tests collected preoperatively.

To characterize delirium or acute cognitive dysfunction after surgery, the medical records of symptoms such as mental confusion, psychomotor agitation or retardation, decreased level of consciousness, time-space disorientation, visual hallucinations, and periods of aggression were investigated. In addition, antipsychotic medications, such as haloperidol, quetiapine, dexmedetomidine, and risperidone, and their duration of use as well as the need for mechanical restraint to the bed in cases of intense agitation were analyzed.

To find any associations between delirium and the patients' clinical characteristics, demographic, and surgical history, age, sex, ethnicity, and education, as well as left ventricular ejection fraction (LVEF), history of depression, use of antidepressants and psychoactive drugs, stroke, acute myocardial infarction (AMI), systemic arterial hypertension, diabetes mellitus (DM), heart failure, New York Heart Association (NYHA) functional class, auditory dysfunction, current and previous smoking, chronic renal failure, anemia, alcoholism, and chronic atrial fibrillation were tested.

- Preoperative tests: creatinine, urea, sodium, potassium, and blood.
- Intraoperative: type of surgery (coronary artery bypass grafting [CABG], valve surgery, aortic arch surgery, combined procedure), anesthesia time and surgery time in minutes, whether the procedure was elective or urgent, and use of cardiopulmonary bypass or not.
- Postoperative outcomes: length of stay in the ICU and in the hospital in days, duration of mechanical ventilation in minutes, need for readmission in the following month, and in-hospital death.

Statistical Analysis

In the description of the data, the qualitative variables are summarized as absolute and relative frequencies (percentages), in the whole sample and in the subgroups with and without delirium. The quantitative measurements are described as the means, standard deviations (SDs), quartiles, and minimum and maximum values. The distribution of quantitative data is presented in histograms and box plots.

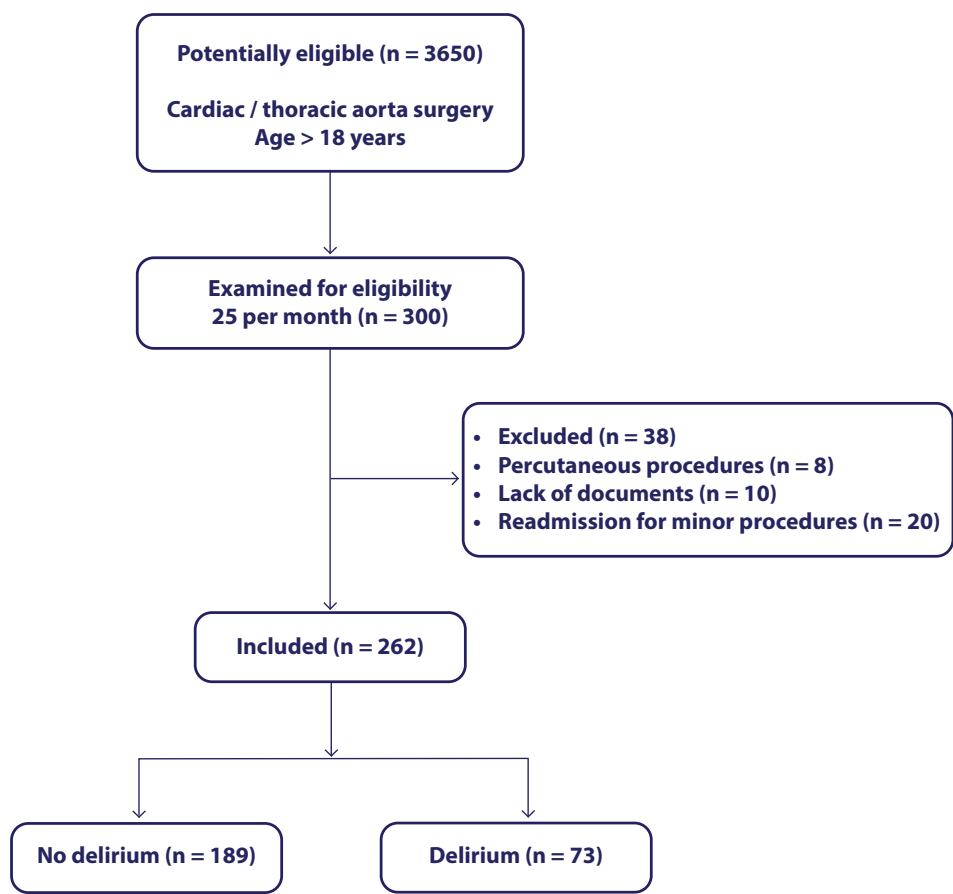


Fig. 1 - Flowchart of patient selection.

The groups that did and did not have delirium were compared on quantitative variables using Student's *t*-test for independent samples or the Mann–Whitney test, depending on the distribution of each variable. Pearson's chi-squared test or Fisher's exact test was used to compare the qualitative variables between groups in cases where there were expected frequencies lower than five. Data normality was analyzed using descriptive statistics, coefficients of skewness, and normal probability plots.

To investigate possible associations between delirium and other demographic, clinical, preoperative, and intraoperative variables, simple and multiple logistic regression models were used. In the first stage, the isolated effect of each variable on the delirium outcome was investigated (univariate approach). The variables with *P* < 0.10 in the univariate analysis were selected for the multivariate models (multiple logistic regression), in which the effects were analyzed simultaneously. Based on a complete multivariate model that included all the variables initially selected, those without statistical significance were excluded stepwise. Thus, variables of no interest were excluded, reaching a final reduced model. In the multivariate models, we grouped some variables by category to obtain greater consistency in the analysis and less imprecise estimates.

The analyses were run with IBM Corp. Released 2012, IBM SPSS Statistics for Windows, version 21, Armonk, NY: IBM Corp., R version 4.2.1, and Jamovi version 2.2 software. A significance level of 5% was adopted for all tests.

RESULTS

Description of Patients

Table 1 presents the characterization of the patients regarding clinical and demographic variables. The mean age of the group was 61.3 years (SD 12.1), ranging from 29 to 93 years. There was a predominance of males (57.4% vs. 42.6%) and white ethnicity (84.6%). The most frequent education level was incomplete elementary school (37% of the patients), 2.3% were illiterate, and only 11.5% had higher education.

Regarding the clinical characteristics, the group had a mean LVEF of 56.44% (SD 11.43%), ranging from 18 to 75%. More than 40% had a history of heart failure. Type 2 DM was present in 32.4% (85) of the patients, arterial hypertension in 23.3% (61), and previous AMI in 23.3% (61). The majority had no history of stroke, atrial fibrillation, or chronic kidney disease (CKD). In addition, 6.5% used alcohol regularly, 13.4% reported using tobacco, and 72% reported having done so previously. Only 3.4% were diagnosed with depression, and 23 (8.8%) were using antidepressant medication, one (0.4%) using benzodiazepines, and 13 (5%) using psychoactive drugs. Few individuals presented visual (3.8%) or auditory (1.1%) dysfunctions. Only 103 patients were evaluated for cardiac function, in whom there was a predominance of NYHA classes I–II in relation to classes III–IV (60.2% vs. 39.8%, respectively).

Table 1. Patients' demographic and clinical characteristics.

Variables	All patients (n = 262)	No delirium	With delirium	P-value
Age, years		n = 189	n = 73	
Mean (SD)	61.28 (12.09)	59.29 (11.83)	66.43 (11.29)	< 0.001 [^]
Median (P ₂₅ - P ₇₅)	63.28 (53.94 - 69.80)	61.34 (52.62 - 67.00)	69.29 (60.58 - 74.8)	
Sex, n (%)		n = 189	n = 73	
Female	112 (42.7%)	77 (40.7%)	35 (47.9%)	0.291 ²
Male	150 (57.3%)	112 (59.9%)	38 (52.1%)	
Ethnicity, n (%)		n = 186	n = 73	
White	219 (83.6%)	160 (86.0%)	59 (80.8%)	0.291 ³
Black	19 (7.3%)	14 (7.5%)	5 (6.8%)	
Yellow	6 (2.3%)	2 (1.1%)	4 (5.5%)	
Brown	15 (5.7%)	10 (5.4%)	5 (6.8%)	
Education, n (%)		n = 172	n = 61	
Illiterate	6 (2.3%)	4 (2.3%)	2 (3.3%)	0.369 ³
Incomplete elementary education	97 (37.0%)	71 (41.3%)	26 (41.6%)	
Completed elementary school	37 (14.1%)	24 (14.0%)	13 (21.3%)	
Incomplete high school	11 (4.2%)	9 (5.2%)	2 (3.3%)	
Completed high school	49 (18.7%)	40 (23.3%)	9 (14.8%)	
Incomplete higher education	3 (1.1%)	1 (0.6%)	2 (3.3%)	
Completed higher education	30 (11.5%)	23 (13.4%)	7 (11.5%)	
LVEF (%)		n = 172	n = 61	
Mean (SD)	56.44 (11.43)	57.38 (10.67)	54.13 (12.90)	0.060 [^]
Median (P ₂₅ - P ₇₅)	60.0 (51.0 - 64.0)	60.0 (53 - 65)	59 (45 - 62)	
Background, n (%)				
Heart failure	107 (40.8%)	81 (43.3%)	26 (35.6%)	0.257 ²
Diabetes mellitus	85 (32.4%)	54 (28.7%)	31 (42.5%)	0.033 ²
Systemic arterial hypertension	61 (23.3%)	138 (73.0%)	63 (86.35)	0.023 ²
AMI	61 (23.3%)	43 (22.8%)	18 (24.7%)	0.743 ²
Atrial fibrillation	35 (13.4%)	27 (14.3%)	8 (11.0%)	0.478 ²
Cerebrovascular accident	31 (11.8%)	19 (10.1%)	12 (16.6%)	0.140 ²
CKD	24 (9.2%)	11 (5.8%)	13 (17.8%)	0.003 ²
Depression	9 (3.4%)	7 (3.7%)	2 (2.7%)	> 0.999 ³
Chronic anemia	1 (0.4%)	1 (0.5%)	0 (0%)	0.189 ³
Visual dysfunction	10 (3.8%)	2 (1.1%)	8 (11.0%)	0.001 ³
Hearing dysfunction	3 (1.1%)	1 (0.5%)	2 (2.7%)	0.189 ³
Current smoking	35 (13.4%)	27 (14.3%)	8 (11.1%)	0.501 ²
Prior smoking	72 (27.5%)	52 (27.5%)	20 (27.4%)	0.985 ²
Alcoholism	17 (6.5%)	9 (4.8%)	8 (11.0%)	0.091 ³

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Medications, n (%)				
Antidepressants	23 (8.8%)	21 (11.1%)	2 (2.7%)	0.032 ²
Psychoactive drugs	13 (5.0%)	7 (3.7%)	6 (8.3%)	0.198 ³
Benzodiazepines	1 (0.4%)	0 (0%)	1 (1.4%)	0.279 ³
Preoperative tests, mean (SD)				
Creatinine (mg/dL)	1.19 (0.5)	1.12 (0.32)	1.37 (0.76)	0.018 [^]
Urea (mg/dL)	47.1 (23.3)	43.6 (21.7)	55.4 (26.1)	0.003 [^]
Na (mEq/L)	139.0 (3.1)	139.1 (3.0)	138.6 (3.5)	0.341 [^]
K (mEq/L)	4.2 (0.4)	4.2 (0.4)	4.4 (0.4)	0.012 [^]
Hemoglobin (g/dL)	13.2 (2.0)	13.5 (1.9)	12.4 (2.1)	< 0.001 [^]
Hematocrit (%)	39.9 (5.5)	39.7 (5.2)	37.0 (5.8)	0.001 [^]
Leukocytes (1000/mm ³)	8.2 (3.8)	8.1 (3.6)	8.4 (4.1)	0.531 [^]
Platelets (1000/mm ³)	219.9 (68.9)	223.7 (65.4)	210.0 (76.8)	0.192 [^]

[^]Corrected t-test; ²Pearson's chi-squared test; ³Fisher's exact test

AMI=acute myocardial infarction; CKD=chronic kidney disease; LVEF=left ventricular ejection fraction; P₂₅=25th percentile; P₇₅=75th percentile; SD=standard deviation

The most frequent type of surgery was myocardial revascularization (41.2%), followed by valve surgery (35.9%). The median anesthesia time was 425 minutes, ranging from 175 to 855 minutes. Most patients underwent elective surgery (74.8%), urgency surgery being the second most frequent (20.20%). Almost all patients (92.4%) underwent surgery with cardiopulmonary bypass support, with a median time of 96 minutes, ranging from 22 to 251 minutes (Table 2).

The median length of stay in the ICU was four days. Within the routine of the immediate postoperative period, a total of 255 patients needed mechanical ventilation for a median of 604 minutes. Most patients with delirium (80%) were hospitalized in the ICU for an average of seven days, but some patients had prolonged hospitalization, for more than one month (Table 3). The length of hospital stay ranged from four to 141 days, with a median of 15 days. In-hospital mortality was 8.4% (22 patients). Seventeen patients (6.5%) were readmitted after hospital discharge. Seventy-three patients (27.9%) presented symptoms of delirium in the postoperative period, which lasted for a median duration of four days (minimum 1; maximum 60 days). The symptoms are listed in Table 4.

The antipsychotic drugs used most often for postoperative delirium were quetiapine (18.7%), haloperidol (12.6%), risperidone (1.9%), and continuous dexmedetomidine (5.3%).

Comparison Between Patients With and Without Delirium

When comparing the individuals who presented with delirium in the postoperative period and those who did not, we found a higher mean age (66.4 vs. 59.3 years, $P < 0.001$), with no differences in sex, ethnicity, education, or ejection fraction. The group with delirium had a higher prevalence of DM (42.5% vs. 28.7%, $P = 0.033$), hypertension (86.3% vs. 73%, $P = 0.023$), CKD (17.8% vs. 5.8%, $P = 0.003$), and visual dysfunction (11% vs. 1.1%, $P = 0.001$),

fewer users of antidepressant medication (2.7% vs. 11.1%, $P = 0.032$), and lower proportion of alcohol drinkers (4.8% vs. 11%, $P = 0.091$). Other antecedents considered in this study, such as congestive heart failure, AMI, stroke, atrial fibrillation, depression, anemia, and smoking, were not significant.

Analyzing the incidence in different age groups (≥ 60 years or < 60 years) and in those with different comorbidities, we observed a higher incidence of delirium among patients older than 60 years (34.4% vs. 17.6%, $P = 0.003$), hypertensive patients (31.3% vs. 16.4%, $P = 0.023$), diabetic patients (36.5% vs. 23.9%, $P = 0.033$), and CKD patients (54.2% vs. 25.2%, $P = 0.003$). Delirium was more common among those with visual impairment (8/10 vs. 65/251, $P = 0.032$). In other words, of the 10 patients with visual impairment, eight had delirium, and of the 23 patients using antidepressants, only two had delirium. Approximately 80% of the patients were taking calcium channel blockers or beta-blockers preoperatively.

The preoperative laboratory tests (Table 1) showed that patients with delirium had higher levels of creatinine (1.17 mg/dL vs. 1 mg/dL, $P = 0.018$), urea (55.4 mg/dL vs. 43.6 mg/dL, $P = 0.003$), and potassium (4.36 mEq/L vs. 4.19 mEq/L, $P = 0.012$) and lower levels of hemoglobin (12.36 g/dL vs. 13.48 g/dL, $P < 0.001$) and hematocrit (37% vs. 39.7%, $P = 0.001$) on average.

Regarding intraoperative characteristics, in the group that presented delirium, there were fewer patients undergoing CABG alone (28.8% vs. 46%, $P = 0.001$) and more patients with combined surgeries (19.2% vs. 5.8%). This group also had a longer average anesthesia time (457 minutes vs. 425 minutes, $P = 0.049$), longer cardiopulmonary bypass time (120 minutes vs. 97 minutes, $P = 0.001$), and more urgent or emergency surgeries (35.3% vs. 19.8%, $P = 0.007$).

Regarding the postoperative outcomes, the groups were different for all the variables analyzed except readmission. Patients with delirium had a longer ICU stay (median seven days vs. three days, $P < 0.001$), longer mechanical ventilation duration (median 977

Table 2. Characteristics of the intraoperative period.

Variables	All patients	No delirium	With delirium	P-value
	(n = 262)	(n = 189)	(n = 73)	
Type of surgery, n (%)				0.001 ³
MRI	108 (41.20)	87 (46.0%)	21 (28.8%)	
Valve surgery	94 (35.90)	72 (38.1%)	22 (30.1%)	
Aortic arch surgery	25 (0.09)	14 (7.4%)	11 (15.1%)	
MRI + valve surgery	21 (0.08)	8 (4.2%)	13 (17.8%)	
MRI + aortic arch surgery	4 (0.01)	3 (1.6%)	1 (1.4%)	
TAVI	8 (0.03)	4 (2.1%)	4 (5.5%)	
Others	2 (0.01)	1 (0.5%)	1 (1.4%)	
Anesthesia time (minutes)		n = 188	n = 73	0.047 [^]
Mean (SD)	434.07 (97.8)	425.21 (84.25)	456.88 (123.96)	
Median (P ₂₅ - P ₇₅)	425 (375 - 475)	424 (365 - 470)	441 (390 - 510)	
Surgical classification, n (%)		n = 187	n = 71	0.007 ³
Elective	196 (74.80)	150 (80.2%)	46 (64.8%)	
Urgency	53 (20.20)	34 (18.2%)	19 (26.8%)	
Emergency	9 (3.40)	3 (1.6%)	6 (8.5%)	
No information	4 (0.01)			
Extracorporeal circulation, n (%)		n = 189	n = 73	0.075 ²
No	20 (7.6)	11 (5.8%)	9 (12.3%)	
Yes	242 (92.4)	178 (94.2%)	64 (87.7%)	
CPB time (minutes)		n = 179	n = 64	0.001 [^]
Mean (SD)	103.3 (38.9)	97.18 (33.52)	120.31 (47.39)	
Median (P ₂₅ - P ₇₅)	96.0 (75 - 118)	94 (74 - 110)	105 (86 - 150)	

[^]Corrected t-test; ²Pearson's chi-squared test; ³Fisher's exact test

CPB=cardiopulmonary bypass; MRI=myocardial revascularization; P₂₅=25th percentile; P₇₅=75th percentile; SD=standard deviation; TAVI=transcatheter aortic valve implantation

vs. 535 min, $P < 0.001$), longer hospital stay (median 20 days vs. 13 days, $P < 0.001$), and a higher incidence of hospital death (22.2% vs. 3.2%, $P < 0.001$) (Table 3).

Factors Associated with Delirium

The infographic on Figure 2 shows the results of the univariate analysis that related the association of each variable independently with the delirium outcome. According to the preestablished criterion of $P < 0.10$, age, history of DM, arterial hypertension, CKD, alcohol drinking, and type of surgery were selected for the multivariate analysis. In general, the results showed that the factors associated with the incidence of delirium were as follows:

- Age: the greater the age, the greater the incidence of delirium (with each year of age, the chance increases, on average, 6.8%, ranging from 3.4 to 10.3%).

- Hypertension: hypertensive patients had more delirium (odds ratio [OR] = 2.2, 95% confidence interval [CI] 0.9 to 5.6), but this result was not significant at the level of 0.05. Most patients had hypertension.
- CKD: the presence of CKD was highly associated with delirium.
- Alcohol: alcohol drinkers were more likely to be delirious in the postoperative period.
- Type of surgery: patients who underwent isolated myocardial revascularization had the least amount of postoperative delirium. All other surgeries, especially CABG with some associated procedure, had a higher chance of delirium when compared to CABG.

DISCUSSION

The results of this study show a high incidence of delirium (27.5%) in the postoperative period of cardiac surgery, similar to values

Table 3. Postoperative outcomes.

Outcomes	All patients (n = 262)	No delirium (n = 189)	With delirium (n = 73)	P-value
Time in ICU (days)				
Mean (SD)	6.1 (7.8)	3.78 (3.01)	12 (12.18)	< 0.001 [^]
Median (P ₂₅ - P ₇₅)	4 (2 - 6)	3 (2 - 4)	7 (5 - 13)	
Length of stay (days)				
Mean (SD)	18.3 (14.2)	15.31 (9.53)	26.19 (20.19)	< 0.001 [^]
Median (P ₂₅ - P ₇₅)	15 (10 - 22)	13 (9 - 18)	20 (13 - 32)	
Mechanical ventilation time (from arrival at the recovery room) (minutes)				
Mean (SD)	1361.8 (2815.2)	816.66 (1709.91)	2802.71 (4298.31)	< 0.001 [^]
Median (P ₂₅ - P ₇₅)	604 (455 - 880)	535 (435 - 775)	977.5 (645 - 2865)	
Readmission, n (%)				
No	244 (93.1)	175 (92.6%)	69 (95.8%)	0.414 ³
Yes	17 (6.5)	14 (7.4%)	3 (4.2%)	
No information	1 (0.4)			
Hospital death, n (%)				
No	238 (90.5)	182 (96.8%)	56 (77.8%)	< 0.001 ²
Yes	22 (8.4)	6 (3.2%)	16 (22.2%)	
No information	2 (0.7)			

[^]same P-value for the Mann–Whitney test and t-test with log data; ²Pearson's chi-squared test; ³Fisher's exact test
 ICU=intensive care unit; P₂₅=25th percentile; P₇₅=75th percentile, SD=standard deviation

Table 4. Presentation of delirium symptoms in the postoperative period.

Symptoms	Patients (n = 73)
Attention	66 (90.4%)
Cognition	67 (91.8%)
Disorientation	54 (74.0%)
Alertness decrease	49 (67.1%)
Perception	1 (1.4%)
Sleep–wake	4 (5.5%)
Humor	6 (8.2%)
Agitation	52 (71.2%)
Psychomotor slowing	31 (42.5%)
Mechanical restraint on bed	25 (34.2%)

found in the literature. Sanson et al.^[5], in a prospective study with a cohort of 215 patients after cardiac surgery, found a 31% incidence of delirium. In a mixed ICU, out of 200 successive admissions with clinical cardiological cases and postoperative cardiac surgery, McPherson et al.^[6] observed a 27% incidence of delirium. Another study reported great variability in the incidence of delirium in patients in the postoperative period of cardiac surgery. This range, from three to 70%, can be attributed to the differing severity of preoperative comorbidities, but the most important factor is the ability of the team to detect the different delusional phenotypes or even the application of specific and recommended tools to aid

in its diagnosis, such as the confusion assessment method for the ICU (CAM-ICU)^[7].

There is some consensus on the risk factors leading to a higher or lower incidence of delirium after cardiac surgery. They include demographic factors such as age, sex, comorbidities, preoperative medications, and perioperative factors. In a recent meta-analysis, Chen et al.^[8] could pool seven prospective studies, four prospective observational studies, and three retrospective analyses totaling 13,286 patients, finding that the incidence of delirium varied between 4.1 and 54.9% in the different studies. In their meta-analysis, the authors found eight risk factors and one protective

Results of multiple logistic regression: associated factors to ACD multivariate analysis				
		95% CI		
Variable	Odds ratio	Inferior	Superior	P-value
Age (years)	1.068	1.034	1.103	<0.001
AH	2.238	0.892	5.613	0.086
CRD	7.175	2.492	20.656	<0.001
Alcoholism	4.561	1.380	15.076	0.013
Type of surgery				
Coronary bypass	1.000	-	-	-
Valvar replacement	3.319	1.423	7.739	0.005
Aorta	5.253	1.734	15.916	0.003
Combined surgeries	10.123	3.366	30.445	<0.001
TAVI	3.624	0.84	15.635	0.084
Emergency	4.299	1.986	9.304	<0.001

Fig. 2 - Multivariate analysis of factors associated with delirium. ACD=acute cognitive dysfunction; AH=arterial hypertension; CI=confidence interval; CRD=chronic renal disease; TAVI=transcatheter aortic valve implantation.

factor. The predictors of delirium were older age, carotid stenosis, DM, history of depression or cognitive dysfunction, and NYHA functional class III or IV. The presence of NYHA functional class I was a protective factor. In the postoperative period, factors related to a higher occurrence of delirium were length of ICU stay and length of mechanical ventilation.

Reinforcing the issue of the application of specific tools for the diagnosis of delirium, an Australian study of 346 postsurgical patients from different specialties admitted to the ICU for observation found a significant incidence of delirium. Of this cohort, 100 patients were included under the established criteria (American Society of Anesthesiologists grade 1, mean age 64.5 ± 11.4 years) without previous comorbidities. The daily assessment was performed using a specific tool, the CAM-ICU. The incidence of postoperative delirium in this cohort was 28%, with 86% of the cases diagnosed on the first day, 14% on the second day, and no cases on the third day. The most common phenotype was hypodynamic (87%). There was no difference between younger and older adults, which is contradictory to other data, including ours^[9].

Several questions regarding the influence of preoperative medication and the incidence of delirium have been raised in the literature, especially in elderly patients^[10]. Mechanisms involving agonists or antagonists of neurotransmitters such as acetylcholine, dopamine, noradrenaline, and upward or downward variations in the serotonergic and GABAergic components of the central nervous system have been investigated^[11]. The hypothesis of increased activity of anticholinergic medication and delirium

is well accepted. Several medications commonly used in the population with known anticholinergic activity may be associated with the onset of delirium. Antiparkinsonians such as benztropine, opioids, the antihistamines diphenhydramine and hydroxyzine, and tricyclic antidepressants were mentioned. Anxiolytics such as benzodiazepines and others acting on the GABAergic system are also implicated in the genesis of delirium^[10]. Kassie et al.^[12] conducted a systematic review seeking to answer these questions about the association of different preoperative medications and the incidence of postoperative delirium. These authors classified 29 studies as follows: 25 prospective studies, three retrospective studies, and one post-hoc randomized controlled trial. Despite the limited number of high-quality studies demonstrating a direct association of preoperative medication and incidence of delirium, it identified that beta-blockers (OR = 2.06 [1.18 – 3.60]) increased delirium in vascular surgery, benzodiazepines (OR = 2.10 [1.23 – 3.59]) in orthopedics, and nifedipine in cardiac surgery. The authors of this meta-analysis concluded that there is a lack of well-controlled studies demonstrating the association of preoperative drugs and the facilitation of postoperative delirium^[12]. In our study, there was a statistically significant difference between the groups regarding comorbidities. The delirium group had a higher prevalence of DM (42.5% vs. 28.7%, $P = 0.023$), CKD (17.8% vs. 5.8%, $P = 0.003$), and visual dysfunction (11% vs. 1.1%, $P = 0.001$), lower use of antidepressant medication (2.7% vs. 11.1%, $P = 0.032$), and fewer alcohol drinkers (4.8% vs. 11%, $P = 0.091$). Considering that 80% of the patients used calcium channel blockers, some influence

of these could be assumed, as in the abovementioned patients who underwent vascular surgery. Another finding was that patients using antidepressants were associated with a higher incidence of delirium, despite the small sample size.

Another important question is whether any factor can be modified perioperatively to make delirium less likely in a population at higher risk undergoing cardiac surgery. Although it was not the scope of our study, the study by Burkhart et al.^[13] may provide some additional information that could corroborate our results. The authors examined data (post-hoc analysis data) of 113 patients aged 65 years or older participating in a cohort who underwent cardiac surgery, who were treated with a cholinesterase inhibitor, and who developed postoperative delirium. In this cohort, the incidence of delirium was 30% as assessed by the CAM-ICU. Higher doses of fentanyl ($> 10 \mu\text{g/kg}$) and the consequent longer duration of mechanical ventilation after surgery were associated with a higher incidence of postoperative delirium in elderly patients after cardiac surgery. Although this item was not available in the medical records, the mean fentanyl dose in our patients was $> 10 \mu\text{g/kg}$, and the patients who presented delirium were ventilated > 24 hours postoperatively.

The pathophysiology of delirium is considered complex and multifactorial, but some considerations are in order for preventing it and reducing its neuropsychological damage. According to Maldonado, several hypotheses could be integrated into a theory, considering a set of factors, such as neurotransmitter dysfunction, disruption of the integration and processing of sensory information, involuntary motor response to internal and external stimuli, loss of neuroconnectivity, and neuropsychiatric damage of different magnitudes^[1].

As it ages, the brain becomes more susceptible to physical and psychological stresses and those caused by systemic diseases or acute traumas such as surgery^[14]. In the present study, patients who presented postoperative delirium were significantly older than those without delirium.

Another hypothesis is the neuroinflammatory hypothesis, in which a break in the blood-brain barrier allows the entry of inflammatory radicals such as cytokines and other inflammatory mediators arising from surgical injury, causing acute brain synaptic dysfunction and subsequent symptoms of stroke and delirium^[1,14]. A third hypothesis is that of oxidative stress. The brain, due to its high lipid and myelin contents and low antioxidant capacity, is particularly sensitive to an increase in reactive oxygen and nitrogen species. Several perioperative insults, such as hypotension, anemia, and fluctuations in oxygen levels, trigger an acute process of increases in reactive species. These have various neurological consequences, such as disruption of ionic gradients, alteration of the synthesis and metabolism of neurotransmitters, and difficulty excreting neurotoxic agents, which could be involved in the genesis of delirium^[15].

The neuroendocrine hypothesis is another theory, proposing that acute stress, such as cardiac surgery with cardiopulmonary bypass, strongly activates the hypothalamic-pituitary-adrenal axis. Delirium is a consequence of the physiological reaction mediated by high levels of glucocorticoids, which in turn act on gene transcription, cell signaling, and modulation of synaptic activity and ultimately alter the psychic behavior of the patient^[16].

Another hypothesis is the disruption of the circadian rhythm, changes in the day and night alternation, common in surgical procedures that presuppose ICU admission. Some studies show that

sleep deprivation that precedes the onset of delirium is common in patients in the postoperative period of cardiac surgery^[17]. The disruption of the circadian rhythm compromises the secretion of melatonin, abruptly reducing its serum levels. Melatonin would have a positive protective effect against delirium. A meta-analysis of randomized controlled trials found that the exogenous use of melatonin was a significant protector against delirium in medical patients admitted to the ICU^[18].

Finally, when faced with different aggressors and even different anesthetics and drugs used in the perioperative period, qualitative and quantitative changes in neurotransmitters can be observed. Lower acetylcholine availability at synapses, excess dopamine or norepinephrine, and changes in glutamate and GABAergic systems are associated with a higher incidence of delirium^[14]. Opioids, for example, commonly used in anesthesia and postoperatively, have been associated with a higher incidence of delirium because they increase dopamine and glutamate while reducing the amount of acetylcholine^[14].

With the development of sophisticated imaging tests, the network connectivity hypothesis is gaining strength. It is based on the complex organization of functional brain circuits that are anatomically present in the posteromedial cortex, anteromedial cortex, and temporal-parietal junctions. These circuits are related to attention, organized thinking, and self-reflection. The disruption of this connectivity explains the symptoms and signs observed in patients with delirium, as described above^[19].

The systems integration failure hypothesis (SIFH) may complicate the already complex pathophysiology of delirium. This hypothesis proposes that changes in neurotransmitters combined with disorganization of neuronal synapse networks lead to acute dysfunction of the central nervous system in responding appropriately to external stimuli, creating disordered cognitive thinking. The SIFH proposal reflects an understanding that all the hypotheses above are complementary, with multiple influences within the complexity of the pathogenesis of delirium^[14].

To prevent delirium, there is no single strategy. Multiple interventions involve changes in the structure of ICUs, such as isolated rooms, environments that simulate day and night, awareness of the teams, use of precise diagnostic tools, identification of patients at higher risk, and appropriate clinical follow-up for early intervention. This would require institutional effort and is costly. There is little evidence about pharmaceutical prophylaxis. There is some evidence for consensus on the avoidance of perioperative use of benzodiazepines, reduction of opioids, and judicious use of processed electroencephalogram to avoid suppression rates^[20]. Dexmedetomidine used in the perioperative period has emerged as a drug with potential efficacy in reducing delirium after cardiac surgery^[21].

Unfortunately, we were unable to transfer these data to our sample because the anesthesia used in the study sample was still based on high doses of fentanyl, sevoflurane, midazolam, and etomidate as hypnotics in most cases. Another limiting factor in our study was the nonuse of adequate tools, such as CAM-ICU. Cases of delirium were recorded by the multidisciplinary team and associations with antipsychotic medications. We can infer that they may be underestimated, especially in the hypoactive phenotype^[22].

The impact of delirium on clinical outcomes in the affected population can be devastating. A systematic review of delirium in different clinical settings showed that the risk of death was increased in patients with delirium compared with controls without

delirium (hazard ratio 1.95, 95% CI 1.51 - 2.52). Delirium contributed to death independently of other confounding factors, such as age, sex, disease severity, presence of comorbidities, and previous dementia^[23]. In another meta-analysis of patients admitted to ICUs, the occurrence of delirium increased the risk of negative outcomes twofold compared to unaffected patients, as well as causing a longer duration of mechanical ventilation and hospitalization^[24]. In a systematic review focusing on late clinical outcomes of the consequences of delirium after cardiac surgery, Crocker et al.^[25] showed that affected patients had a higher probability of death, readmission after discharge, and poor quality of life after hospital discharge. In our study, the predictive factors related to a higher incidence of delirium were age and the presence of comorbidities such as CKD, arterial hypertension, DM, and visual dysfunction. Regarding the negative outcomes, there is agreement with earlier studies, as higher mortality, longer duration of mechanical ventilation, longer hospitalization, and a higher rate of readmission characterize delirium patients. As a late complication of delirium with great social and economic impact, permanent cognitive and psychiatric sequelae such as posttraumatic stress has been observed^[1].

Limitations

Several weaknesses compromise our results, including the fact that this was a retrospective search of electronic medical records, which entails possible failures in the identification of delirium and loss of intraoperative information such as fluctuations in blood pressure and oxygenation levels, as well as a lack of standardization of anesthesia. Finally, the nonuse of diagnostic tools such as CAM-ICU in the postoperative period, within established protocols, may have underestimated the incidence, especially of hypoactive phenotypes, and there was no late follow-up to check for permanent sequelae.

CONCLUSION

In conclusion, delirium is a frequent complication following cardiac surgery, occurring in more than 20% of patients, and contributes to mortality, postoperative cognitive decline, physical status compromise, and increased healthcare and social costs. In our casuistic, advanced age, DM, hypertension, chronic renal disease, visual dysfunction, and CABG were more prevalent and significantly associated with delirium. As the population undergoing cardiac surgery continues to age and present with multiple comorbidities, the incidence of delirium is expected to rise sharply. This growing incidence underscores the urgent need for cardiovascular teams, including anesthesiologists, surgeons, and ICU care providers, to take an active role in mitigating the impact of delirium in at-risk patients. Given the multifactorial nature of delirium, a wide range of interventions have been assessed. Among these, several have proven effective, including opioid and benzodiazepine reduction, cerebral perfusion monitoring, postoperative pain management, and, most importantly, modifications in ICU structure and care protocols.

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Authors' Roles & Responsibilities

PODM	Substantial contributions to the acquisition and analysis of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published
SPZ	Substantial contributions to the design of the work; and the analysis of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published
FRBGG	Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; final approval of the version to be published
DAO	Drafting the work or revising it critically for important intellectual content; final approval of the version to be published
JOCAJ	Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; drafting the work or revising it critically for important intellectual content; agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; final approval of the version to be published

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