

# Can We Identify Risk Factors for Postoperative Delirium in Cardiac Coronary Patients? Our Experience

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## ABSTRACT

**Introduction:** Delirium is a temporary mental disorder that frequently occurs among elderly hospitalized patients. Patients who undergo cardiac operations have an increased risk of postoperative delirium, which is associated with higher mortality and morbidity rates, a prolonged hospital stay, and reduced cognitive and functional recovery.

**Patients and Methods:** In our prospective study, we included 370 consecutive adult patients who underwent on-pump coronary artery surgery between January 1, 2011, and July 1, 2011. We selected 21 potential risk factors and divided them into preoperative, intraoperative, and postoperative groups. Delirium was diagnosed with the Confusion Assessment Method.

**Results:** Postoperative delirium was diagnosed in 74 patients (20%). Four predictive factors were associated with postoperative delirium: diabetes mellitus, cerebrovascular disease, peripheral vascular disease, and prolonged intubation ( $P < .05$ ).

**Conclusion:** Three of the four predictive factors significantly associated with delirium are preoperative. They are relatively easy to measure and can be used to identify patients at higher risk. Fast extubation of these patients and preventive interventions can be taken to prevent negative consequences of this postoperative complication.

## INTRODUCTION

Delirium is defined as a reversible, global impairment of cognitive processes that is coupled with disorientation, impaired short-term memory, altered sensory perceptions, an abnormal thought process, and inappropriate behavior [Szokol 2001]. It is one of the most frequently encountered complications observed postoperatively. Generally, the

incidence of postoperative delirium is approximately 10% to 30% and is as high as 70% in elderly patients [Dyer 1995]. Delirium has been associated with prolonged hospital stays, reduced cognitive and functional recovery, higher frequencies of nursing home admission, and higher mortality rates [McK-hann 2002]. Patients who undergo cardiac operations have an increased risk of delirium. At this time, there is no available method capable of predicting postoperative delirium.

The aim of this study was to develop a delirium checklist (preoperative, intraoperative, and postoperative) to identify patients at increased risk of postoperative delirium after elective coronary on pump surgery. This study will examine the predictive validity of those factors. In the future, preventive interventions could be taken for patients at increased risk for postoperative delirium.

## PATIENTS AND METHODS

The study was conducted at Clinic for Cardiac surgery, Clinical Centre of Serbia. In this prospective study, we included 370 consecutive adult patients (>30 years old) who underwent on-pump coronary artery surgery between January 1, 2011, and July 1, 2011. The study was approved by the clinical board and Ethics Committee. All patients were informed in detail and gave signed consent to take the part in the study.

Cardiopulmonary bypass was established with arterial inflow through the ascending aorta and venous drainage through the right atrium or caval veins. The pump flow rate was maintained between 2.0 and 2.5 L/min per m<sup>2</sup> as a function of temperature. The mean arterial pressure was maintained between 40 and 80 mm Hg. To induce light to moderate hypothermia, we lowered the systemic blood temperature to between 28C and 34C, with active rewarming to 36.5C occurring at the end of cardiopulmonary bypass.

Our anesthesia protocol was the same for all patients included in the study and consisted of induction of anesthesia with the combination of fentanyl (an opioid agent), pancuronium (a muscle relaxant), and midazolam, sevoflurane, or propofol (intravenous anesthesia agents). We identified fentanyl as a potential risk factor, because Burkhart et al [2010] had reported that fentanyl was associated with postoperative delirium in cardiac surgery.

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Fourteen patients died during their hospital stays, and they were excluded from the study (mortality, 3.7%).

After a review of the literature, we selected 21 potential risk factors for postoperative delirium. The selected potential predisposing factors were divided into three groups—preoperative, operative, and postoperative. The preoperative variables were sex, age (>60 years), diabetes mellitus, arterial hypertension, preoperative atrial fibrillation, history of cerebrovascular disease, peripheral vascular disease, history of neurologic disease, preoperative use of alcohol and opiates, history of delirium, dementia, depression, visual and hearing impairment, markedly abnormal renal function, and a left ventricular function 30%. Intraoperative variables were operation time, total cardiopulmonary bypass time, circulatory arrest time, and the fentanyl dose used for anesthesia. Postoperative variables were intubation time, postoperative inotropic support, postoperative atrial fibrillation, a high perioperative transfusion requirement, and neurologic complications.

Delirium was assessed with the Confusion Assessment Method (CAM). The sensitivity of the CAM is 94% to 100%, and its specificity is 90% to 95% [Inouye 1990; Truman 2003]. The CAM is significantly correlated with the Mini-Mental State Examination, the Visual Analog Scale for confusion and the Digit Span Test. The CAM consists of two parts. Part 1 is screens for overall cognitive impairment. Part 2 includes four features that have been found to have the greatest ability to distinguish delirium or reversible confusion from other types of cognitive impairment. These features are (1) an acute onset of changes or fluctuations in mental status, (2) inattention, (3) disorganized thinking, and (4) an altered level of consciousness. We determined a patient to be delirious if she or he manifested features 1, 2, and either feature 3 or feature 4.

**Statistical Analysis**

All data are presented as the mean and SD, or as a percentage. Frequencies were tabulated for each risk factor of the patients. Differences in prevalence were identified with the  $\chi^2$  test after continuous variables were broken up into categories. The Mann-Whitney *U* test was used for nonparametric analysis when data had larger values. The Mann-Whitney *U* test is one of the most well-known nonparametric tests of statistical significance. A *P* value <.05 was considered statistically significant, and a *P* value <.01 was considered highly significant. All statistical analyses were performed with SPSS software (version 17.0; SPSS/IBM, Chicago, IL, USA).

**RESULTS**

Participating in the study were 370 patients who underwent their on-pump coronary artery surgeries in the first half of 2011.

We selected 21 potential risk factors, which we divided into preoperative, operative, and postoperative groups. These factors were as follows: sex, age (>60 years), diabetes mellitus, arterial hypertension, preoperative atrial fibrillation, history of cerebrovascular disease, peripheral vascular disease, history of neurologic disease, preoperative use of alcohol and opiates, history of delirium, dementia, depression, visual and hearing

impairment, markedly abnormal renal function, a left ventricular function 30%, operation time, total cardiopulmonary bypass time, circulatory arrest time, the fentanyl dose used for anesthesia, intubation time, postoperative inotropic support, postoperative atrial fibrillation, a high perioperative transfusion requirement, and neurologic complications. Tables 1 and 2 summarize the potential risk factors for the patients participating in the study.

Table 1. Characteristics of Patients

Characteristic	Yes, n	No, n	Yes, %
Age > 60 y	257	99	72.2
Male/female sex	271/85		76.1/23.9
Inotropic drug support	103	253	28.9
Cerebrovascular disease	17	339	4.7
Diabetes	90	266	25.3
Transfusion requirement	146	210	41.1
Mental disease	14	342	3.9
Abnormal renal function	42	314	11.8
Preoperative fibrillation	41	315	11.5
Postoperative fibrillation	118	238	33.1
Peripheral vascular disease	20	336	5.6
Abuse of alcohol and opiates	108	248	30.3
Neurologic disease	24	332	6.7
Ejection fraction < 30%	27	329	7.6

Table 2. Mean Values for Cardiopulmonary Bypass (CPB), Aorta Cross-Clamping (ACC), Operation Time, Fentanyl Dose, and Intubation Time after Coronary Artery Surgery (n = 356)

Variable	Minimum	Maximum	Mean	SD
CPB, min	32.0	201.0	68.890	22.3690
ACC, min	14.0	133.0	41.542	15.0922
Operation time, h	3.0	35.0	4.304	1.8064
Fentanyl dose, mL	0	31.0	20.132	2.4887
Intubation time, h	9.0	145.0	15.198	7.5132

Table 3. Nonparametric Test ( $\chi^2$  Test) for Age and Sex Distribution of Patients

Variable	Delirium, n (%)	No Delirium, n (%)	<i>P</i>
Age > 60 y	60 (81.1)	197 (69.9)	>.05
Sex			
Male	56 (75.7)	215 (76.2)	>.05
Female	18 (24.3)	67 (23.8)	>.05
Total	74	282	356

The majority of the patients were male (76.1%), and most of the study participants (72.2%) were older than 60 years. We detected diabetes mellitus in 25.3% of the patients, cerebrovascular disease in 4.7%, mental disease in 3.9%, abnormal renal function in 11.8%, preoperative fibrillation in 11.8%, an ejection fraction <30% in 7.6%, and peripheral vascular disease in 5.6%.

The mean total cardiopulmonary bypass time was 68.89 min, the mean circulatory arrest time was 41.54 min, the mean total operation time was 4.3 hours, the mean fentanyl dose was 20.1 mL, and the mean intubation time was 15.2 hours.

We divided the patients into two groups, those who experienced delirium and those who did not. The two groups showed no significant differences with respect to age and sex (Table 3). Postoperative delirium was diagnosed in 74 patients (20%). Table 4 presents a checklist of risk factors for delirium and the  $\chi^2$  analyses of their respective frequencies in the two groups. Table 5 summarizes the Mann-Whitney *U* test results for the nonparametric variables.

Table 4.  $\chi^2$  Tests of All Nonparametric Variables Shows the Main Predictors for Delirium after Coronary Artery Surgery\*

Variable	Delirium, n (%)	No Delirium, n (%)	<i>P</i>
Inotropic drug support	25 (33.8)	27 (27.7)	>.05
Hypertension	70 (94.6)	250 (88.6)	>.05
<b>Cerebrovascular disease</b>	<b>13 (17.6)</b>	<b>4 (1.4)</b>	<b>&lt;.01</b>
<b>Diabetes</b>	<b>27 (36.5)</b>	<b>63 (22.3)</b>	<b>&lt;.05</b>
High transfusion requirement	35 (47.3)	111 (39.4)	>.05
History of mental disease	3 (4.0)	11 (3.9)	>.05
Abnormal renal function	9 (12.4)	33 (11.7)	>.05
Preoperative fibrillation	13 (17.6)	28 (10.0)	>.05
Postoperative fibrillation	31 (41.9)	87 (30.8)	>.05
<b>Peripheral vascular disease</b>	<b>14 (18.9)</b>	<b>6 (2.1)</b>	<b>&lt;.01</b>
Abuse of alcohol and opiates	25 (33.8)	83 (29.4)	>.05
Neurologic disease	4 (5.4)	20 (7.1)	>.05
Ejection fraction < 30%	7 (9.5)	20 (7.1)	>.05

\*Statistically significant ( $P < .05$ ) predictors of delirium are in boldface.

Table 5. Mann-Whitney *U* Test of All Variables Shows the Main Predictors for Delirium after Coronary Artery Surgery\*

Variable	Delirium	No Delirium	<i>P</i>
Operation time, h	4 (3–16)	4 (3–6)	>.05
CPB, min	71 (32–201)	67 (34–142)	>.05
ACC, min	38 (14–133)	40.5 (14–110)	>.05
<b>Intubation time, h</b>	<b>18 (9–25)</b>	<b>14 (10–145)</b>	<b>&lt;.05</b>
Fentanyl dose, mL	20 (16–26)	20 (0–31)	>.05

\*Data are presented as the median (range). Statistically significant ( $P < .05$ ) predictor is in boldface. CPB indicates cardiopulmonary bypass; ACC, aorta cross-clamping.

Four predictors were independently associated with postoperative delirium in our statistical analysis: diabetes mellitus ( $P < .05$ ), cerebrovascular disease ( $P < .01$ ), peripheral vascular disease ( $P < .01$ ), and prolonged intubation ( $P < .05$ ) (Tables 4 and 5).

There were no significant differences between the two groups in the incidences of the other potential risk factors ( $P > .05$ ).

## DISCUSSION

Neuropsychological and psychiatric disorders occurring after surgery have been well known since the 1950s and 1960s [Fox 1954], and they continue to be a subject of active research. Postoperative delirium is one of the most common complications, especially in older patients [Inouye 1996]. Delirium is a clinical diagnosis that cannot be confirmed with laboratory or neuroimaging tests. The clinical picture of delirium varies and includes hyperactive, hypoactive, and mixed types [Culp 1997]. The etiology and pathogenesis of delirium remains little understood despite many studies and is probably multifactorial in origin. Delirium has a fluctuating course; therefore, it can be easily missed during a routine examination. In addition, administered sedatives and analgesics can mimic the symptoms of this postoperative complication, or, alternatively, symptoms of delirium can be interpreted as side effects of these medications. Patients with postoperative delirium have prolonged hospital stays, reduced cognitive and functional recovery, higher frequencies of nursing home admission, and higher mortality rates. It is important to investigate the causes and risk factors of delirium to develop effective treatment and prevention techniques. Many variables (preoperative, intraoperative, and postoperative) have been described as risk factors for this postoperative complication.

Our study included 370 on-pump coronary patients who underwent their operations in the first half of 2011. We selected 21 variables as potential risk factors after reviewing previously published studies. Of these variables, four factors were independently associated with postoperative delirium in the present study—diabetes mellitus, cerebrovascular disease, peripheral vascular disease, and prolonged intubation.

Other studies have also associated such risk factors as prolonged postoperative intubation and peripheral vascular disease with this postoperative complication. Prolonged intubation was significantly associated with delirium in studies by Kazmierski et al [2010], Burkhart et al [2010], and Stransky et al [2011]. A study by Norkiene et al [2007] found peripheral vascular disease to be an independent risk factor for postoperative delirium in cardiac surgery.

The results we have obtained for the prediction of postoperative delirium differ from the results of some other studies. The study of Yildizeli et al [2005], for example, showed a significant association with postoperative delirium for the following factors: abnormal postoperative levels of sodium, potassium, or glucose; sleep deprivation; an older age; and operation time. Miyazaki et al [2011] conducted a study of risk factors for stroke and delirium after off-pump coronary surgery, the results of which suggested that stenosis of the

carotid arteries of >50%, creatinine concentrations >1.3 mg/dL, and a history of hypertension, atrial fibrillation, and smoking were associated with these morbidities. Preoperative stroke and the duration of cardiopulmonary bypass were detected as risk factors for postoperative delirium in older patients after coronary bypass surgery in a study by Rolfson and colleagues [1999]. On the other hand, Mu et al [2010] showed that a high serum level of cortisol was associated with an increased risk for this postoperative complication after coronary surgery.

Although alcohol and opiate abuse have appeared to be strongly associated to postoperative delirium [Marcantonio 1994], our study found no significant association with such abuse. Possibly, our results are attributable to false data provided by the patients or to the small size of the study group. Nevertheless, patients with alcohol and opiate abuse were more common in the delirium group than in the group with no delirium (33.8% versus 29.4%, not statistically significant). Advanced age is one of the most commonly reported independent predictors of postoperative delirium [Bucnerius 2004], probably because of its close association with the atherosclerosis disease process. In our study, however, there was no significant difference between the delirium and no-delirium groups with respect to older age.

The differences between our results and those of other studies may be explained by our selection of patients and their characteristics. Our group of selected patients included only those undergoing on-pump coronary artery procedures, they were older than the patients selected in other studies (72.2% were older than 60 years), and they had more comorbidities, which is expected given their advanced ages.

Peripheral and cerebrovascular diseases were expected to be associated factors, because they indicate an advanced atherosclerosis process and a limited response to pharmacologic treatment, which could have caused this postoperative complication.

The incidence of delirium in our study was 20%, which corresponds to that of many other studies.

Factors statistically related to postoperative delirium were relatively easy to measure, and they could be used to identify patients at greater risk of postoperative delirium after on-pump coronary surgery. In such patients, preventive interventions can be taken, such as haloperidol prophylaxis [Winawer 2001], or intramuscular injection of diazepam and a continuous intravenous infusion of flunitrazepam and pethidine [Aizawa 2002]. Katznelson et al [2009] reported that preoperative use of statins successfully reduced postoperative delirium, and Hanania et al [2002] reported the successful use of melatonin. Shehabi et al [2009] tested dexmedetomidine for delirium prophylaxis, but their study demonstrated that dexmedetomidine reduced the duration but not the incidence of delirium.

Pharmacologic treatment is essential to prevent any negative consequences of delirium. Haloperidol, a high-potency antipsychotic, is the most commonly used drug. It is useful in treating delusions, paranoia, and perceptual disturbance. Because most of our patients with postoperative delirium had

agitation and hallucinations and because they required rapid pharmacologic intervention, haloperidol was used as an initial treatment. Yapici et al [2011] reported dexmedetomidine as a good treatment choice for the delirium state after cardiac surgery, so we can consider it as our second pharmacologic choice for these patients.

The prognosis of delirium is related to prompt recognition and appropriate management of potential risk factors. Consequently, we analyzed preoperative, intraoperative, and postoperative variables possibly related to this postoperative complication. Studies have clearly shown that patients who develop postoperative delirium have increased rates of postoperative complications [Marin 2010] and longer hospital stays than patients who do not develop this kind of complication.

In future studies, we could consider the following long-term outcomes of these patients: long-term mortality of patients with postoperative delirium; comparison of the long-term mortality of patients with postoperative delirium with that of patients without postoperative delirium; episodes of mental dysfunctions or any changes in mental status; and percentages of postoperative delirium occurring after other cardiac operations or other surgical procedures. These directions were suggested by psychiatrists who were involved in this study. Their participation was very important, and we hope that the next study will involve these new ideas on this subject.

This study is the first of its kind in cardiac surgery in our country. It is especially important because the results could lead to a reduction in hospital costs, which would be very important, considering the social situation in our country.

## CONCLUSION

Postoperative delirium is one of the most frequent surgical complications, especially in cardiac surgery. In our study, four potential risk factors were associated with this postoperative complication: diabetes mellitus, cerebrovascular disease, peripheral vascular disease, and prolonged intubation. Three of these variables are preoperative, and they could be used to identify patients at higher risk. Fast extubation of these patients and preventive interventions could be taken to prevent the negative consequences of postoperative delirium.

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