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# An easily overlooked clinical phenomenon after coronary artery bypass graft surgery: postoperative delirium

## *Koroner arter baypas greft ameliyatı sonrasında atlanması kolay bir klinik olgu: Postoperatif deliryum*

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***ABSTRACT***

***Background:*** In this study, we aimed to investigate the prevalence of postoperative delirium in patients undergoing coronary artery bypass grafting and to identify possible risk factors associated with this complication.

***Methods:*** Between January 2009 and December 2013, data of a total of 935 patients (747 males, 188 females; mean age 64.3±8.4 years, range 32 to 86 years) who underwent coronary artery bypass grafting were retrospectively analyzed. The patients were divided into two groups including group 1 patients (n=210) with early postoperative delirium and group 2 patients (n=725) attending to scheduled postoperative follow-up visits.

***Results:*** Delirium was significantly more common in the patients with demographic characteristics such as older age and male sex, history of alcohol intake, preoperative atrial fibrillation, increased creatinine levels, and chronic obstructive pulmonary disease ($p<0.05$). The mean preoperative and postoperative platelet volume and C-reactive protein levels were higher in group 1 ($p=0.0001$). The mean aortic cross-clamp and cardiovascular bypass time, intubation time, Acute Physiology and Chronic Health Evaluation II score, and the length of stay in the intensive care unit and hospital were significantly higher in the patients with delirium ($p<0.05$). Sternum revision ($p=0.0001$) and new-onset atrial fibrillation ($p=0.03$) were significantly higher in group 1. Early neurological events were observed in 13 patients (6.2%) in group 1 and in 10 patients (1.4%) in group 2 ($p=0.0001$). Mortality was observed in 10 patients (4.8%) in group 1 and three patients (0.4%) in group 2, suggesting that the difference was statistically significant ($p=0.0001$).

***Conclusion:*** Our study results show that complications can be minimized by analyzing the associated risk factors in the development of preoperative, perioperative, and postoperative delirium with a full collaboration with liaison psychiatry in the intensive care unit for the patients who are at risk for delirium.

***Keywords:*** Coronary artery bypass grafting; delirium; morbidity; mortality.

***ÖZ***

***Amaç:*** Bu çalışmada koroner arter baypas greftleme yapılan hastalarda postoperatif deliryum prevalansı araştırıldı ve bu komplikasyon ile ilişkili muhtemel risk faktörleri belirlendi.

***Çalışma planı:*** Ocak 2009 - Aralık 2013 tarihleri arasında, koroner arter baypas greftleme yapılan toplam 935 hastanın (747 erkek, 188 kadın; ort. yaş 64.3±8.4 yıl; dağılım 32-86 yıl) verileri retrospektif olarak incelendi. Hastalar grup 1'de (n=201) erken evre postoperatif deliryumlu hastalar ve grup 2'de (n=725) ameliyat sonrası planlanan takip vizitlerine gelen hastalar olacak şekilde iki gruba ayrıldı.

***Bulgular:*** Deliryum, ileri yaş, erkek cinsiyeti, alkol kullanımı öyküsü, ameliyat öncesi atriyal fibrilasyon, kreatinin düzeylerinde artış ve kronik obstrüktif akciğer hastalığı gibi demografik özellikleri olan hastalarda anlamlı düzeyde daha sık görüldü ($p<0.05$). Ameliyat öncesi ve ameliyat sonrası ortalama trombosit hacmi ve C-reaktif protein düzeyleri, grup 1'de daha yüksekti ($p=0.0001$). Ortalama aortik kros klemp ve kardiyopulmoner baypas süresi, entübasyon süresi, Akut Fizyoloji ve Kronik Sağlık Değerlendirmesi II skoru, yoğun bakım ünitesi ve hastanede kalış süresi deliryumlu hastalarda anlamlı olarak daha yüksekti ($p<0.05$). Sternum revizyonu ($p=0.0001$) ve yeni başlangıçlı atriyal fibrilasyon ($p=0.03$) grup 1'de anlamlı düzeyde daha yüksekti. Erken dönem nörolojik olaylar grup 1'de 13 hastada (%6.2) ve grup 2'de 10 hastada (%1.4) görüldü ($p=0.0001$). Grup 1'de 10 hastada (%4.8) ve grup 2'de üç hastada (%0.4) mortalite gözlendi ($p=0.0001$); bu fark istatistiksel olarak anlamlı idi ($p=0.0001$).

***Sonuç:*** Çalışma sonuçlarımız, deliryum riski taşıyan hastalar için yoğun bakım ünitesinde liyezon psikiyatrisi ile iş birliği içerisinde ameliyat öncesi, ameliyat sırası ve ameliyat sonrası deliryum gelişiminde ilişkili risk faktörleri analiz edilerek komplikasyonların en aza indirgenebileceğini göstermektedir.

***Anahtar sözcükler:*** Koroner arter baypas greftleme; delirium; morbidite; mortalite.

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Coronary artery bypass grafting (CABG) is a life-saving procedure which is associated with an improved quality of life.[1] Cerebral complications are responsible for the most of the mortality and morbidity events associated with cardiac surgery.[2] Cerebral injury following cardiac surgery may emerge as an open neurological complication or as a neuropsychological dysfunction in a level which cannot be noticed in normal conditions.[1]

The causes of higher morbidity and mortality of the patients hospitalized in the intensive care units (ICUs) have been associated commonly with cardiac, renal, and pulmonary complications; however, acute brain dysfunction has been ignored.[2] Facing postoperative psychosocial difficulties related to either the existing disease or those experienced during the treatment process in the progression of the life-threatening serious diseases is commonly encountered. In patients with a disease requiring intensive care during treatment, psychiatric manifestations such as anxiety, depression, cooperation difficulties, and delirium can be seen.[3]

Delirium (organic brain syndrome) is a temporary organic mental syndrome beginning suddenly, characterized by the impairment of cognitive functions, alterations in the consciousness state, attention-deficit, increased or decreased psychomotor activity, and the irregularity in sleep-wakefulness cycle.[3] It is one of the most common psychiatric disorders in the earlier stage following cardiac surgery and it is potentially life-threatening.[4] The incidence of postoperative cognitive dysfunction and delirium has been reported to be 30% to 80%.[5] In the literature, delirium incidence has been reported to be 41.7% after CABG and to be 10.3% after cardiac surgery.[6]

In this study, we aimed to investigate the prevalence of postoperative delirium in patients undergoing coronary artery bypass grafting and to identify possible risk factors associated with this complication.

## PATIENTS AND METHODS

In this study, the retrospective analysis of a total of 1,408 patients who underwent open cardiac surgery between January 2009 and December 2013 in the Cardiovascular Surgery Department of Acibadem Kocaeli Hospital was performed. The patients with signs of postoperative delirium were evaluated using the Confusion Assessment Method (CAM-ICU) scores and through the use of anti-psychotics such as dexmedetomidine hydrochloride or haloperidol.[7]

The exclusion criteria were preoperative dementia, history of psychiatric disorder such as depression and cognitive disorder, history of opioid and substance use, acute and chronic renal failure, history of head injury, peripheral artery disease, valvular disease, carotid artery or congenital heart surgery with CABG, congestive heart failure, previous myocardial infarction within the past one month, previous cerebrovascular accident within the past six months, neoplastic disease including benign and malignant tumors, endocrinological disorders (hypothyroidism, hyperthyroidism), autoimmune diseases, systemic inflammatory disease, the use of steroids or non-steroidal anti-inflammatory drugs, immunosuppressive drug treatment within the past two weeks before surgery, the presence of the clinical infection signs [fever 37.5 °C, C-reactive protein (CRP) ≥5 mg/dL or leukocyte count >12000/μL] before surgery, application of femoral artery cannulation due to the ascending aorta calcification, emergency surgery, CABG surgery on a beating heart, and reoperation. In our clinic, examinations of the anastomosis sites of the aorta were performed by palpation, as we do not perform computed tomography (CT) preoperatively on a regular basis. In patients who were ineligible for side clamping, proximal anastomoses were performed under a single cross-clamping. These patients were excluded from the study.

A total of 935 patients (747 males, 188 females; mean age 64.3±8.4 years, range 32 to 86 years) who did not receive any psychiatric treatment in the preoperative period with normal carotid and vertebral artery systems and who underwent elective isolated CABG were included in the study. The patients were divided into two groups. Group 1 (n=210) consisted of patients in whom manifestations of delirium developed within the first 72 hours of surgery, while group 2 (n=725) included patients who attended to scheduled postoperative follow-up visits.

All data were accessed by using the archives and the record system of the hospital. The demographic and clinical characteristics of the patients, complete blood counts routinely studied preoperatively and postoperatively (leukocytes, platelets, hematocrit, and hemoglobin), creatinine, and CRP levels were recorded. Data including the number of distal anastomosis, the use of blood products, duration of aortic cross-clamp, cardiopulmonary bypass time, intubation time, and length of stay in the ICU and hospital were analyzed. In addition, the Acute Physiology and Chronic Health Evaluation II (APACHE II) scores for all patients were recorded.

Arterial hypertension was considered in patients with a measurement of blood pressure of above

140 mmHg systolic and 90 mmHg diastolic for at least three times or active use of anti-hypertensives. Diabetes mellitus was defined as a fasting blood glucose level of above 126 mg/dL in at least two different measurements or active use of anti-diabetics. Smoking was defined as current smoking or ex-smokers who quitted smoking in the last 10 years. Hyperlipidemia was accepted as a total cholesterol of >220 mg/dL and low density lipoprotein (LDL) cholesterol of >130 mg/dL or use of anti-hyperlipidemics. Cerebrovascular accident was accepted as acutely developed temporary or permanent new major (type II) focal or global deficit within the postoperative 24 hours and lasting at least 72 hours.[8] All patients having the diagnosis of cerebrovascular accident were assessed by the neurologist and the diagnoses were confirmed through imaging studies.

The study protocol was approved by the institutional ethics committee. A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

All patients received 0.5 mg oral alprazolam on the night before surgery. Intramuscular 5 mg midazolam was injected 30 minutes before the operation as premedication. Intravenous midazolam (0.1 mg/kg), fentanyl (0.01 mg/kg) and rocuronium bromide (0.6 mg/kg) were administered for induction. Intravenous rocuronium bromide (0.15 mg/kg) and midazolam (0.03 mg/kg) were given for maintenance.

Median sternotomy was applied following the routine anesthesia application during surgery. Bypass grafts (saphenous vein and internal mammary artery) were prepared. Systemic heparinization was ensured by administrating 300 IU/kg heparin in a fashion which activated clotting time (ACT) would be higher than 450 seconds. Cardiopulmonary bypass was initiated by inserting two-stage venous cannula into the ascending aorta and into the right atrium. In all patients, non-pulsatile roller pump and membrane oxygenator were used for CPB. Surgical procedures were established in moderate systemic hypothermia (28-30 ºC). Cardiopulmonary bypass was applied in a fashion which flow rate would be 2.2 to 2.5 L/min/$m^2$; the mean perfusion pressure was set between 50 and 80 mmHg, while hematocrit values were set between 20% and 25%. Myocardium protection was done via antegrade hypothermic and hyperpotasemic blood cardioplegia. In all patients, the left internal mammary artery was used as the graft in the revascularization of the left anterior descending artery and saphenous vein was used as the graft in the revascularization of other coronary arteries. All proximal anastomoses were done on a beating heart under partial clamp.

All patients were taken into the ICU as intubated. The patients who have spontaneous respiration and whose orientation and cooperation returned to normal were extubated provided that their hemodynamic and respiratory functions were stable. Meanwhile, respiratory functions were frequently assessed spirometrically and with the measurements of blood gases. In addition, electrolyte imbalance, arterial oxygen, and lactic acid values were monitored closely and periodically via arterial blood gas analysis. Also, 50 mg intravenous dexketoprofen and 1 g intravenous paracetamol were ensured to all patients in the postoperative care unit.

All patients in which delirium manifestations were seen were assessed by a psychiatrist and neurologist. Haloperidol (0.5-5 mg/day, intramuscular) was initiated as the first-line treatment to the patients in whom postoperative delirium diagnosis was established. Dexmedetomidine hydrochloride infusion treatment was initiated to the patients with agitation as loading dose at a rate of 1 µg/kg/hour. When agitation and other symptoms were regressed, 0.5 µg/kg/hour maintenance dose was started. Dexmedetomidine hydrochloride infusion treatment was applied to all patients for 48 hours. The hemodynamics of the patients after the treatment were stable and they were transferred to the clinical follow-up provided that they were unable to achieve verbal communication.

**Statistical analysis**

Statistical analysis was performed using the SPSS version 12.0 software (SPSS Inc., Chicago, IL, USA). Normally distributed data were expressed in mean ± standard deviation, while abnormally distributed data were expressed in median (minimum-maximum). The data obtained by dividing were given as percentages (%). Among the data measured, the normality of the distribution was evaluated by histogram or Kolmogorov-Smirnov test, whereas the homogeneity of the distribution was evaluated by the Levene's test for equality of variance. The difference between the groups was evaluated by Student t-test in normal and homogenous distribution and by Mann-Whitney U test in abnormal and homogenous distribution. Parametric or non-parametric Pearson chi-square or Fisher's exact tests were used to analyze the differences between the groups. Forward stepwise multivariate logistic regression models were created to identify the independent predictors of postoperative delirium.

Variables with a *p* value of less than 0.10 in univariate analyses were included in the multivariate model. Survival analysis was performed by Kaplan Meier method and the statistical differences were confirmed with log-rank test. A *p* value of <0.05 was considered statistically significant.

## RESULTS

The CAM-ICU scores of all patients are shown in Table 1. The demographic characteristics and the clinical features of the patients are summarized in Table 2. There were statistically significant differences in the mean age (p=0.0001), sex (p=0.005), alcohol

**Table 1. The confusion assessment method for the intensive care unit (CAM-ICU)**

| Features and descriptions | Absent | Present |
|---|---|---|
| **I. Acute onset or fluctuating course** | | |
| A. Is there evidence of an acute change in mental status from the baseline?<br>B. Or, did the (abnormal) behavior fluctuate during the past 24 hours, that is, tend to come and go or increase and decrease in severity as evidenced by fluctuations on the Richmond Agitation Sedation Scale (RASS) or the Glasgow Coma Scale? | | |
| **II. Inattention** | | |
| Did the patient have difficulty focusing attention as evidenced by a score of less than 8 correct answers on either the visual or auditory components of the Attention Screening Examination (ASE)? | | |
| **III. Disorganized thinking** | | |
| Is there evidence of disorganized or incoherent thinking as evidenced by incorrect answers to three or more of the four questions and inability to follow the commands?<br>Questions<br>1. Will a stone float on water?<br>2. Are there fish in the sea?<br>3. Does 1 pound weigh more than 2 pounds?<br>4. Can you use a hammer to pound a nail?<br>Commands<br>1. Are you having unclear thinking?<br>2. Hold up this many fingers. (Examiner holds two fingers in front of the patient.)<br>3. Now do the same thing with the other hand (without holding the two fingers in front of the patient). (If the patient is already extubated from the ventilator, determine whether the patient's thinking is disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject.) | | |
| **IV. Altered level of consciousness** | | |
| Is the patient's level of consciousness anything other than alert, such as being vigilant or lethargic or in a stupor or coma?<br>**Alert:** Spontaneously fully aware of environment and interacts appropriately<br>**Vigilant:** Hyper alert<br>**Lethargic:** Drowsy but easily aroused, unaware of some elements in the environment or not spontaneously interacting with the interviewer; becomes fully aware and appropriately interactive when prodded minimally<br>**Stupor:** Difficult to arouse, unaware of some or all elements in the environment or not spontaneously interacting with the interviewer; becomes incompletely aware when prodded strongly; can be aroused only by vigorous and repeated stimuli and as soon as the stimulus ceases, stuporous subject lapses back into unresponsive state<br>**Coma:** Unarousable, unaware of all elements in the environment with no spontaneous interaction or awareness of the interviewer so that the interview is impossible even with maximal prodding | | |
| **Overall CAM-ICU Assessment (Features 1 and 2 and either Feature 3 or 4):** | **Yes____** | **No____** |

**Table 2. Demographic and clinical properties of the patients**

| Characteristics | Patients with delirium Group 1 (n=210) | | | | | Patients without delirium Group 2 (n=725) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | Mean±SD | Median | Range | n | % | Mean±SD | Median | Range | *p* |
| Age (years) | | | 64.9±7.9 | 67 | 40-84 | | | 59.0±8.2 | 60 | 32-86 | 0.0001** |
| Sex | | | | | | | | | | | |
| Male | 182 | 24.4 | | | | 565 | 75.6 | | | | 0.005* |
| Female | 28 | 14.9 | | | | 160 | 85.1 | | | | 0.005* |
| Hypertension | 126 | 60.0 | | | | 422 | 58.2 | | | | 0.64* |
| Diabetes mellitus | 89 | 42.4 | | | | 217 | 29.9 | | | | 0.001* |
| Hearing impairment | 13 | 6.2 | | | | 11 | 1.5 | | | | 0.0001* |
| Smoking | 81 | 38.6 | | | | 292 | 40.3 | | | | 0.66* |
| Chronic obstructive pulmonary disease | 15 | 7.1 | | | | 25 | 3.4 | | | | 0.02* |
| Alcohol use | 69 | 32.9 | | | | 80 | 11.0 | | | | 0.0001* |
| Preoperative atrial fibrillation | 27 | 12.9 | | | | 30 | 4.1 | | | | 0.0001* |
| Hyperlipidemia | 109 | 51.9 | | | | 384 | 53.0 | | | | 0.79* |
| Ejection fraction | | | 55.1±9.0 | 55 | 35-72 | | | 55.9±8.6 | 56 | 30-72 | |

SD: Standard deviation; * Pearson chi-square test or Fisher's exact test; ** Mann-Whitney U test.

intake (p=0.0001), hearing disorder (p=0.0001), preoperative atrial fibrillation (AF) (p=0.0001), and the presence of the chronic obstructive pulmonary disease (p=0.02) between the groups.

Pre- and postoperative blood chemistry test results are shown in Table 3. There were statistically significant differences in the mean preoperative CRP (p=0.0001), creatinine (p=0.0001), and mean platelet volume (MPV) levels (p=0.0001) between the groups. In addition, a significant difference in the mean postoperative first day CRP (p=0.0001) and MPV levels (p=0.01) was observed.

The perioperative and postoperative data of the patients are summarized in Table 4. There were statistically significant differences in the aortic cross-clamp time (p=0.0001), total CPB time (p=0.0001), the number of distal anastomosis (p=0.0001), the number of proximal anastomosis (p=0.0001), intubation time (p=0.01), APACHE II score (p=0.0001), inotropic support use (p=0.03), and the length of stay in the ICU (p=0.0001) and hospital (p=0.0001) between the groups.

The manifestations of postoperative delirium occurred in 64 patients (30.5%) within the first 24 hours, in 93 patients (44.3%) between 24 and 48 hours, and in 53 patients (25.2%) between 48 and 72 hours.

Of 878 patients with normal sinus rhythm at baseline, new-onset AF was developed in 48 patients (26.2%) in group 1 and in 132 patients (19%) in group 2, indicating a statistically significant difference between the groups (p=0.03). Fifteen patients (7.1%) in group 1 and six patients (0.8%) in group 2 underwent sternal revision due to the sternal detachment, as one of the major causes of postoperative morbidity and sternal infection, suggesting, a statistically significant difference (p=0.0001).

Neurological events (i.e., transient ischemic attack, amaurosis fugax, speech disorder, hemiplegia or

**Table 3. Preoperative and early postoperative blood chemistry results**

| | Patients with delirium Group 1 (n=210) | | | Patients without delirium Group 2 (n=725) | | | |
|---|---|---|---|---|---|---|---|
| | Mean±SD | Median | Range | Mean±SD | Median | Range | *p* |
| Preoperative hemoglobin (mg/dL) | 13.4±1.5 | 13.8 | 10.4-16.5 | 13.4±1.4 | 13.6 | 10.4-16.7 | 0.62** |
| Preoperative creatinine (mg/dL) | 1.4±0.3 | 1.4 | 0.7-1.9 | 0.9±0.2 | 0.8 | 0.5-2.1 | 0.0001** |
| Preoperative thrombocyte counts (x$10^3$/μL) | 266±61 | 256 | 154-412 | 265±61 | 256 | 147-452 | 0.79** |
| Preoperative C-reactive protein (mg/L) | 1.0±0.8 | 0.76 | 0.16-4.95 | 0.6±0.4 | 0.51 | 0.16-4.90 | 0.0001** |
| Preoperative mean platelet volume (fL) | 8.7±0.7 | 8.8 | 7.2-10.5 | 8.3±0.6 | 8.3 | 6.9-10.4 | 0.0001** |
| Postoperative first day hemoglobin (mg/dL) | 9.1±1.1 | 8.9 | 7.4-12.7 | 9.2±1.1 | 9 | 7.4-12.9 | 0.46** |
| Postoperative first day C-reactive protein (mg/L) | 29.2±4.2 | 29.8 | 14.2-39 | 24.6±4.2 | 24.8 | 14.7-37.6 | 0.0001** |
| Postoperative first day mean platelet volume (fL) | 9.1±0.8 | 9.1 | 7.8-11.4 | 8.9±0.7 | 8.9 | 7.5-11.5 | 0.01** |

SD: Standard deviation; * Pearson chi-square test or Fisher's exact test; ** Mann-Whitney U test.

**Table 4. Intraoperative and postoperative data of patients**

| Characteristics | Patients with delirium Group 1 (n=210) | | | | | Patients without delirium Group 2 (n=725) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | n | % | Mean±SD | Median | Range | n | % | Mean±SD | Median | Range | *p* |
| Aortic cross clamp time (min) | | | 58.0±11.4 | 59 | 23-91 | | | 50.0±12.1 | 50 | 19-82 | 0.0001* |
| Cardiopulmonary bypass time (min) | | | 88.7±13.8 | 89 | 45-126 | | | 80.5±16.2 | 84 | 40-123 | 0.0001* |
| Number of distal anastomoses | | | 3.8±0.9 | 4 | 1-7 | | | 3.2±0.9 | 3 | 1-6 | 0.0001* |
| Number of proximal anastomoses | | | 2.8±0.9 | 3 | 0-4 | | | 2.2±0.9 | 2 | 0-4 | 0.0001* |
| Use of blood products | 80 | 38.1 | | | | 282 | 38.9 | | | | 0.83** |
| Amount of drainage (mL) | | | 362±190 | 300 | 150-1200 | | | 341±137 | 300 | 150-1250 | 0.99* |
| Intubation time (hours) | | | 6.3±2.5 | 6 | 3-19 | | | 5.9±2.7 | 6 | 3-54 | 0.01* |
| Stay in the intensive care unit (hours) | | | 44.2±16.0 | 44 | 18-87 | | | 23.2±18.3 | 21 | 17-305 | 0.0001* |
| APACHE II scores | | | 11.5±2.4 | 12 | 6-16 | | | 8.5±1.5 | 8 | 5-15 | 0.0001* |
| Total duration of hospital stay (days) | | | 7.8±2.0 | 8 | 5-15 | | | 5.7±1.4 | 5 | 5-18 | 0.0001* |
| Use of inotropic support | 23 | 11.0 | | | | 47 | 6.5 | | | | 0.03** |

SD: Standard deviation; * Mann-Whitney U test; ** Pearson chi-square test or Fisher's exact test; APACHE II: Acute Physiology and Chronic Health Evaluation II.

hemiparesis) occurred in the hospital and within the first month in 13 patients (6.2%) in group 1 and in 10 patients (1.4%) in group 2, indicating a statistically significant difference (p=0.0001). Also, mortality occurred in the hospital and within the first month in 10 patients (4.8%) in group 1 and in three patients (0.4%) in group 2, suggesting a statistically significant difference between the groups (p=0.0001). In patients with postoperative delirium and cerebrovascular accident, the neurological examination revealed amnesia in eight patients, dysarthria in three patients, transient left hemiplegia in one patient, and amaurosis fugax in one patient. In patients with cerebrovascular accident, cranial CT revealed ischemic infarction in three patients.

The univariate and multivariate regression analyses of the factors affecting the postoperative delirium are shown in Table 5. In the multivariate analysis of the variables which were found to be statistically significant in the univariate analysis associated with postoperative delirium were age, male sex, diabetes mellitus, alcohol consumption, preoperative AF, increased preoperative CRP levels, increased postoperative first day CRP levels, increased preoperative MPV levels, increased postoperative first day MPV levels, and increased APACHE II scores. These were found to be independent predictors of postoperative delirium.

The mean follow-up was 38.7±17.8 (range, 0 to 65) months. The mean survival of patients with postoperative delirium was 59.9±1.2 months (95% CI: 57.6-62.1 months) with a rate of 88.8%, while the mean survival of patients without postoperative delirium was 63.2±0.3 months (95% CI: 57.6-62.1 months) with a five-year survival rate of 96.6% (p=0.0001, Figure 1).

## DISCUSSION

In the present study, we demonstrated that postoperative delirium was substantially common in isolated CABG surgery and was associated with the postoperative morbidity and mortality. We also showed that delirium manifestation was more common in elderly males consuming alcohol in the preoperative period, having primary AF, having chronic obstructive pulmonary disease with increased creatinine values. In addition, we observed higher rates of new-onset postoperative AF, redo surgery, cerebrovascular events, and mortality in patients with delirium. A higher number of patients with postoperative delirium had also prolonged length of stay in the ICU and hospital. The long-term survival was poor in these patients.

Delirium is a common complication following CABG surgery, accounting for 32% to 73% of the cases.[9] In a prospective study including 243 patients, Mu et al.[10] reported that postoperative delirium occurred in 50.6% following CABG surgery. In another prospective study, Eriksson et al.[11] also found the incidence of delirium to be 23%. In another cohort study, the delirium incidence following CABG surgery was reported to be 30.5%.[12] In consistent with these study findings, we found that delirium manifestation developed in 22.5% of the patients who underwent elective isolated CABG surgery.

The gold standard in the diagnosis of delirium is to be clinically diagnosed by a psychiatrist through medical history and physical examination findings, according to the criteria of the American Psychiatric Association's Diagnostic and Statistical Manual Edition IV (DSM-IV) in which all other psychiatric diagnoses are classified.[13] In the diagnosis of delirium, acute alteration in the cognitive function (i.e., memory

**Table 5. Univariate and multivariate regression analyses of risk factors for postoperative delirium**

| Variables | Postoperative delirium | | | | | |
|---|---|---|---|---|---|---|
| | Unadjusted | | | Adjusted | | |
| | OR | 95% CI | *p* | OR | 95% CI | *p* |
| Sex | | | | | | |
| Male | 1.84 | 1.19-2.84 | 0.006 | 2.92 | 1.30-6.58 | 0.01 |
| Age (years) | 1.10 | 1.08-1.12 | 0.0001 | 1.09 | 1.05-1.14 | 0.0001 |
| Ejection fraction (%) | 0.99 | 0.97-1.01 | 0.26 | – | – | – |
| Diabetes mellitus | 1.72 | 1.26-2.36 | 0.001 | 3.29 | 1.69-6.39 | 0.0001 |
| Hypertension | 1.08 | 0.79-1.47 | 0.64 | – | – | – |
| Hyperlipidemia | 0.96 | 0.71-1.30 | 0.79 | – | – | – |
| Smoking | 0.93 | 0.68-1.28 | 0.66 | – | – | – |
| Alcohol use | 3.94 | 2.73-5.71 | 0.0001 | 3.59 | 1.61-7.98 | 0.002 |
| Preoperative atrial fibrillation | 3.42 | 1.98-5.89 | 0.0001 | 3.14 | 1.10-8.98 | 0.03 |
| Chronic obstructive pulmonary disease | 2.15 | 1.11-4.17 | 0.02 | 0.36 | 0.05-2.41 | 0.29 |
| Hearing impairment | 4.28 | 1.89-9.71 | 0.0001 | 1.10 | 0.09-12.92 | 0.94 |
| Preoperative creatinine (mg/dL) | 112.10 | 59.83-210.04 | 0.0001 | 120.52 | 40.71-356.79 | 0.0001 |
| Preoperative platelet ($x10^3/\mu L$) | 1.00 | 0.99-1.01 | 0.80 | – | – | – |
| Preoperative CRP (mg/L) | 3.75 | 2.73-5.16 | 0.0001 | 1.64 | 0.89-3.01 | 0.11 |
| Preoperative hemoglobin (mg/dL) | 1.02 | 0.92-1.14 | 0.71 | – | – | – |
| Preoperative MPV (fL) | 2.90 | 2.21-3.82 | 0.0001 | 6.87 | 3.16-14.95 | 0.0001 |
| Postoperative first day CRP (mg/L) | 1.31 | 1.25-1.37 | 0.0001 | 1.32 | 1.21-1.45 | 0.0001 |
| Postoperative first day MPV (fL) | 1.32 | 1.08-1.62 | 0.007 | 0.23 | 0.12-0.44 | 0.0001 |
| Aortic cross clamp time | 1.06 | 1.04-1.08 | 0.0001 | 1.05 | 0.96-1.15 | 0.29 |
| Number of distal anastomoses | 2.27 | 1.88-2.73 | 0.0001 | 1.92 | 0.70-5.24 | 0.21 |
| Cardiopulmonary bypass time | 1.04 | 1.02-1.06 | 0.0001 | 0.97 | 0.93-1.02 | 0.29 |
| Intubation time | 1.06 | 1.00-1.12 | 0.06 | 0.99 | 0.87-1.13 | 0.89 |
| Use of blood products | 0.97 | 0.71-1.33 | 0.83 | – | – | – |
| Use of inotropic support | 1.77 | 1.05-3.00 | 0.03 | 0.61 | 0.17-2.23 | 0.46 |
| APACHE II scores | 2.02 | 1.84.2.23 | 0.0001 | 1.95 | 1.66-2.30 | 0.0001 |
| Amount of drainage | 1.00 | 0.99-1.01 | 0.09 | 1.00 | 0.99-1.01 | 0.89 |

OR: Odds ratio; CI: Confidence interval; CRP: C-reactive protein; MPV: Mean platelet volume.

loss, orientation, speech and perception disorders) should accompany to the attention deficit and to the impaired consciousness, according to the DSM-IV criteria and manifestations should develop in short-term with fluctuations in time, caused by a medical condition.[14] In the literature several terms such as aggression, agitation, ICU psychosis, acute brain disorder, and acute clouding of consciousness are used; however, these terms do not exactly correspond to the delirium manifestation. The basic characteristic which distinguishes delirium from agitation, aggression, and psychosis is the attention deficit.[2]

Despite several studies, the pathophysiology of delirium has not been exactly understood, yet.[15] One of the major causes blamed for the etiopathogenesis of postoperative delirium is the reduction in the cerebral cholinergic function.[16] It has been suggested that delirium symptoms are caused by alterations in memory, cognitive function, mood, and motor functions in relation with the insufficiency in cholinergic neurotransmitters.[16] It has been assumed that systemic inflammation, embolism or oxidative stress may also lead to postoperative cerebral injury in which cognitive disorders seen after CABG surgery and delirium manifestation.[17]

Furthermore, it has been reported that stress and increased interleukin-1 (IL-1), IL-6, and tumor necrosis factor alpha (TNF-α) among the pro-inflammatory cytokines may induce delirium.[16,18] Similarly, in our study, the higher values of inflammatory parameters such as CRP and MPV which were studied preoperatively and postoperatively in the patients with delirium suggest that this manifestation is related to the inflammation.

The cause of delirium is multifactorial. Usually, it emerges as a result of a complex relationship

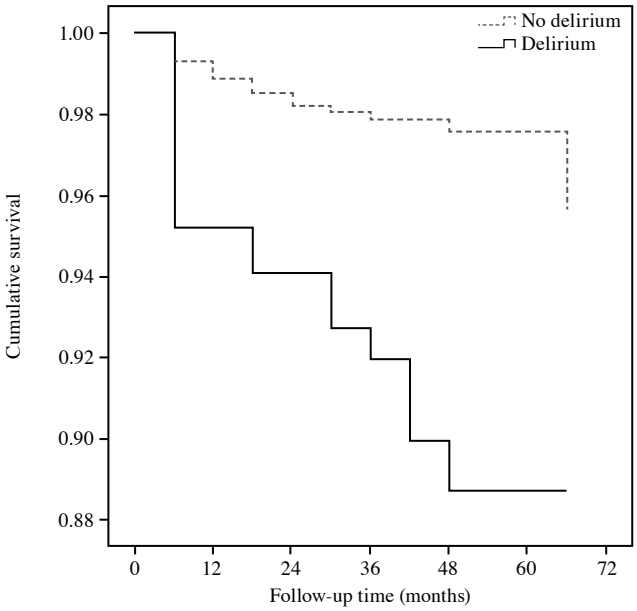


**Figure 1.** Kaplan Meier survival curves according to delirium and non-delirium cohorts.

between the predisposing and triggering factors.[19] To date, several studies have attempted to identify the risk factors; however, the results are controversial.[20] Predisposing risk factors for delirium is the characteristics that the individual has on admission.[21] Increasing age is a well-established risk factor for delirium. This suggests that it can be the basis of the occurrence of the elderly brain delirium.[19] Rolfson et al.[21] showed that delirium was more common in elderly patients after CABG surgery. Similarly, in our study, the mean age of the patients with delirium manifestations was significantly higher. In consistent with our findings, it was reported that delirium manifestation developed in the postoperative period increased the mortality and morbidity with prolonged length of stay in the ICU and hospital, thereby, leading to increased the treatment cost.[5] In another study, Atalan and Sevim[22] also found that postoperative delirium after cardiac surgery was associated with prolonged postoperative cognitive dysfunction.

The risk factors of this clinical manifestation are advanced age, dementia, cognitive disorder, depression history, male sex, sensory deprivation (vision and hearing problems), higher creatinine values, stroke, epilepsy, congestive heart disease, sleep deprivation, social isolation, physical restraint, use of bladder catheter, use of psychoactive drug, dehydration, malnutrition, immobility, surgical intervention, infection, electrolyte imbalance, stress, pain and fear, neurological disorders, cobalamin deficiency, burns, substance abuse, endocrine diseases, hypothermia, pathologies of central nervous system, metabolic causes, history alcohol and tobacco consumption, drug abuse, and longer hospitalization in the ICU.[3,4,12,23,24] In our study, we found that postoperative delirium occurred significantly more in patients with alcohol consumption history, hearing disorder, and those with higher creatinine values.

It has been also reported that the presence of preoperative diabetes mellitus is associated with the incidence of the cerebral complications such as stroke, cognitive dysfunction, and delirium in patients after cardiac surgery.[25] In a prospective study conducted by Nötzold et al.,[26] they compared the diabetic patients in which they performed CPB and CABG surgery with non-diabetics. They reported that cognitive dysfunction was significantly seen more in the earlier postoperative period in diabetics. We also detected that postoperative delirium was seen significantly more in the diabetic patients.

In a study including patients with CABG and heart valve surgery, Hermann et al.[27] demonstrated that aortic cross-clamp time was not different in the group in which postoperative delirium developed. In another study in which 30 patients with CABG were studied, it was shown that the duration of CABG was longer in patients with postoperative delirium with a higher number of distal anastomoses.[28] Similarly, in the present study, we found that aortic cross-clamp and CPB times were longer and the number of distal anastomoses were higher in the patients with delirium manifestations.

An objective evaluation of the status of patients in the ICUs using scoring systems and of the severity of the disease with survival estimation has become increasingly important.[3] In our study, we observed that the ICU APACHE II scores were significantly higher in the patients with delirium. The higher values of APACHE II grades demonstrated the severity of the diseases. In a study conducted by Balas et al.[29] on the patients staying in the ICU, the mean APACHE II score was 17.5 in the patients with delirium manifestation. We have observed the mean APACHE II score 12 in the delirium group, and 8 in the non-delirium group.

Moreover, delirium has been suggested to be related with higher mortality rates.[5] Although it has such a clinical importance, delirium cannot be noticed in many patients by the clinicians.[30] Furthermore, postoperative delirium is related to many side effects

such as self-extubation of the patient, prolonged length of stay in the ICU and in the hospital, increased healthcare cost.[15] In our study, we also found that the length of stay in the ICU and hospital were longer in patients with delirium compared to the patients who were under a scheduled follow-up. In addition, we showed that early and long-term mortality in the patients with delirium occurred at a similar extent of previous study findings.[5,13]

For patients who are diagnosed with delirium, the treatment approach is physiological support, communication, improvement of the environmental factors, psychosocial support, consultation, cognitive and attention restriction, and medical treatment.[13] Among the pharmacological treatments, there is dexmedetomidine, an alpha-2 agonist selective used for sedation in the ICU, beside anti-psychotic agents such as thioridazine and haloperidol.[31,32]

On the other hand, the major limitation to our study is that although large-scale sample size (>500) contributed to the statistical power of the study, the study was not designed in a fashion that would allow a prospective follow-up study. It is a retrospective and observational study in which cause-effect relationship was unable to be established.

In conclusion, delirium is a serious problem commonly seen in patients undergoing cardiopulmonary bypass and coronary artery bypass grafting with high morbidity and mortality rates, if left untreated. Based on our study findings, we suggest that patients undergoing coronary artery bypass grafting should be followed closely in the intensive care unit for the development of delirium. Furthermore, complications can be minimized by analyzing the associated risk factors in the development of preoperative, perioperative, and postoperative delirium with a full collaboration with liaison psychiatry in the intensive care unit for the patients who are at risk for delirium.

**Declaration of conflicting interests**

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