ORIGINAL RESEARCH

# Diabetes and elevated preoperative HbA1c level as risk factors for postoperative delirium after cardiac surgery: an observational cohort study

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**Introduction:** Postoperative delirium (POD) is a common complication of cardiac surgery associated with increased mortality, morbidity, and long-term cognitive dysfunction. Diabetic patients, especially those with poor diabetes control and long-standing hyperglycemia, may be at risk of developing delirium. The aim of this study was to analyze whether the occurrence of POD in cardiac surgery is associated with diabetes or elevated preoperative glycated hemoglobin (HbA1c) level.

**Materials and methods:** We performed a cohort analysis of prospectively collected data from a register of cardiac surgery department of a university hospital. Delirium assessment was performed twice a day during the first 5 days after the operation based on *Diagnostic Statistical Manual of Mental Disorders*, fifth edition criteria.

**Results:** We analyzed a cohort of 3,178 consecutive patients, out of which 1,010 (31.8%) were diabetic and 502 (15.8%) were diagnosed with POD. Patients with delirium were more often diabetic (42.03% vs 29.86%, $P<0.001$) and on oral diabetic medications (34.66% vs 24.07%, $P<0.001$), no difference was found in patients with insulin treatment. Preoperative HbA1c was elevated above normal ($\geq6\%$) in more delirious than nondelirious patients (44.54% vs 33.04%, $P<0.001$), but significance was reached only in nondiabetic patients (20.44% vs 14.86%, $P=0.018$). In univariate analysis, the diagnosis of diabetes was associated with an increased risk of developing POD (OR: 1.703, 95% CI: 1.401–2.071, $P<0.001$), but only for patients on oral diabetic medications (OR: 1.617, 95% CI: 1.319–1.983, $P<0.001$) and an association was noted between HbA1c and POD (OR: 1.269, 95% CI: 1.161–1.387, $P<0.001$). Multivariate analysis controlled for diabetes showed that POD was associated with age, heart failure, preoperative creatinine, extracardiac arteriopathy, and preoperative HbA1c level.

**Conclusion:** More diabetic patients develop POD after cardiac surgery than nondiabetic patients. Elevated preoperative HbA1c level is a risk factor for postcardiac surgery delirium regardless of the diagnosis of diabetes.

**Keywords:** glycated hemoglobin, POD, mortality, outcome, ICU

## Introduction

Postoperative delirium (POD) is an acute central nervous system pathology commonly occurring after cardiac surgery.[1,2] Delirium can be defined as an acute brain dysfunction manifested by fluctuation of mental status compared with baseline, inattention, altered level of consciousness, and disorganized thinking.[3] Both POD and intensive care unit (ICU) delirium have been linked to serious negative consequences, including postoperative cognitive dysfunction, prolonged mechanical ventilation, and prolonged hospital and ICU stay, as well as increased health care costs and long-term cardiovascular events

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after cardiac surgery.[4–8] There are many modifiable and non-modifiable risk factors associated with delirium in critically ill patients.[9] A number of predisposing and accelerating risk factors contributed to postcardiac surgery delirium in previous studies.[10,11] Getting more knowledge about risk factors in ICU delirium is important to increase our understanding of the pathophysiology and identification of patients at risk to prevent the condition and ultimately improve results.

Hyperglycemia is an important factor associated with increased mortality in critically ill patients in ICU and undergoing cardiac surgery.[12] It has been shown that insulin resistance and stress-induced hyperglycemia reflect the risk of death in critically ill patients.[13] Major randomized controlled trials aimed at proving that maintaining normoglycemia with targeted insulin therapy reduces morbidity and mortality were performed in surgical ICU patients.[14] Hyperglycemia during the perioperative period is common, particularly in patients undergoing cardiac surgery due to specific factors: administration of heparin, use of dextrose-containing cardioplegia solutions, cardiopulmonary bypass, and hypothermia.[15–17]

Based on previous studies of diabetes, glycemic variability, and mortality in critically ill patients, it can be assumed that diabetes and glycemic dysregulation identified by elevated preoperative glycated hemoglobin (HbA1c) level may be identified as a risk factor postcardiac surgery. Moreover, HbA1c is regarded as a good indicator of long-term (3 months) glycemic control and is the most commonly used biomarker to diagnose prediabetes and diabetes.[18–20]

For many years, diabetes has been reported to be associated with cognitive dysfunction, including vascular dementia and Alzheimer's disease, yet the exact underlying pathology was not entirely elucidated.[21] Cognitive dysfunction in relation to brain glucose levels may be caused by one of the following causes: insulin resistance, altered glucose metabolism, vascular lesions, and/or β-amyloid and tau metabolism.[22] Similarly, it has been suggested that both hyperglycemia and hypoglycemia can be identified as risk factors associated with ICU delirium, but this was found in studies that were subject to various methodological limitations.[23,24]

Therefore, the hypothesis of this study was that the diagnosis of diabetes and/or elevated preoperative HbA1c level may be associated with the occurrence of POD in cardiac surgery.

## Materials and methods

Prospectively collected data from a register of cardiac surgery department of a university hospital of Pomeranian Medical University in Szczecin, Poland, acquired during 3 consecutive years (2014–2016) were analyzed retrospectively. From the general cohort of patients undergoing cardiac surgery at our department during that time, we analyzed data regarding all patients for the presence or absence of POD and further analyzed only the diabetic cohort (Figure 1). Finally, we included all patients undergoing major cardiac surgery (3,178 patients), irrespective of the type of surgery or case priority.

Prospectively collected database contains information regarding demographic data and concomitant medical conditions (coronary artery disease, congestive heart failure, hypertension, arrhythmia, diabetes mellitus or impaired glucose tolerance, renal disease, COPD, and smoking). Perioperative risk was calculated according to the EuroSCORE Logistics II scale.[25] Preoperative anesthetic assessment, as well as intraoperative surgical and anesthetic approach, was performed according to local guidelines and protocols. Standard pre- and postoperative laboratory blood analysis was performed, including preoperative HbA1c level. The dataset covered all major cardiac procedures performed under general anesthesia: coronary artery bypass grafting (CABG), CABG with concomitant valve operations (CABG + valve), isolated or multiple valve replacement and/or valve repair, transthoracic aortic valve implementation, ascending aorta aneurysm (AAA) surgery, and CABG with AAA surgery. All patients were anesthetized according to a local protocol, using a standard set of drugs and doses for each patient. After the operation, each patient remained intubated and mechanically ventilated and was transferred to the postoperative cardiac ICU. For postoperative pain control, multimodal analgesia was used. The postoperative outcome measures were ICU length of stay, hospital length of stay, and postoperative mortality at 30 days after the operation.

We used the following criteria for HbA1c level according to the American Diabetes Association: HbA1c <5.7% was regarded as normal, HbA1c 5.7%–6.4% was defined as prediabetes, and HbA1c >6.5% was defined as diabetes.[18] We also used the level >6.0% as the cutoff for the upper limit of the laboratory value for HbA1c at our institution.

In the postoperative period, all patients admitted to the postcardiac surgery ICU and cardiac surgery ward were screened for the presence of delirium by ICU physicians, cardiac surgeons, consultant neurologist, and nurses according to standard criteria of *Diagnostic Statistical Manual of Mental Disorders*, fifth edition (DSM-5) criteria for delirium, during the first 5 days after the operation.[3] The time frame of 5 days was chosen as it is the average hospitalization time and reflects early postcardiac surgery delirium. Standard
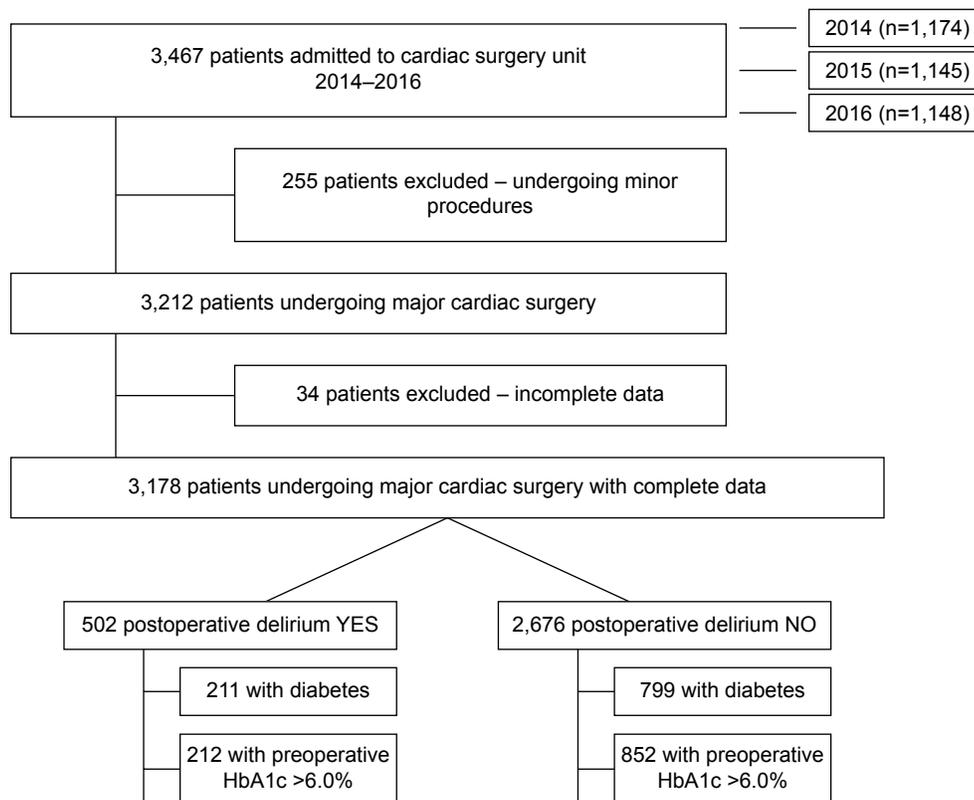
**Figure 1** Study flowchart.

delirium screening tools were not in use at the facility during data collection; delirium diagnosis was based on clinical assessment guided by DSM-5 criteria. DSM-5 diagnostic criteria for delirium are as follows: 1) disturbance in attention (ie, reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment); 2) disturbance developed over a short period of time (hours to days), changed from baseline, and fluctuated in severity during the course of a day; 3) additional disturbance in cognition (eg, memory deficit, disorientation, language, visuospatial ability, or perception). Moreover, criteria from 1 and 2 could not have been better explained by another condition, preexisting, established, or evolving neurocognitive disorder or coma, and there was no evidence from medical history, physical examination, and/or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or exposure to toxin, substance withdrawal, or because of multiple etiologies.[3] Delirium evaluation was performed twice daily by at least two health care professionals (doctor and/or nurse) after the patient has been weaned off mechanical ventilation and extubated. Data regarding delirium were further extracted from detailed nursing and medical staff charts.

## Ethical statement

Retrospective nature of the analysis was the basis for a waiver from the Bioethical Committee of the Pomeranian Medical University in Szczecin, Poland, decision no KB-0012/79/01/18. Prospective data collection was performed according to the guidelines of the Declaration of Helsinki. Written informed consent for general anesthesia and surgery was obtained from each patient as part of routine preoperative document workup and included consent for data collection and medical record review. Patient confidentiality was ensured with the use of anonymous, dehumanified data.

## Statistical analysis

We used descriptive statistics to characterize the study population, categorical variables were presented as proportions and analyzed using the chi-squared test, and continuous variables were presented as mean with SD. The incidence of delirium was calculated for patients with and without diabetes and Chi-square test or Chi-square test with Yates correction was used for comparison between both groups. The Shapiro–Wilk test was used to check normality of distribution. Data analysis for two groups was performed using a Mann–Whitney $U$ test. Univariate logistic regression

analysis for each variable was performed and presented as OR with 95% CIs. Multivariate logistic regression analysis was performed for risk factors that were significant in univariate analysis and presented with narrow CIs. All data were analyzed using licensed software Statistica 12 (StatSoft, Inc., Tulsa, OK, USA). *P*-value of <0.05 was regarded as statistically significant.

## Results

We analyzed a cohort of 3,178 patients, out of which 1,010 (31.8%) were diabetic and 502 (15.8%) were diagnosed with POD. Study group characteristics regarding demographic data, concomitant diseases, and pre-, intra-, and postoperative parameters are shown in Table 1. Patients with POD were

older (70 vs 65 years, *P*<0.001), more often had ischemic heart disease (*P*=0.026), diabetes (*P*<0.001), arterial hypertension (*P*=0.007), internal carotid artery stenosis (*P*<0.001), COPD (*P*<0.006), chronic (*P*<0.001) and acute renal failure (*P*=0.022), ejection fraction <30% (*P*<0.001), New York Heart Association III and IV (*P*<0.001), and extracardiac arteriopathy (*P*<0.001). When looking at preoperative data, HbA1c was significantly higher in patients with delirium (6.18±1.15 vs 5.91±0.95, *P*<0.001), as was creatinine level (*P*<0.001).

The univariate analysis confirms a relationship between chosen preoperative factors and postcardiac surgery delirium (Table 2). For diabetic patients, the OR for developing delirium was 1.703 (CI: 1.401–2.071, *P*<0.001). Moreover,

**Table 1** Preoperative and perioperative characteristics of patients

| Variable | No delirium (n=2,676) | Delirium (n=502) | *P*-value |
|---|---|---|---|
| Demographic data | | | |
| Age (years), mean ± SD | 65.10±9.59 | 70.09±8.43 | <0.001 |
| Gender, female, n (%) | 777 (29.04) | 153 (30.48) | NS |
| Smoking, n (%) | 821 (30.68) | 137 (27.29) | NS |
| BMI, mean ± SD, kg/m² | 28.73±4.62 | 28.69±4.39 | NS |
| Concomitant diseases | | | |
| Ischemic heart disease, n (%) | 2,205 (82.40) | 434 (86.45) | 0.026 |
| Diabetes, n (%) | 799 (29.86) | 211 (42.03) | <0.001 |
| Glucose intolerance, n (%) | 98 (3.66) | 12 (2.39) | NS |
| TIA, n (%) | 34 (1.27) | 5 (1.00) | NS |
| Stroke, n (%) | 134 (5.01) | 36 (7.17) | NS |
| Arterial hypertension, n (%) | 1,810 (67.64) | 370 (73.71) | 0.007 |
| AF paroxysmal, n (%) | 215 (8.03) | 49 (9.76) | NS |
| AF persistent, n (%) | 183 (6.84) | 42 (8.37) | NS |
| ICA stenosis, n (%) | 159 (5.94) | 50 (9.96) | <0.001 |
| COPD, n (%) | 153 (5.72) | 45 (8.96) | 0.006 |
| Chronic renal failure, n (%) | 183 (6.84) | 63 (12.55) | <0.001 |
| Acute renal failure, n (%) | 23 (0.86) | 10 (1.99) | 0.022 |
| Ejection fraction <30%, n (%) | 174 (6.50) | 55 (10.96) | <0.001 |
| NYHA III and IV, n (%) | 697 (26.05) | 193 (38.45) | <0.001 |
| Extracardiac arteriopathy | 375 (14.31) | 124 (25.00) | <0.001 |
| Preoperative data | | | |
| HbA1c %, mean ± SD | 5.91±0.95 | 6.18±1.15 | <0.001 |
| Creatinine (mg/dL) at admission, mean ± SD | 1.00±0.61 | 1.16±0.89 | <0.001 |
| GFR at admission (mL/min/1.73 m²), mean ± SD | 79.93±26.73 | 68.99±21.66 | <0.001 |
| Operative risk | | | |
| EuroSCORE Logistic 2, mean ± SD | 3.01±4.64 | 4.57±5.57 | <0.001 |
| Operation type | | | |
| Isolated CABG, n (%) | 1,663 (62.14) | 262 (52.19) | <0.001 |
| CABG + valve, n (%) | 386 (14.42) | 136 (27.09) | <0.001 |

(*Continued*)

**Table 1** (*Continued*)

| Variable | No delirium (n=2,676) | Delirium (n=502) | *P*-value |
|---|---|---|---|
| CABG + AAA, n (%) | 44 (1.64) | 9 (1.79) | NS |
| TAVI, n (%) | 24 (0.90) | 4 (0.80) | NS |
| Aortic aneurysm, n (%) | 168 (6.28) | 33 (6.57) | NS |
| Isolated valve, n (%) | 391 (14.61) | 58 (11.55) | NS |
| Case priority | | | |
| Planned, n (%) | 1,961 (73.28) | 350 (69.72) | NS |
| Urgent, n (%) | 563 (21.04) | 113 (22.51) | |
| Emergent, n (%) | 152 (5.68) | 39 (7.77) | |
| Postoperative complications | | | |
| Stroke/TIA, n (%) | 85 (3.18) | 26 (5.18) | 0.025 |
| Atrial fibrillation, n (%) | 537 (20.07) | 158 (31.47) | <0.001 |
| Respiratory failure, n (%) | 191 (7.14) | 106 (21.12) | <0.001 |
| Pneumonia, n (%) | 58 (2.17) | 49 (9.76) | <0.001 |
| Acute kidney injury, n (%) | 55 (2.06) | 30 (5.98) | <0.001 |
| AKI with CRRT, n (%) | 239 (8.93) | 121 (24.10) | <0.001 |
| Sepsis, n (%) | 11 (0.41) | 3 (0.60) | NS |
| Outcome data | | | |
| Hospital LOS (days), mean ± SD | 9.21±9.10 | 13.79±14.77 | <0.001 |
| ICU LOS (days), mean ± SD | 2.71±4.80 | 3.73±6.73 | <0.001 |
| Mortality, n (%) | 130 (4.86) | 27 (5.38) | NS |

**Abbreviations:** AAA, ascending aorta aneurysm; AF, atrial fibrillation; AKI, acute kidney injury; BMI, body mass index (kg/m²); CABG, coronary artery bypass grafting; CRRT, continuous renal replacement therapy; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; ICA, internal carotid artery; ICU, intensive care unit; LOS, length of stay; n, number of patients; NS, not significant; NYHA, New York Heart Association; TAVI, transcatheter aortic valve implantation; TIA, transient ischemic attack.

an association was noted between HbA1c and POD (OR: 1.269, CI: 1.161–1.387, *P*<0.001). Multivariate analysis controlled for diabetes has shown that POD was associated with increasing age, heart failure, preoperative creatinine, extracardiac arteriopathy, and preoperative HbA1c level (OR: 1.20, 95% CI: 1.07–1.35, *P*=0.003) (Figure 2).

Therefore, we decided to perform a further analysis between HbA1c and different types of diabetes and the occurrence of POD after cardiac surgery. In the whole group of patients, preoperative HbA1c was elevated >6% more often in delirious than nondelirious patients (44.54% vs 33.04%, *P*<0.001), but significance was reached only in nondiabetic patients (20.44% vs 14.86%, *P*=0.018, Table 3).

Diabetes was associated with an increased risk of developing delirium (OR: 1.703, CI: 1.401–2.071, *P*<0.001), but only for patients on oral diabetic medications (OR: 1.617, CI: 1.319–1.983, *P*<0.001). Moreover, HbA1c level, elevated above 6.5%, was an independent risk factor for postcardiac surgery delirium (OR: 1.817, CI: 1.449–2.278, *P*<0.001), as seen in Table 4.

We aimed to look at the characteristics and outcome of diabetic patients and what factors determine the occurrence of postcardiac surgery delirium in diabetics. Table 5 provides

a summary of demographic and pre-, intra-, and postoperative factors.

When analyzing postoperative complications (Table 6), in diabetic delirious patients, there were more episodes of stroke or TIA (7.11% vs 3.50%, *P*=0.021), atrial fibrillation (28.91% vs 17.77%, *P*<0.001), respiratory failure (22.27% vs 6.76%, *P*<0.001), pneumonia (9.00% vs 2.13%, *P*<0.001), but not sepsis. Interestingly, the mortality rate did not differ between the two groups (6.64% vs 5.26%, *P* = not significant). Both ICU length of stay (3.77±6.22, *P*<0.001) and hospital length of stay (15.61±18.34 vs 9.41±12.27, *P*<0.001) were longer in diabetics with delirium.

## Discussion

The pathophysiology of postoperative and ICU delirium is not entirely understood, yet it is obvious that multiple predisposing conditions and precipitating factors are involved. In this study, we found that diabetes mellitus was associated with the development of POD in a large cohort of patients undergoing cardiac surgery. Moreover, patients who developed POD presented with elevated preoperative levels of HbA1c, regardless of the diagnosis of diabetes. To our knowledge, this is the first analysis to report on association

**Table 2** Univariate analysis including all preoperative variables associated with postoperative delirium after cardiac surgery

| Variables associated with delirium (n=3,178) | OR | −95% CI | +95% CI | *P*-value |
|---|---|---|---|---|
| Demographic data | | | | |
| Age (in years)[a] | 1.063 | 1.051 | 1.076 | <0.001 |
| Female gender | 1.071 | 0.871 | 1.319 | NS |
| Smoking | 0.848 | 0.685 | 1.049 | NS |
| BMI (kg/m$^2$) | 0.998 | 0.977 | 1.019 | NS |
| Concomitant diseases | | | | |
| Ischemic heart disease | 1.363 | 1.036 | 1.794 | 0.027 |
| Diabetes | 1.703 | 1.401 | 2.071 | <0.001 |
| Glucose intolerance | 0.644 | 0.351 | 1.182 | NS |
| Transient ischemic attack | 0.782 | 0.304 | 2.009 | NS |
| Stroke | 1.466 | 1.001 | 2.145 | 0.049 |
| Arterial hypertension | 1.341 | 1.082 | 1.662 | 0.007 |
| AF persistent | 1.238 | 0.894 | 1.715 | NS |
| AF paroxysmal | 1.244 | 0.877 | 1.765 | NS |
| Internal carotid artery stenosis | 1.751 | 1.255 | 2.444 | 0.001 |
| COPD | 1.624 | 1.148 | 2.297 | 0.006 |
| Chronic renal failure | 1.955 | 1.443 | 2.649 | <0.001 |
| Acute renal failure | 2.344 | 1.109 | 4.956 | 0.026 |
| Ejection fraction <30% | 1.769 | 1.285 | 2.434 | <0.001 |
| NYHA class III and IV | 1.773 | 1.453 | 2.165 | <0.001 |
| Extracardiac arteriopathy | 1.996 | 1.585 | 2.515 | <0.001 |
| Preoperative laboratory factors | | | | |
| Creatinine (mg/dL) at admission | 1.285 | 1.148 | 1.439 | <0.001 |
| HbA1c % | 1.269 | 1.161 | 1.387 | <0.001 |
| Operative risk | | | | |
| EuroSCORE Logistic 2 | 1.051 | 1.034 | 1.068 | <0.001 |

**Note:** [a]OR for an increase of 1 year in age.
**Abbreviations:** AF, atrial fibrillation; HbA1c, glycated hemoglobin; n, number of patients; NS, not significant; NYHA, New York Heart Association.

between HbA1c level and delirium and to analyze the outcome of diabetic patients and nondiabetic patients in the light of POD occurrence.

The number of studies investigating the possible interplay between glucose, diabetes, HbA1c, and the incidence of postoperative or ICU delirium is very limited. Diabetes mellitus has been identified as a significant independent predictor of higher postoperative morbidity, increased incidence of delirium, and prolonged hospital stay after cardiac surgery.[26] There are three observational studies that reported hyperglycemia as a factor worsening the risk of delirium.[27–29] Heymann et al aimed at finding an association between ICU delirium and blood glucose levels and performed a retrospective analysis and contrary to our results reported that diabetes had no influence on the onset of hyperactive delirium.[27] A retrospective analysis done by Ganai et al suggested a relationship between hyperglycemia and delirium in patients after abdominal surgery.[29]

Factors associated with delirium include an upregulation of sympathetic tone and downregulation of parasympathetic tone due to surgical stress, impaired cholinergic function, reversible impairment of cerebral oxidative metabolism involvement of multiple neurotransmitter pathway abnormalities, and neuroinflammation.[30] Hyperglycemia is a known factor inducing inflammation (neuroinflammation) at the cellular level and a physiological response to inflammation, whereas the effect of insulin both endogenous and exogenous during treatment is not only to normalize glycemia but also anti-inflammatory.[31,32] It has been shown that maintaining normoglycemia with insulin therapy improves survival and reduces morbidity in surgical ICU patients.[33] In critically ill patients undergoing cardiac surgery, the influence of abnormal blood glucose concentrations in the perioperative period on morbidity and mortality cannot be overestimated.[34,35]

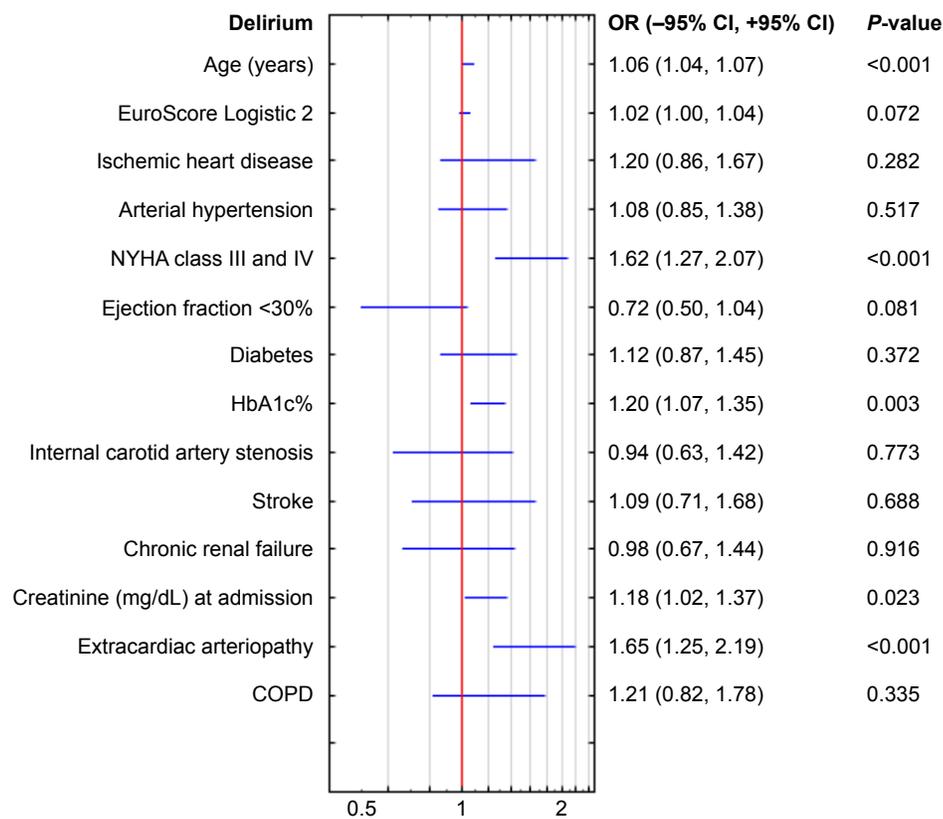Furthermore, it has been hypothesized that tight glucose control with insulin treatment would be a useful strategy to

| Delirium | OR (–95% CI, +95% CI) | P-value |
|---|---|---|
| Age (years) | 1.06 (1.04, 1.07) | <0.001 |
| EuroScore Logistic 2 | 1.02 (1.00, 1.04) | 0.072 |
| Ischemic heart disease | 1.20 (0.86, 1.67) | 0.282 |
| Arterial hypertension | 1.08 (0.85, 1.38) | 0.517 |
| NYHA class III and IV | 1.62 (1.27, 2.07) | <0.001 |
| Ejection fraction <30% | 0.72 (0.50, 1.04) | 0.081 |
| Diabetes | 1.12 (0.87, 1.45) | 0.372 |
| HbA1c% | 1.20 (1.07, 1.35) | 0.003 |
| Internal carotid artery stenosis | 0.94 (0.63, 1.42) | 0.773 |
| Stroke | 1.09 (0.71, 1.68) | 0.688 |
| Chronic renal failure | 0.98 (0.67, 1.44) | 0.916 |
| Creatinine (mg/dL) at admission | 1.18 (1.02, 1.37) | 0.023 |
| Extracardiac arteriopathy | 1.65 (1.25, 2.19) | <0.001 |
| COPD | 1.21 (0.82, 1.78) | 0.335 |

**Figure 2** Multivariate analysis for patients with delirium.
**Abbreviation:** HbA1c, glycated hemoglobin.

**Table 3** Preoperative diabetes-related data and glycated hemoglobin for patients with and without delirium

| Total no of patients (n=3,178) | No delirium (n=2,676) | | Delirium (n=502) | | P-value |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Diabetes mellitus | 799 | 29.86 | 211 | 42.03 | <0.001 |
| Diabetes – insulin | 139 | 5.19 | 37 | 7.37 | 0.050 |
| Diabetes – oral diabetic medications | 661 | 24.70 | 174 | 34.66 | <0.001 |
| Glucose intolerance | 98 | 3.66 | 12 | 2.39 | NS |
| HbA1c ≥5.7% | 1,375 | 53.32 | 313 | 65.76 | <0.001 |
| HbA1c ≥6% | 852 | 33.04 | 212 | 44.54 | <0.001 |
| HbA1c ≥6.5% | 442 | 17.14 | 130 | 27.31 | <0.001 |
| Diabetes mellitus | | | | | |
| HbA1c ≥5.7% | 670 | 86.34 | 177 | 87.62 | NS |
| HbA1c ≥6% | 584 | 75.26 | 156 | 77.23 | NS |
| HbA1c ≥6.5% | 379 | 48.84 | 112 | 55.45 | NS |
| Glucose intolerance | | | | | |
| HbA1c ≥5.7% | 45 | 47.87 | 6 | 50.00 | NS |
| HbA1c ≥6% | 15 | 15.96 | 2 | 16.67 | NS |
| HbA1c ≥6.5% | 4 | 4.26 | 1 | 8.33 | NS |
| No diabetes | | | | | |
| HbA1c ≥5.7% | 705 | 39.10 | 136 | 49.64 | <0.001 |
| HbA1c ≥6% | 268 | 14.86 | 56 | 20.44 | 0.018 |
| HbA1c ≥6.5% | 63 | 3.49 | 18 | 6.57 | 0.014 |

**Abbreviations:** HbA1c, glycated hemoglobin; n, number of patients; NS, not significant.

**Table 4** Univariate diabetes-related variables associated with postoperative delirium after cardiac surgery

| Variables associated with delirium (n=3,178) | OR | −95% CI | +95% CI | P-value |
|---|---|---|---|---|
| Diabetes mellitus | 1.703 | 1.401 | 2.071 | <0.001 |
| Diabetes – insulin treatment | 1.452 | 0.997 | 2.115 | NS |
| Diabetes – treatment by oral medications | 1.617 | 1.319 | 1.983 | <0.001 |
| Glucose intolerance | 0.644 | 0.351 | 1.182 | NS |
| HbA1c ≥6% | 1.628 | 1.335 | 1.985 | <0.001 |
| HbA1c ≥6.5% | 1.817 | 1.449 | 2.278 | <0.001 |

**Abbreviations:** HbA1c, glycated hemoglobin; n, number of patients; NS, not significant.

**Table 5** Preoperative and perioperative characteristics of diabetic patients

| Variable | No delirium diabetic (n=799) | Delirium diabetic (n=211) | P-value |
|---|---|---|---|
| Demographic data | | | |
| Age (years), mean ± SD | 67.00±7.88 | 70.06±7.77 | <0.001 |
| Gender, female, n (%) | 241 (30.16) | 81 (38.39) | 0.023 |
| Smoking, n (%) | 229 (28.66) | 57 (27.01) | NS |
| BMI (kg/m$^2$), mean ± SD | 30.29±4.53 | 29.93±4.32 | NS |
| Concomitant diseases | | | |
| Ischemic heart disease, n (%) | 730 (91.36) | 197 (93.36) | NS |
| Diabetes – insulin controlled, n (%) | 139 (17.40) | 37 (17.54) | NS |
| Diabetes – oral medications, n (%) | 661 (82.73) | 174 (82.46) | NS |
| HbA1c %, mean ± SD | 6.74±1.19 | 6.89±1.34 | NS |
| HbA1c ≥5.7%, n (%) | 670 (86.34) | 177 (87.62) | NS |
| HbA1c ≥6%, n (%) | 584 (75.26) | 156 (77.23) | NS |
| HbA1c ≥6.5%, n (%) | 379 (48.84) | 112 (55.45) | NS |
| TIA, n (%) | 11 (1.38) | 2 (0.95) | NS |
| Stroke, n (%) | 60 (7.51) | 15 (7.11) | NS |
| Arterial hypertension, n (%) | 651 (81.48) | 180 (85.31) | NS |
| AF paroxysmal, n (%) | 64 (8.01) | 21 (9.95) | NS |
| AF persistent, n (%) | 53 (6.63) | 17 (8.06) | NS |
| Extracardiac arteriopathy, n (%) | 147 (18.40) | 67 (31.75) | <0.001 |
| ICA stenosis, n (%) | 66 (8.26) | 22 (10.43) | NS |
| COPD, n (%) | 43 (5.38) | 25 (11.85) | <0.001 |
| Chronic renal failure, n (%) | 84 (10.51) | 36 (17.06) | 0.009 |
| Acute renal failure, n (%) | 12 (1.50) | 6 (2.84) | NS |
| Ejection fraction <30%, n (%) | 61 (7.63) | 32 (15.17) | <0.001 |
| NYHA III and IV, n (%) | 196 (24.53) | 94 (44.55) | <0.001 |
| EuroSCORE Logistic 2, mean ± SD | 3.23±5.08 | 4.9±5.28 | <0.001 |
| Creatinine (mg/dL) at admission, mean ± SD | 1.07±0.63 | 1.22±0.97 | 0.001 |
| GFR at admission (mL/min/1.73 m$^2$), mean ± SD | 74.86±29.11 | 66.01±21.71 | <0.001 |
| Operation type | | | |
| Isolated CABG, n (%) | 586 (73.34) | 108 (51.18) | <0.001 |
| CABG + valve, n (%) | 108 (13.52) | 72 (34.12) | <0.001 |
| CABG + AAA, n (%) | 10 (1.25) | 4 (1.90) | NS |
| TAVI, n (%) | 9 (1.13) | 1 (0.47) | NS |
| Aortic aneurysm, n (%) | 19 (2.38) | 4 (1.90) | NS |
| Isolated valve, n (%) | 67 (8.39) | 22 (10.43) | NS |

*(Continued)*

**Table 5** (*Continued*)

| Variable | No delirium diabetic (n=799) | Delirium diabetic (n=211) | *P*-value |
|---|---|---|---|
| Case priority | | | |
| Planned, n (%) | 590 (73.84) | 149 (70.62) | NS |
| Urgent, n (%) | 174 (21.78) | 48 (22.75) | |
| Emergent, n (%) | 35 (4.38) | 14 (6.64) | |

**Abbreviations:** AAA, ascending aorta aneurysm; AF, atrial fibrillation; CABG, coronary artery bypass grafting; GFR, glomerular filtration rate; HbA1c, glycated hemoglobin; ICA, internal carotid artery; n, number of patients; NS, not significant; NYHA, New York Heart Association; TAVI, transcatheter aortic valve implantation; TIA, transient ischemic attack.

reduce the risk of POD. van Keulen et al performed a study to test the hypothesis that patients without diabetes who experienced glucose dysregulation (hypo- or hyperglycemia, or both) to be at higher risk of developing ICU delirium than patients with diabetes.[24] Contrary to our results, van Keulen et al reported that the diagnosis of diabetes mellitus was not associated with the development of ICU delirium. The authors found that hyperglycemia or both hypo- and hyperglycemia was associated with ICU delirium, yet only in nondiabetic patients.

Saager et al did a study in cardiac surgery patients aimed at testing the hypothesis that tight glucose control with a hyperinsulinemic strategy may reduce the risk of POD.[36] Contrary to their own hypothesis, the authors found that tight intraoperative glucose control with the use of normoglycemic hyperinsulinemic clamp actually increased the incidence but not severity of postcardiac surgery delirium. It is important to note that the authors recruited both patients with and without diabetes into their study, and within the diabetic group, both insulin and noninsulin-controlled diabetics. Similar to our results, there were more insulin-controlled diabetics in their study who did not develop delirium and more noninsulin-controlled diabetics in the group with delirium.[36]

In must be noted that the HbA1c level assessment as a monitor for antecedent glycemia has been under discussion for some time. Several studies looked at HbA1c as a risk factor for postoperative complications in cardiac surgery because the number of diabetic patients presenting with coronary artery disease continues to rise. Nicolini et al performed a study aimed to assess whether elevated HbA1c level is associated with adverse outcome in patients undergoing CABG.[37] In this study, HbA1c identified patients at risk of sternal wound infection, but no other postoperative outcomes.[37] A study by Narayan et al is associated with HbA1c level of 6.5% or higher with a significant increase in the incidence of sternal wound infection and respiratory complications in patients undergoing CABG.[38] van den Boom et al have shown that although the HbA1c level was positively associated with perioperative glucose, it was not associated with increased 30-day mortality in cardiac procedures. The authors concluded that

**Table 6** Postoperative complications and outcome for diabetic patients with and without postcardiac surgery delirium

| Postoperative complications | No delirium diabetic (n=799) | Delirium diabetic (n=211) | *P*-value |
|---|---|---|---|
| Stroke/TIA, n (%) | 28 (3.50) | 15 (7.11) | 0.021 |
| Atrial fibrillation, n (%) | 142 (17.77) | 61 (28.91) | <0.001 |
| Respiratory failure, n (%) | 54 (6.76) | 47 (22.27) | <0.001 |
| Pneumonia, n (%) | 17 (2.13) | 19 (9.00) | <0.001 |
| Sepsis, n (%) | 2 (0.25) | 0 (0.00) | NS |
| Acute kidney injury, n (%) | 22 (2.75) | 14 (6.64) | 0.007 |
| AKI with CRRT, n (%) | 84 (10.51) | 57 (27.01) | <0.001 |
| Creatinine (max), mean ± SD | 1.41±1.02 | 1.94±1.28 | <0.001 |
| GFR (min), mean ± SD | 61.56±25.92 | 43.87±23.91 | <0.001 |
| Postoperative outcome | | | |
| ICU LOS (days), mean ± SD | 2.74±5.64 | 3.77±6.22 | <0.001 |
| Hospital LOS (days), mean ± SD | 9.41±12.27 | 15.61±18.34 | <0.001 |
| Mortality at 30 days, n (%) | 42 (5.26) | 14 (6.64) | NS |

**Abbreviations:** AKI, acute kidney injury; CRRT, continuous renal replacement therapy; GFR, glomerular filtration rate; ICU, intensive care unit; LOS, length of stay; n, number of patients; NS, not significant; TIA, transient ischemic attack.

perioperative glucose control is related to surgical outcomes, yet the HbA1c, that reports preoperative glycemia control, is a less useful predictor.[39] Importantly, none of the above studies looked at postcardiac surgery delirium as a postoperative outcome after cardiac surgery.

It must also be underlined that in our study the internal carotid artery stenosis, but not stroke or transitory ischemic attack, was associated with POD after cardiac surgery. This is contrary to the findings of Cereghetti et al.[40] On the contrary, our study showed that in diabetic delirious patients, there were more episodes of stroke or TIA postoperatively.

Our study is not without limitations. We would like to underline that our study was a single-center retrospective analysis; therefore, it was merely associative and not predictor of causality research, and therefore, further prospective, multicenter activities are necessary to deepen our knowledge of diabetes and ICU delirium. Although the number of patients included was relatively high, as mentioned above the nature of the analysis was retrospective; therefore, some data may not be retrievable. We did not have the information regarding the type of delirium for all patients in our database nor regarding its severity. For a better understanding of the matter under discussion in diabetic and nondiabetic patients, a prospective study should be performed with a thorough examination of cognitive function and delirium severity assessment, as well as HbA1c and perioperative glycemia. Moreover, we used only HbA1c as a measure for the assessment of diabetes control, yet other and newer tests are available, including fructosamine, 1,5-anhydroglucitol, glycated albumin, or fetuin-A.

## Conclusion

Occurrence of POD after cardiac surgery is associated with the diagnosis of diabetes and an elevated preoperative level of HbA1c. More diabetic patients develop POD after cardiac surgery than nondiabetic patients. Elevated preoperative level of HbA1c was an independent risk factor for postcardiac surgery delirium regardless of the diagnosis of diabetes.

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## Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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