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Implications of Elevated Serum Cortisol in the Onset of Postoperative Delirium Following Off-Pump Coronary Artery Bypass Grafting: Insights from a Bangladesh-Based Single Center Experience

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Abstract

Background: Following coronary artery bypass grafting (CABG), delirium emerges as a prevalent complication. This study aimed to assess the correlation between elevated serum cortisol levels and the occurrence of postoperative delirium subsequent to off-pump CABG. **Methods:** Conducted in the Department of Cardiac Surgery at BSMMU from October 2020 to September 2022, this comparative cross-sectional study included a total of 44 participants. Subjects, meeting specific criteria, were purposefully assigned to two groups based on off-pump CABG. Group A (n = 22) consisted of patients with normal serum cortisol levels, while Group B (n = 22) comprised individuals with high serum cortisol levels on the first postoperative day. Delirium onset was assessed at the bedside in the ICU on the 1st, 2nd, 3rd, 4th, and 5th postoperative days using standard tools, namely the Richmond Agitation Sedation score (RASS) and The Confusion Assessment Method (CAM-ICU). Data were collected based on the presence or absence of delirium. Statistical analysis utilized SPSS version 26.0, employing an independent Student's t-test for continuous data and chi-square and Fischer's exact test for categorical data. A p-value ≤ 0.05 was considered statistically significant. **Results:** Group-A had a mean age of 54.50 ± 17.97, and Group-B had a mean age of 55.22 ± 15.45, both with a male predominance (81.81% and 86.36% respectively). The mean serum cortisol level was significantly higher in Group B (829.71 ± vs. 389.98 ± 68.77). Postoperative delirium occurred in 27.3% of Group B patients, statistically significant compared to the 4.5% in Group A. However, patients in Group B who developed delirium experienced significantly longer postoperative ICU and hospital stays (79.29 ± 12.27 vs. 11.44 ± 2.85, p ≤ 0.05). There was one mortality in Group B, which was statistically not significant. **Conclusion:** This study observed a significant association between elevated serum cortisol levels in the postoperative period and the occurrence of postoperative delirium after off-pump coronary artery bypass grafting.

Keywords

Coronary Artery Bypass Grafting (CABG), Serum Cortisol, Postoperative Delirium, Bangladesh

1. Introduction

Postoperative delirium is a significant yet often overlooked complication following coronary artery bypass grafting (CABG), and it is correlated with prolonged intensive care unit (ICU) stays and increased hospitalization duration [1].

The American Psychiatric Association's fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines delirium by five key features, including disturbance in attention and awareness, a rapid development of disturbance with fluctuating severity, additional disturbances in cognition, absence of better explanations by pre-existing neurocognitive disorders, and evidence linking the disturbance to another medical condition [2].

The incidence of post-cardiac surgery delirium ranges from 26% to 52%, with some studies reporting percentages as high as 70% [3] [4]. Particularly common in elderly patients undergoing major surgical procedures, postoperative delirium occurs in 21% to 50% of cases [5]. Among patients older than 60 years, the reported incidence is consistent, ranging from 30% to 52% [6] [7]. This condition has been associated with severe consequences, including postoperative cognitive dysfunction, prolonged mechanical ventilation, extended hospital and ICU stays, heightened healthcare costs, and increased long-term cardiovascular events after CABG [8].

Coronary artery disease, a leading cause of death globally, necessitates life-saving treatments such as coronary artery bypass grafting (CABG). However, CABG is accompanied by neuropsychiatric complications, notably delirium, which significantly impacts postoperative recovery and prognosis [9] [10]. Comorbidities such as atrial fibrillation, prior stroke, anemia, peripheral vascular disease, and psychiatric conditions like cognitive impairment contribute to postoperative delirium [11] [12].

The emerging understanding of the pathophysiology of delirium includes the association of increased serum cortisol levels with its development. Prolonged and excessive secretion of glucocorticoids due to physiological and emotional stress from major surgery may contribute to delirium [13]. Despite numerous studies, the precise pathophysiology of delirium remains poorly understood [14]. Cortisol, a crucial stress hormone, is secreted in response to surgical stimuli severity, with a reciprocal control mechanism, the hypothalamic-pituitary-adrenal axis, existing between the brain and glucocorticoid hormones. Elevated cortisol levels could impact cognition by affecting hippocampal or prefrontal cortical function, thus directly or indirectly manipulating cognition [15].

For these reasons, high serum cortisol has been proposed as an important factor in predicting delirium after CABG. While not universally supported, several studies have demonstrated an association between high serum cortisol levels and the development of delirium. This study seeks to evaluate the association of high serum cortisol in the development of delirium in patients after off-pump coronary artery bypass grafting, aiming to contribute to early patient management for improved postoperative outcomes.

2. Materials and Methods

2.1. Study Design and Population

This comparative cross-sectional study, conducted at the Department of Cardiac Surgery, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, aimed to explore the association between high serum cortisol and postoperative delirium in patients undergoing elective off-pump coronary artery bypass grafting (OPCABG). Spanning from October 2020 to September 2022, the study involved 44 patients divided into two groups: Group A, exhibiting normal serum cortisol levels, and Group B, showing high serum cortisol levels on the 1st postoperative day. The decision to opt for a smaller sample size was carefully considered by both the investigators and the institutional review board, taking into account the unique challenges posed by the COVID-19 pandemic. Despite the constraints imposed by the pandemic, the study aimed to provide valuable insights into the relationship between serum cortisol levels and postoperative outcomes. By acknowledging the pandemic context and adapting the study design accordingly, the researchers endeavored to maintain scientific rigor while prioritizing participant safety and research feasibility. The study included adult patients with preoperative normal serum cortisol undergoing elective OPCABG, while excluding those with specific medical conditions such as schizophrenia, primary adrenal insufficiency, hepatic or renal insufficiency, prolonged glucocorticoid therapy, low left ventricular ejection fraction, concomitant surgeries other than OPCABG, and redo cardiac surgery, aiming to minimize selection bias through careful participant screening and transparent recruitment procedures. In order to exclude participants with pre-existing neurocognitive disorders, we arranged for a single neurological consultation for patients expressing a wish to participate in the study.

2.2. Data Collection Procedure

Data collection involved a semi-structured questionnaire, a checklist for medical records, and assessment tools such as the Richmond Agitation Sedation Scale (RASS) (Table 1) and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (Figure 1). Blinding procedures were implemented for assessors involved in delirium assessment using RASS and CAM-ICU. Following

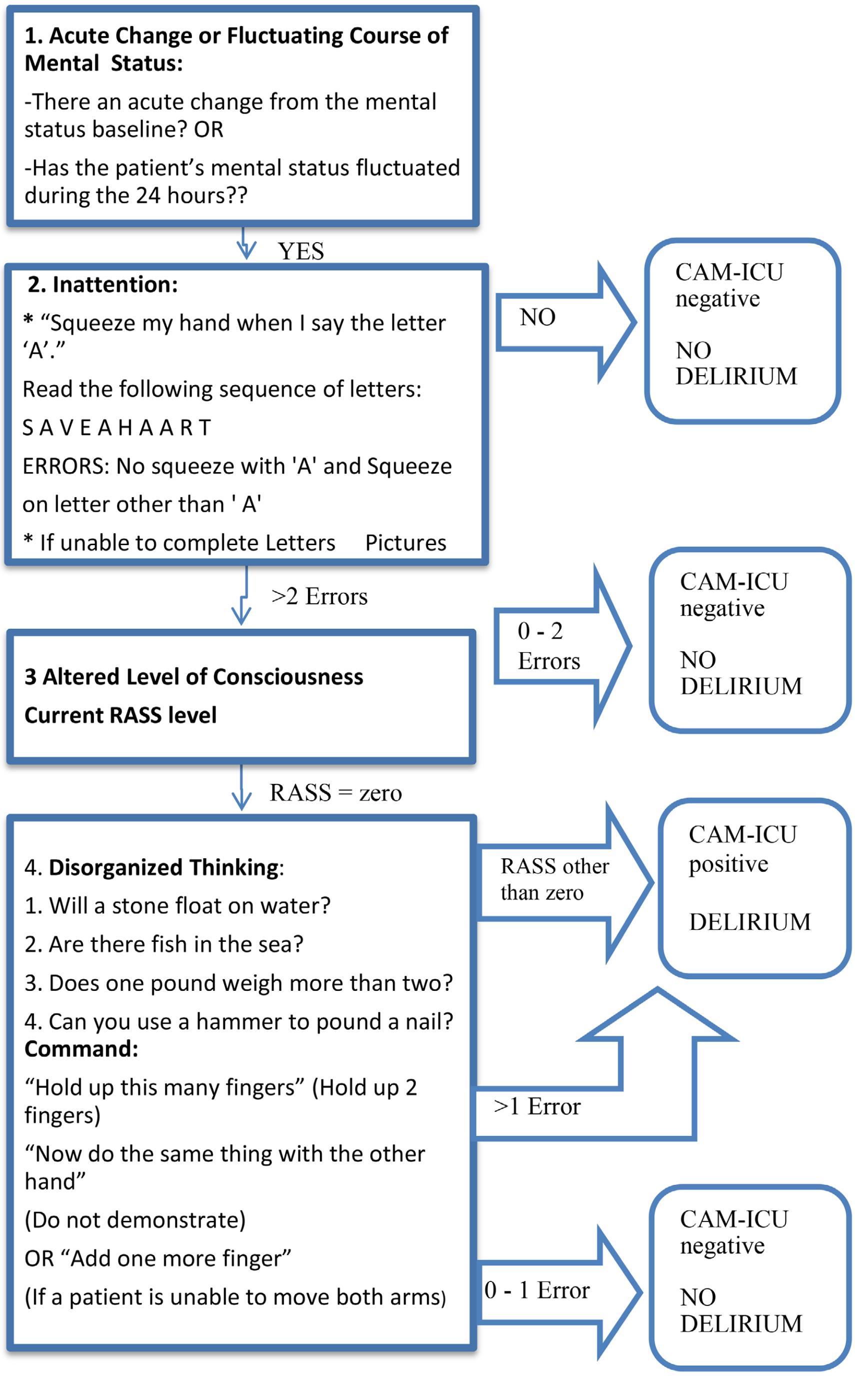

Figure 1. Flow sheet demonstrating the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).

Table 1. Representation of the Richmond Agitation Sedation Score (RASS).

Scale	Label	Description	
+4	Combative	Overtly combative, violent, immediate danger to staff	OBSERVATION
+3	Very agitated	Pulls or removes tubes or catheter; aggressive	
+2	Agitated	Frequent non-purposeful movements fight the ventilator	
+1	Restless	Anxious but movements not aggressive vigorous	
0	Alert and Calm	Spontaneously pays attention to care giver	
−1	Drowsy	Not fully alert, but has sustained awakening (Eye-opening/eye contact) to voice (≥***10 seconds***)	VOICE
−2	Light sedation	Briefly awakens with eye contact to voice (≤***10 seconds***)	
−3	Moderate sedation	Movement or eye-opening to voice (***but not eye contact***)	
−4	Deep sedation	No response to voice, but movement or eye opening to ***physical stimulation.***	TOUCH
−5	Unarousable	No response to ***Voice or physical stimulation***	

completion of surgery, all selected patients were transferred to the intensive care unit (ICU) where they were intubated and ventilated. On the first postoperative day in the ICU, fasting blood samples for measuring serum cortisol concentration were obtained from all patients. These samples were drawn either via a central or peripheral venous line after 10 minutes of rest in a supine position, typically between 7 and 8 am Serum cortisol concentration was analyzed by the microbiology and immunology laboratory of BSMMU using either the BECKMAN COULTER UniCel DxI 600 (Access Immuno-assay System) or the SIEMENS ADVIA centaur XP USA. The normal range for serum cortisol concentration was established as 138 to 690 nmol/L. As mentioned earlier, based on their cortisol levels, patients were categorized into two groups: Group A, comprising individuals with normal serum cortisol levels (138 - 690 nmol/l), and Group B, consisting of those with high serum cortisol levels (>690 nmol/l). Both groups were evaluated for the presence of delirium twice daily, every 12 hours (from 7 am to 9 am and from 7 pm to 9 pm), using the Richmond Agitation Sedation Scale (RASS) and the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), as assessed by the investigator. Postoperative patients were assessed daily in the ICU on the 1st, 2nd, 3rd, 4th, and 5th postoperative days for the incidence of delirium. Delirium diagnosis was based on specific criteria, including acute onset or fluctuation of mental status, inattention, disorganized thinking, and altered level of consciousness, with patients required to display specific combinations of these symptoms. The onset of delirium was documented, and all clinical and socio-demographic information was recorded in a predesigned case record form.

2.3. Statistical Analysis

The collected data were processed using SPSS, and both descriptive and inferential statistical analyses were applied, with significance set at a p-value ≤ 0.05. The methodology incorporated quality control checks, pretesting, and ethical safeguards to ensure the validity and reliability of the findings.

2.4. Ethical Considerations

The study adhered to ethical considerations, including approval from the Institutional Review Board (ref no. BSMMU/2021/8509), informed written consent, and strict confidentiality measures.

2.5. Operational Definitions

Operational Definitions for the current study were as follows:

- Delirium: A condition characterized by disturbances in attention and awareness, fluctuating severity, additional cognitive impairments, and not attributed to other neurological conditions, as per criteria outlined by [2]. In this study, delirium onset was measured using the delirium questionnaire by Mu *et al.*, [16] with higher scores indicating a greater incidence.
- Cortisol: A glucocorticoid hormone synthesized in the adrenal cortex, regulated by the HPA axis, with a normal range of 138 - 690 nmol/L (standard reference from BSMMU laboratory), according to Mu *et al.* [16]. Serum cortisol concentration was measured using the cortisol questionnaire by Mu *et al.* [16] [17], with higher levels indicating increased surgical stress.
- Ventilation time: The duration of ventilation required postoperatively, including potential re-intubation, as per Bojar (6th edition, 2021) [18].
- Prolonged ventilation time: Mechanical ventilation support needed for over 24 hours postoperatively, according to STS data specifications [19].
- Duration of ICU stay: The period from ICU admission to transfer to the postoperative ward, as defined by STS data specifications [19].
- Prolonged duration of ICU stays: Length of stay exceeding 3 days in the ICU, according to STS Adult Cardiac Surgery Database Risk Model Variables - Data Version 2.73 [19].
- Post-operative length of hospital stays: The duration of hospitalization, including ICU, post-ICU, and cardiac surgery ward, as described in the study.
- Prolonged postoperative length of hospital stays (PLOS): Hospital stay exceeding 14 days, according to STS Adult Cardiac Surgery Database Risk Model Variables - Data Version 2.73. [19].

- RASS (Richmond agitation sedation score): An instrument for assessing alertness and agitation in critically ill patients, as detailed by Mu *et al.* [16] (**Table 1**).
- Confusion Assessment Method for the Intensive Care Unit (CAM-ICU): Developed by Dr. Sharon Inouye in 1990, the CAM-ICU is a reliable bedside tool for detecting delirium in non-psychiatric settings. With high sensitivity and specificity, it offers a quick and accurate assessment of delirium, making it invaluable for clinical use [20]. **Figure 1** depicts the flow sheet for the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).

3. Results

The age distribution of patients across the study groups is depicted in **Table 2**. A notable proportion of patients, 36.36% in Group A and 45.45% in Group B, were within the 55 - 64 years age range. Statistical analysis indicated that the mean age difference between the two groups was not statistically significant ($p > 0.05$). Specifically, the mean age was 54.50 ± 17.97 in Group A and 55.22 ± 15.45 in Group B, suggesting a similar distribution of age across both cohorts.

Table 3 illustrates the distribution of patients by gender in both study groups. In Group A, 81.81% of patients were male and 18.18% were female, while in Group B, 86.36% were male and 13.64% were female. Statistical analysis revealed no significant difference in gender distribution between the two groups.

Table 4 presents the distribution of patients categorized by their preoperative cortisol levels. In both Group A and Group B, the mean ± SD serum cortisol levels (in nmol/l) were 323.93 ± 94.51 and 330.21 ± 38.64, respectively. Notably, there was no statistically significant difference observed between the two groups in terms of preoperative cortisol levels.

Table 2. Comparison of patient age between two groups.

^{A}**Age groups (years)**	Respondents (N = 44)			
	Group A f (%) $n_1 = 22$	Group B f (%) $n_2 = 22$	Total f (%) N = 44	p value
35 - 44	4 (18.2)	4 (18.2)	8 (18.2)	0.376^{ns}
45 - 54	5 (22.72)	4 (18.8)	9 (20.45)	0.365^{ns}
55 - 64	8 (36.36)	10 (45.45)	18 (40.9)	0.456^{ns}
65 - 75	5 (22.72)	4 (18.2)	9 (20.45)	0.572^{ns}
^{B}**Mean Age, ±SD**	54.50 ± 17.97	55.22 ± 15.45		0.805^{ns}

N = Total number of respondents. n_1 = Respondents in group A, and n_2 = Respondents in group B. ns = Not significant. SD = Standard Deviation. Data were presented as frequency (f) and mean ± SD. Figures in the parentheses denote the corresponding %. Statistical analysis was done by ^{A} Chi-square test and ^{B} independent t-test. p-value ≤ 0.05 was considered significant.

Table 3. Gender distribution across two groups.

Gender	Respondents (N = 44)			
	Group A f (%) $n_1 = 22$	Group B f (%) $n_2 = 22$	Total f (%) N = 44	p value
Male	18 (81.81)	19 (86.36)	37 (84.10)	0.680^{ns}
Female	4 (18.18)	3 (13.64)	7 (15.90)	

N = Total number of respondents. n_1 = Respondents in group A, and n_2 = Respondents in group B. ns = Not significant. Data were presented as frequency (f), Figures in the parentheses denote the corresponding %. Statistical analysis was done by Chi-square test. p-value ≤ 0.05 was considered significant.

Table 4. Gender distribution across two groups.

	Respondents (N = 44)			
	Group A f (%) $n_1 = 22$	Group B f (%) $n_2 = 22$	Total f (%) N = 44	p value
Cortisol level (nmol/l)	323.93 ± 94.51	330.21 ± 38.64	37 (84.10)	0.802^{ns}

N = Total number of respondents. n_1 = Respondents in group A, and n_2 = Respondents in group B. ns = Not significant. Data were presented as mean ± SD. Statistical analysis was done by independent t-test. p-value ≤ 0.05 was considered significant.

Preoperative clinical history, such as smoking, ischemic heart disease/myocardial infarction (IHD/MI), hypertension, and diabetes mellitus (DM), was compared between patients in Group A and Group B, showing no statistically significant differences ($p > 0.05$), as depicted in **Table 5**. Similarly, analysis of drug history did not reveal any significant findings.

Table 6 presents data concerning per-operative attributes. The duration of anesthesia, crucial in postoperative delirium management, was observed to be 4.48 ± 1.12 hours in Group A and 4.82 ± 1.41 hours in Group B, with a non-significant p-value of 0.398. Similarly, the mean ± SD duration of surgery was 163.83 ± 43.168 minutes in Group A and 188.05 ± 52.675 minutes in Group B. Atrial fibrillation (AF) was detected in 3 patients (13.60%) in Group A and 2 patients (9.10%) in Group B, while ventricular tachycardia (VT) occurred in 2 patients (9.10%) in Group A and 1 patient (4.50%) in Group B. Notably, statistical analysis revealed no significant differences in terms of the duration of surgery or perioperative complications ($p > 0.05$).

Table 7 displays post-operative cortisol levels and the incidence of delirium. The mean ± SD post-operative serum cortisol level (nmol/l) was 389.98 ± 68.77 in Group A and 829.71 ± 79.80 in Group B, with a statistically significant difference (p-value = 0.001). Delirium was assessed from the 1st to the 5th postoperative day (POD). Notably, delirium occurred in 1 patient (4.5%) in Group A and 6 patients (27.3%) in Group B, with a statistically significant difference (p-value = 0.039).

Table 5. Comparative analysis of preoperative clinical profiles between the two groups.

Clinical profile	Respondents (N = 44)		
	Group A f (%) $n_1 = 22$	Group B f (%) $n_2 = 22$	p value
Risk factors			
Smoker	16 (72.70)	17 (77.30)	0.728^{ns}
IHD/MI	18 (81.80)	18 (81.80)	1.00^{ns}
HTN	10 (45.50)	11 (50.0)	0.763^{ns}
DM	17 (77.27)	19 (86.40)	0.434^{ns}
Drug history			
Diuretics	9 (40.90)	10 (45.50)	0.673^{ns}
OHD	5 (22.72)	6 (27.27)	0.358^{ns}
Insulin	5 (22.73)	4 (18.20)	0.353^{ns}

n_1 = Respondents in group A, and n_2 = Respondents in group B. ns = Not significant. Data were presented as frequency (f), Figures in the parentheses denote the corresponding %. Statistical analysis was done by Chi-square test. p-value ≤ 0.05 was considered significant.

Table 6. Comparison of patients according to peroperative findings between the groups.

Surgical profile	Respondents (N = 44)		
	Group A f (%) $n_1 = 22$	Group B f (%) $n_2 = 22$	p value
^{A}Duration of anesthesia (hours)	4.48 ± 1.12	4.82 ± 1.41	0.398^{ns}
^{A}Duration of surgery in min (Mean ± SD)	163.83 ± 43.168	188.05 ± 52.675	0.171^{ns}
^{B}Peroperative arrhythmia			
Atrial Febrilation	3 (13.60)	2 (9.10)	0.788^{ns}
Ventricular Tachycardia	2 (9.10)	1 (4.50)	0.785^{ns}

N = Total number of respondents. n_1 = Respondents in group A, and n_2 = Respondents in group B. ns = Not significant. SD = Standard Deviation. Data were presented as frequency (f) and mean ± SD. Figures in the parentheses denote the corresponding %. Statistical analysis was done by ^{A} Chi-square test and ^{B} independent t-test. p-value ≤0.05 was considered significant.

Table 8 presents the sodium (Na^+) and potassium (K^+) levels of patients up to the 5th postoperative day (POD). Statistical analysis revealed that there was no significant difference in these levels (p-value > 0.05).

Table 9 illustrates the comparison of postoperative outcomes between Group A and Group B. The mean ± SD duration of ICU stay was 63.89 ± 10.36 hours

Table 7. Comparison of first post-operative serum cortisol level and delirium between two groups.

	Respondents (N = 44)		
	Group A f (%) $n_1 = 22$	Group B f (%) $n_2 = 22$	p value
ACortisol level (nmol/l)	389.98 ± 68.77	829.71 ± 79.80	0.001s
BDelirium (assessed by RASS and CAM-ICU protocol)			
1st POD	0 (0)	0 (0)	-
2nd POD	0 (0)	1 (4.5)	0.488ns
3rd POD	1 (4.5)	2 (9.1)	0.550ns
4th POD	0 (0)	2 (9.1)	0.148ns
5th POD	0 (0)	1 (4.5)	0.312ns
BTotal	1 (4.5)	6 (27.3)	0.039s

N = Total number of respondents. n_1 = Respondents in group A, and n_2 = Respondents in group B. ns = Not significant and s = significant. SD = Standard Deviation. Data were presented as frequency (f) and mean ± SD. Figures in the parentheses denote the corresponding %. Statistical analysis was done by A Independent t-test and B Chi-square test. p-value ≤ 0.05 was considered significant.

Table 8. Comparison of post-operative electrolyte levels between the groups.

Post-operative electrolytes level Mean ± SD	Respondents (N = 44)		
	Group A f (%) $n_1 = 22$	Group B f (%) $n_2 = 22$	p value
Operative day			
Na^+ (mEq/l)	143.67 ± 4.60	137.65 ± 6.61	0.674ns
K^+ (mmol/l)	3.80 ± 0.18	3.98 ± 0.16	0.911ns
1st POD			
Na^+ (mEq/l)	140.19 ± 7.20	139.38 ± 7.51	0.725ns
K^+ (mmol/l)	4.01 ± 0.02	3.88 ± 0.30	0.897ns
2nd POD			
Na^+ (mEq/l)	138.56 ± 6.00	138.72 ± 5.35	0.926ns
K^+ (mmol/l)	3.85 ± 0.20	3.89 ± 0.22	0.641ns
3rd POD			
Na^+ (mEq/l)	137.68 ± 6.30	138.65 ± 6.51	0.825ns
K^+ (mmol/l)	3.91 ± 0.03	3.76 ± 0.19	0.641ns

Continued

4th POD			
Na^+ (mEq/l)	138.37 ± 5.33	138.38 ± 5.26	0.999ns
K^+ (mmol/l)	3.90 ± 0.22	3.93 ± 0.21	0.641ns
5th POD			
Na^+ (mEq/l)	145.67 ± 2.60	143.25 ± 2.51	0.741ns
K^+ (mmol/l)	3.90 ± 0.17	3.90 ± 0.19	0.951ns

N = Total number of respondents. n_1 = Respondents in group A, and n_2 = Respondents in group B. ns = Not significant. SD = Standard Deviation. Data were presented as mean ± SD. Statistical analysis was done by independent t-test. p-value ≤ 0.05 was considered significant.

Table 9. Comparison of postoperative outcomes between the two groups.

Surgical profile	Respondents (N = 44)		
	Group A f (%) n_1 = 22	Group B f (%) n_2 = 22	p value
ADuration of anesthesia (hours)	4.48 ± 1.12	4.82 ± 1.41	0.398ns
ADuration of surgery in min (Mean ± SD)	163.83 ± 43.168	188.05 ± 52.675	0.171ns
BPeroperative arrhythmia			
Atrial Febrilation	3 (13.60)	2 (9.10)	0.788ns
Ventricular Tachycardia	2 (9.10)	1 (4.50)	0.785ns

N = Total number of respondents. n_1 = Respondents in group A, and n_2 = Respondents in group B. ns = Not significant. SD = Standard Deviation. Data were presented as frequency (f) and mean ± SD. Figures in the parentheses denote the corresponding %. Statistical analysis was done by A Chi-square test and B independent t-test. p-value ≤ 0.05 was considered significant.

for Group A and 79.29 ± 12.27 hours for Group B, indicating a statistically significant difference (p-value 0.001). There was no statistically significant difference in the mean ± SD duration of ventilator use between the groups, with Group A at 6.88 ± 0.31 hours and Group B at 7.01 ± 0.45 hours (p-value 0.276). However, there was a significant difference in hospital stay duration, with Group A at 8.38 ± 2.10 days and Group B at 11.44 ± 2.85 days (p-value 0.001). Additionally, one mortality was reported in Group B, representing 4.5% of patients in this group (p-value 0.312).

4. Discussion

High serum cortisol is recognized as a significant contributor to cognitive impairment and the development of delirium following OPCABG. For this study, a total of 44 patients were selected based on inclusion and exclusion criteria, with each group consisting of 22 patients categorized by serum cortisol levels assessed on the first postoperative day. Group A comprised patients with normal postoperative serum cortisol levels, while Group B included those with elevated levels. Sedation levels were evaluated using the Richmond Agitation Sedation Scale (RASS), and delirium was diagnosed using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), assessed twice daily for five consecutive days following OPCABG, with onset and occurrence of delirium recorded. Analysis of demographic variables revealed a mean age of 54.50 ± 17.97 for Group A and 55.22 ± 15.45 for Group B, with no statistically significant difference observed ($p > 0.05$). Similar findings were reported by Mu *et al.* [17] who identified advanced age as an independent predictor of postoperative delirium alongside high serum cortisol levels. Gender distribution analysis showed that out of 44 study subjects, 84.10% were male and 15.90% were female, with no significant difference between groups ($p = 0.680$), consistent with previous studies by Burkhart *et al.* [6] and Cox *et al.* [21] (2010, 2015). The pre-operative mean cortisol level was comparable between the two groups ($p = 0.802$), consistent with findings by Eshmaway *et al.* [22], but inconsistent with those of Kazmierski *et al.* [23]. No significant differences were observed in the distribution of risk factors such as smoking, IHD/MI, HTN, and Diabetes, nor in the type of drugs used by patients between the groups ($p > 0.05$), consistent with Mu *et al.*'s findings [16]. In terms of surgical factors, anesthesia and surgery duration, as well as perioperative arrhythmia, showed no significant differences between groups ($p > 0.05$), consistent with Mu *et al.*'s findings [17]. Postoperatively, 27.3% of patients in Group B experienced delirium, significantly higher than the 4.5% in Group A ($p = 0.039$). Mu *et al.* also found a positive association between high postoperative serum cortisol and delirium onset. Duration of ICU and hospital stay was significantly longer in Group B ($p = 0.001$), consistent with Mu *et al.* [16] and Hudetz *et al.*'s [24] findings. One patient died during the study from sepsis, although statistically not significant. Overall, the study supports the association between elevated postoperative serum cortisol levels and increased delirium incidence, highlighting its potential for early detection and improved patient management.

While the current study did not employ specific statistical tests for controlling confounding variables, we implemented several methodological strategies to mitigate their influence. These included the establishment of strict inclusion and exclusion criteria to minimize heterogeneity among study groups, transparent reporting of patient characteristics and comorbidities, and the involvement of experienced multidisciplinary teams in patient care. These measures were undertaken to address potential confounders such as atrial fibrillation, prior stroke, anemia, peripheral vascular disease, and psychiatric conditions. While statistical tests for controlling confounding variables are commonly utilized, our study design and methodology were carefully crafted to reduce confounding effects without the need for additional statistical tests. We believe that the inclusion of this explanation enhances the transparency and validity of our findings.

5. Conclusion

This study demonstrates a clear association between elevated serum cortisol levels following coronary bypass grafting and the onset of postoperative delirium. Significantly higher rates of delirium were observed among patients with elevated cortisol levels compared to those with normal levels. These findings suggest that monitoring serum cortisol levels may serve as a valuable predictive tool for identifying individuals at risk of postoperative delirium. Implementing such monitoring protocols could potentially lead to more effective management strategies for delirium following off-pump coronary artery bypass grafting, ultimately resulting in improved postoperative outcomes.

6. Limitation of the Study

A notable limitation of the study is the insufficient preoperative baseline psychiatric and cognitive screening tests, attributed to the challenges posed by the COVID-19 pandemic, which restricted detailed psychiatric examination procedures. Consequently, evaluation by a specialist psychiatrist upon admission was necessary. Despite our efforts to ensure at least a single consultation from a neurologist or psychiatric specialist for each patient, the absence of comprehensive baseline assessments may have impacted the thoroughness of our evaluation. This limitation is particularly pertinent as preoperative mental disorders, including depression, cognitive impairment, and dementia, are widely acknowledged as significant predictors of postoperative delirium. Additionally, immediate postoperative baseline serum cortisol concentrations were not measured, which could have provided insights into patients' baseline cortisol levels and their potential impact on postoperative delirium. Furthermore, while hypercortisolemia may directly influence delirious symptoms, it remains unclear whether it is a cause or a consequence of delirium-related stress. Thus, further research is warranted to elucidate the mechanisms underlying the relationship between circulating cortisol levels and delirium.

7. Recommendation of the Study

1) It is recommended to incorporate routine postoperative serum cortisol level estimation during the initial postoperative period following off-pump coronary artery bypass grafting. This practice can aid in predicting the occurrence of delirium, thereby facilitating better patient stratification in this regard.

2) Further validation of the study's findings is warranted through larger prospective studies conducted across multiple centers. These studies should encompass a broader spectrum of cases, including high-risk patients and those undergoing on-pump CABG procedures, to ensure comprehensive validation and generalizability of the results.

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Authors' Contributions

The first author conceptualized and designed the study, collected data from the hospital, conducted data analysis, and drafted the manuscript. The second author contributed to the manuscript preparation and provided critical analysis of the study. All authors were involved in the interpretation of the findings and have approved the final version of the manuscript.

Conflicts of Interest

The authors have no conflicts of interest to disclose regarding the publication of this paper.

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