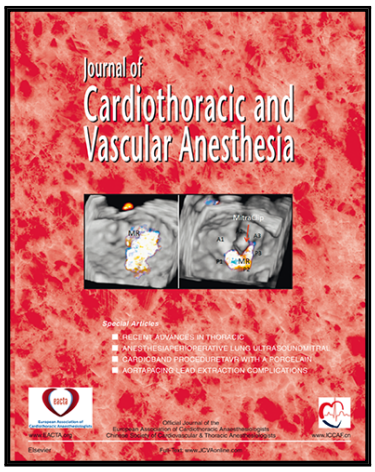

Hyperlipidemia and Postoperative Hallucinations After Cardiac Surgery: Insights from the VAACS Cohort Study

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Hyperlipidemia and Postoperative Hallucinations After Cardiac Surgery: Insights from the VAACS Cohort Study

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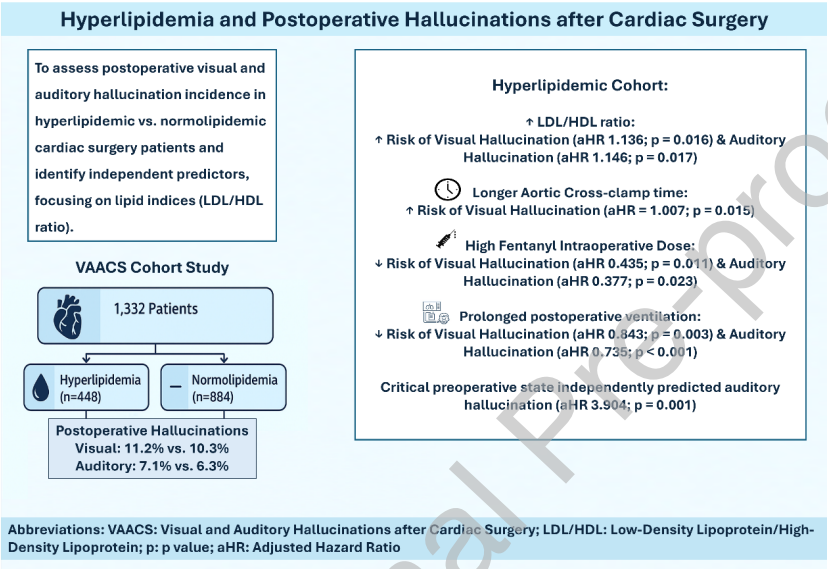
Hyperlipidemia and Postoperative Hallucinations After Cardiac Surgery: Insights from the VAACS Cohort Study

Graphical abstract



Structured Abstract

Objective:

To evaluate the cumulative incidence and predictors of postoperative visual and auditory hallucinations among hyperlipidemic and normolipidemic patients undergoing cardiac surgery, with particular focus on lipid indices, especially the LDL/HDL ratio.

Design:

Multicenter, prospective cohort study with daily postoperative assessments from days 1–4 and follow-up to day 7, employing Kaplan–Meier estimation and multivariable Cox proportional hazards regression.

Setting:

Ten tertiary cardiac surgery centers across the West Bank of Palestine.

Participants:

Adults (≥18 years) undergoing coronary artery bypass grafting (CABG) or valve surgery (N = 1,332), stratified as hyperlipidemic (n = 448) or normolipidemic (n = 884) according to preoperative lipid profiles. Patients with incomplete records, cognitive impairment, language barriers, or psychiatric illness were excluded.

Interventions:

None (observational study).

Measurements and Main Results:

Postoperative hallucinations were assessed using the validated Questionnaire for Psychotic Experiences (QPE). By day 7, visual hallucinations occurred in 11.2% of hyperlipidemic and 10.3% of normolipidemic patients, while auditory hallucinations occurred in 7.1% and 6.3%, respectively. The LDL/HDL ratio independently predicted both visual and auditory hallucinations in hyperlipidemic (visual: aHR 1.136, p = 0.016; auditory: aHR 1.146, p = 0.017) and normolipidemic (visual:

aHR 1.123, p = 0.038; auditory: aHR 1.110, p = 0.047) cohorts. Longer aortic cross-clamp time increased visual hallucination risk (aHR 1.007; p = 0.015), while intraoperative fentanyl exposure reduced both visual (aHR 0.435; p = 0.011) and auditory (aHR 0.377; p = 0.023) hallucinations. A critical preoperative state predicted auditory hallucinations in hyperlipidemic patients (aHR 3.904; p = 0.001).

Conclusions:

Elevated LDL/HDL ratio is a significant predictor of postoperative hallucinations. Integrating lipid profile evaluation into perioperative risk assessment may enhance neuropsychiatric outcomes following cardiac surgery.

Keywords:

Hyperlipidemia; Cardiac Surgery; Hallucinations; LDL/HDL Ratio; Neuropsychiatric Complications; VAACS Study.

Introduction:

Cardiac surgeries encompass a broad range of specialized interventions targeting the heart and thoracic aorta, including valve replacements and repairs, and coronary artery bypass grafting (CABG). Globally, cardiac surgeries are among the most frequently performed operations, with approximately 2 million procedures conducted annually (1). Visual and auditory hallucinations are notable concerns, with studies such as the Northumberland study reporting an incidence of 21.9% within the first four days postoperatively (2). The overall prevalence of these distressing neuropsychiatric symptoms, including hallucinations, has been estimated between 20% and 58%, depending on diagnostic criteria, patient age, and typical comorbidities in cardiothoracic populations (3)(4).

Hallucinations often present as a component of postoperative delirium(3)(5). These hallucinations can severely disrupt recovery by inducing anxiety, provoking self-harm through manipulation of surgical wounds or catheters, and leading to medication refusal or noncompliance with rehabilitation programs (6)(4). Consequently, they are associated with prolonged hospitalization, delayed adjustments in cardiac treatment plans, and increased morbidity rates (7)(8) Recent attention has turned to hyperlipidemia as a potential contributing factor to neuropsychiatric disturbances, including hallucinations.

Perioperative lipoprotein dynamics in cardiac surgery correlate with stroke and mortality risk, highlighting prognostic value beyond atherogenesis (9) . HDL particle levels/antioxidant capacity track oxidative injury and postoperative AKI, linking lipid biology to perioperative organ outcomes(10) . Emerging work associates intraoperative lipoproteins with postoperative delirium (11). Additionally, preoperative LDL-C relates to major adverse cardiovascular events after major non-cardiac surgery, underscoring generalizable perioperative relevance (12).

Emerging perioperative data suggest that lipid dysregulation may prime the brain for postoperative neuropsychiatric injury through endothelial dysfunction, impaired cerebral autoregulation, microembolic burden during cardiopulmonary bypass, and heightened oxidative/inflammatory signaling. Within this framework, higher LDL (and lower HDL) plausibly amplifies vulnerability to perceptual disturbances after cardiac surgery via blood–brain barrier perturbation, microvascular ischemia, and pro-inflammatory cascades(13–18)However, the specific relationship between preoperative lipid profile and postoperative visual and auditory

hallucinations has not been defined in cardiac-surgery cohorts, motivating the present study As a Result, we hypothesize that abnormal lipid metabolism contributes to increased vulnerability to postoperative hallucinations in cardiac surgery patients, with elevated LDL/HDL ratios predisposing to neuropsychiatric disturbances through mechanisms involving oxidative stress, inflammation, and impaired cerebral perfusion.

Methods:

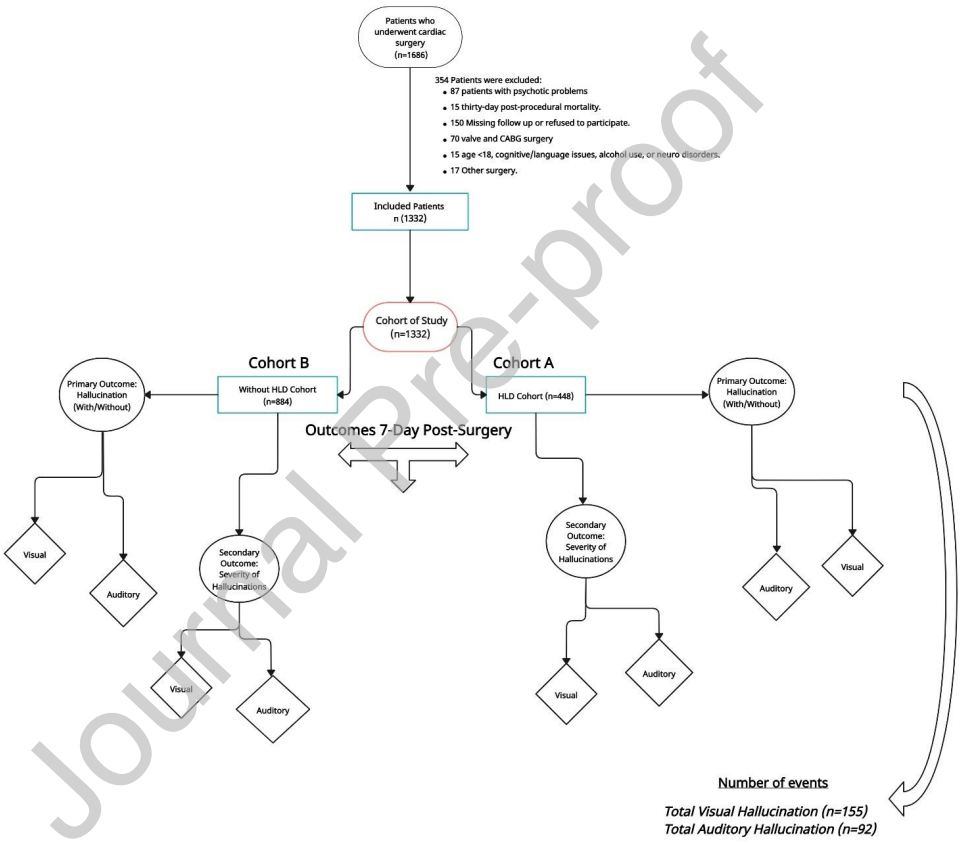
Study design, setting, and population:

This study was conducted as part of the Visual and Auditory After Cardiac Surgery (VAACS) study (ISRCTN18368253), a multicenter prospective cohort project investigating postoperative neuropsychiatric outcomes following cardiac surgery. The present report represents a pre-specified sub-study focusing on the association between lipid status and postoperative hallucinations. Data were collected between September 2022 and June 2025 across ten tertiary cardiac surgery centers in the West Bank of Palestine, ensuring broad geographic and demographic representation. Participating hospitals included Ibn Sina Specialist Hospital, Specialized Arab Hospital, An-Najah National University Hospital, Al Razi Hospital, Al-Mezan Hospital, Al-Ahli Hospital, Arab Society for Rehabilitation, Palestine Medical Complex, Nablus Specialty Hospital, and Al-Makassed Hospital. All centers perform high-volume coronary and valvular procedures using standardized surgical and anesthetic protocols.

A total of 1,686 adult patients who underwent cardiac surgery were screened for eligibility. Patients were excluded if they had pre-existing psychotic disorders, 30-day postoperative mortality, incomplete follow-up, combined valve plus CABG procedures, were younger than 18 years, or had cognitive or language barriers, alcohol or substance use, or neurological disorders. After applying these criteria, 1,332 patients were included and classified into hyperlipidemia (HLD) and non-HLD cohorts based on their preoperative lipid profiles. Figure 1 illustrates the flow of patient screening, exclusion, and cohort allocation.

Figure 1. Study Flow Diagram of Patient Screening, Inclusion, and Cohort Allocation.

HLD vs. No HLD Cohort (3-Year Multicenter Study)



All variables for this sub-analysis were collected prospectively within the VAACS registry; hyperlipidemia status was determined from the preoperative lipid panel obtained immediately before surgery, irrespective of prior statin use or historical lipid assessments, and redo surgery, along with other baseline factors, was prespecified for inclusion as a covariate in multivariable models. Patients will be divided into hyperlipidemia and normal lipid groups based on preoperative lipid profiles. Hyperlipidemia will be defined as LDL ≥ 130 mg/dL, HDL ≤ 40 mg/dL in males or ≤ 50 mg/dL in females, triglycerides ≥ 150 mg/dL, or total cholesterol ≥ 200 mg/dL (12).

Data collection instrument:

Data were collected using the Questionnaire for Psychotic Experiences (QPE) to assess postoperative auditory and visual hallucinations during the perioperative period, a validated tool widely used in psychiatric and neurocognitive research (19,20). The QPE was administered once daily between 08:00 and 11:00 a.m. on postoperative days 1–4, with a follow-up evaluation on day 7 either in person or by telephone, ensuring consistency across centers and minimizing circadian or sedation-related variability.

Each interview was conducted after the patient had regained full consciousness and hemodynamic stability. Data were recorded prospectively during patient care using structured digital forms. In addition to documenting the presence, frequency, and severity of hallucinations using the QPE subscales, observers recorded brief qualitative descriptions of the experiences for contextual interpretation. All interviewers trained medical students and interns received formal instruction from a certified psychiatrist on

recognizing psychotic symptoms, maintaining patient privacy, and communicating sensitively to prevent distress during interviews. These standardized procedures ensured the collection of ethical, accurate, and reproducible data across all participating centers.

Outcomes and Assessments

Postoperative visual and auditory hallucinations were the primary outcomes, assessed separately to reflect their distinct profiles. We utilized the Questionnaire for Psychotic Experiences (QPE), administered daily from postoperative days 1–4 by trained medical graduates, with follow-up through day 7 via clinical checks or phone. Hallucination severity was evaluated using the QPE's validated 4-item subscale (score range 0–20). The Arabic-translated QPE demonstrated good internal consistency (Cronbach's α = 0.86 for visual, 0.71 for auditory domains) (19). Positive QPE screens were communicated to the responsible bedside team on the same day of assessment. Clinical management (e.g., analgesia/sedation review, oxygenation optimization, delirium-prevention measures) was performed at the discretion of treating clinicians according to local protocols; the study did not mandate or standardize interventions. When hallucinations were accompanied by clinically significant distress, agitation, risk of device manipulation, or concern for self-harm, the research assessor immediately notified the attending team to consider psychiatry and/or neurology consultation per site policy. All notifications were documented in the medical record. **See eAppendix 1 in Supplement 1 file for further details.**

Electronic medical records and study variables:

Data were collected from electronic medical records using a standardized extraction form applied uniformly across all participating centers. The primary outcomes were the occurrence of postoperative visual and auditory hallucinations within seven days of surgery, as assessed by the Questionnaire for Psychotic Experiences (QPE). Each outcome was analyzed separately to reflect its distinct clinical and phenomenological profile. Predictor and covariate data were categorized as follows: **Demographic variables:** age, sex, and body mass index (BMI), **Medical history:** diabetes mellitus, hypertension, heart failure, chronic obstructive pulmonary disease (COPD), chronic kidney disease, recent myocardial infarction, endocarditis, extracardiac arteriopathy, and smoking or alcohol use, **Surgical characteristics:** procedure type (CABG or valve surgery), redo surgery, use of cardiopulmonary bypass, aortic cross-clamp and bypass times, left ventricular ejection fraction (LVEF), and operative duration, **Perioperative medications:** statins, vasopressors, inotropes, opioids (fentanyl, morphine, pethidine), immunosuppressive drugs, and antibiotics, **Laboratory variables:** hemoglobin, white blood cell count, creatinine, calcium, total protein, albumin, C-reactive protein (CRP), and **LDL/HDL ratio** , **Postoperative indicators:** mechanical ventilation duration, transfusion requirements, EuroSCORE II risk index, and length of ICU and hospital stay. All data fields were defined using uniform clinical criteria and verified by double entry to ensure completeness and reproducibility across study sites. **Data collection procedures:**

Following postoperative stabilization, participants were identified and approached in the Cardiac Care Units of ten hospitals across the West Bank. Once patients regained full awareness and were in a stable condition, they were informed about the study's purpose and procedures. Those who agreed to participate provided written consent before any assessment. Each patient underwent a one-time evaluation for visual and auditory hallucinations using the QPE, which has demonstrated

strong reliability in clinical settings. The interviews were conducted by a trained team of medical students who received focused instruction on administering the tool, applying infection prevention measures, and handling delicate psychological topics in a respectful and empathetic manner. To ensure the assessment was tailored to each patient's background, the team reviewed clinical and surgical information from the electronic medical records before the interview. One of the study's primary aims was to investigate whether there is a relationship between hyperlipidemia and the likelihood of experiencing postoperative hallucinations. For this reason, patients were categorized based on whether they had a history of hyperlipidemia. Data from the interviews was entered directly into a digital platform using a consistent and structured format. All entries were verified for accuracy through a double-checking process. Patients with incomplete records, language barriers, cognitive limitations, or a known psychiatric history were excluded from analysis. Hallucination assessments and time-to-event recording commenced only after informed consent, ensuring that no pre-consent data were included in the analysis.

Procedure details:

CABG and Valve Surgeries

All patients underwent either CABG or valve surgery, with surgical indications based on symptoms, imaging, and risk assessments. CABG was performed via median sternotomy under CPB with moderate hypothermia and cardioplegia. Valve surgeries followed standard CPB protocols, with valve selection individualized by age, comorbidities, and EuroSCORE II risk. Patients were monitored postoperatively in the ICU and screened for hallucinations using the QPE tool during the first postoperative week (23). Hyperlipidemia status was used to stratify patients for comparative neuropsychiatric outcome analysis. **See Supplement 1 File for detailed surgical protocols and monitoring strategies.**

Ethical considerations:

The study was approved by the institutional review boards (IRBs) of all ten participating centers. All participants provided written informed consent postoperatively in accordance with IRB-approved deferred-consent procedures for minimal-risk observational research. Patients were approached only after regaining consciousness and documented decisional capacity; when capacity was uncertain, consent was sought from a legally authorized representative or deferred until capacity returned. Screening was conducted consecutively across intensive care and step-down units, and each center used standardized daily approach windows (typically 08:00–12:00) to ensure uniform recruitment once patients were awake and medically stable. No research procedures occurred before consent, and participation could be declined or withdrawn at any time without affecting clinical care.

Statistical analysis:

All statistical analyses were conducted using STATA version 17. Statistical significance was defined as a two-tailed $p < 0.05$. Continuous variables were summarized as means ± standard deviations or medians with interquartile ranges (Q1–Q3), and categorical variables as counts and percentages. Between-group comparisons were performed using independent t-tests or Mann–Whitney U tests for continuous data, and χ^2 or Fisher's exact tests for categorical data.

The internal consistency of the Arabic-translated Questionnaire for Psychotic Experiences (QPE) used in this study was confirmed in prior validation work, with Cronbach's α values ranging from 0.70 to 0.75 across domains (19,20).

Kaplan–Meier survival analysis was used to estimate the cumulative incidence of postoperative visual and auditory hallucinations over a 7-day follow-up, stratified by lipid profile status (hyperlipidemic vs. normolipidemic). Univariate analyses were performed to identify potential predictors of hallucinations within each subgroup.

Covariates were selected *a priori* based on existing literature and clinical relevance (24–26), and variables with univariate $p < 0.10$ were included in multivariable Cox proportional hazards regression models to determine independent predictors. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported. The proportional hazards assumption was verified, and variance inflation factors (VIF < 2) confirmed the absence of multicollinearity. The analytic approach adhered to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines (20). All tests were two-sided, and a p-value < 0.05 was considered statistically significant.

Results

Table 1 presents a comparison between patients who developed postoperative visual hallucinations and those who did not, stratified by lipid status. Among hyperlipidemic patients, visual hallucinations were significantly associated with shorter postoperative mechanical ventilation duration [4.74 (2.98–6.50) vs. 6.21 (2.70–9.72) hours, p = 0.030], and a higher LDL/HDL ratio (3.52 ± 0.78 vs. 2.91 ± 0.69, p = 0.001). In contrast, the use of statins showed no significant difference (79.4% vs. 80.5%, p = 0.847). Among normolipidemic patients, hallucinations were associated with redo surgery (13.04% vs. 6.18%, p = 0.026), renal impairment (6.52% vs. 2.14%, p = 0.025), hemodialysis dependence (4.34% vs. 0.75%, p = 0.014), immunosuppressive drug use (6.52% vs. 1.01%, p = 0.002), and higher EuroSCORE II [4.24 (0.58–9.06) vs. 3.12 (2.32–3.92), p < 0.001]. The LDL/HDL ratio remained significantly elevated (2.88 ± 0.73 vs. 2.65 ± 0.66, p = 0.034), whereas ventilation duration was not statistically different [6.09 (2.03–10.15) vs.

5.38 (1.07–9.69), p = 0.309]. **For an expanded version of this comparison, including full laboratory and medication details, see eTable 1 in Supplement 1**

Table 1. Comparison of Clinical, Procedural, and Risk Parameters in Patients with and Without Postoperative Visual Hallucinations, Stratified by Lipid Status

Variable	Category	Hyperlipidemia n= 448			Normal lipid n=884		
		Visual hallucination n =63	No Visual hallucination n=385	P-value	Visual hallucination n= 92	No Visual hallucination n= 792	P-value
Demographic variables							
Age, years	Mean ± SD	60.61±7.09	60.56±8.96	0.968 [a]	57.01±12.81	27.68±11.54	0.607[a]
BMI, kg/m2	Mean ± SD	24.58±4.43	24.35±3.89	0.669[a]	23.63±2.93	23.77±4.25	0.756[a]
Gender	Male	42(66.6%)	296(76.8%)	0.152[b]	66(71.73%)	597(75.37%)	0.447[b]
Medical History							

Diabetes		39(61.9%)	237(61.55%)	0.889[b]	35(38.04%)	306(38.63%)	0.912[b]
Hypertension		32(50.7%)	206(53.50%)	0.797[b]	30(32.60%)	249(31.43%)	0.814[b]
NYHA class	1	54(85.7%)	343(89.09%)	0.839[b]	81(88.04%)	676(85.35%)	0.800[b]
	2	5(7.9%)	26(6.75%)		8(8.69%)	78(9.84%)	
	3	3(4.7%)	14(3.63%)		3(3.26%)	32(4.04%)	
	4	0(0.0%)	3(0.77%)		92(100%)	792(100%)	
Redo surgery		1(1.5%)	17(4.41%)	0.489[b]	12(13.04%)	49(6.18%)	0.026[b]
Extracardiac arteriopathy		9(14.2%)	65(16.88%)	0.717[b]	9(9.78%)	61(7.70%)	0.538[b]
Pulmonary disease		6(9.52%)	38(9.87%)	1.000[b]	9(9.78%)	76(9.59%)	1.000[b]
Active endocarditis		0(0.00%)	1(0.25%)	1.000[b]	1(1.08%)	10(1.26%)	1.000[b]
Critical preoperative state		7(11.11%)	51(13.24%)	0.839[b]	10(10.86%)	94(11.86%)	0.866[b]
Recent myocardial infarction		19(30.15%)	83(21.55%)	0.141[b]	16(17.39%)	132(16.66%)	0.883[b]

Type of Surgery	CABG	51(80.95%)	316(82.07%)	1.000[b]	64(69.56%)	566(71.46%)	0.716[b]
	Valve surgery	11(17.46%)	70(18.18%)		28(30.43%)	226(28.53%)	
Renal impairment		0(0.00%)	12(3.11%)	0.387[b]	6(6.52%)	17(2.14%)	0.025[b]
Hemodialysis-dependent		0(0.00%)	2(0.51%)	1.000[b]	4(4.34%)	6(0.75%)	0.014[b]
Cirrhosis		0(0.00%)	0(0.00%)	NA	0(0.00%)	2(0.25%)	1.000[b]
HIV		0(0.00%)	0(0.00%)	NA	0(0.00%)	1(0.12%)	1.000[b]
Alcohol abuse		0(0.00%)	2(0.51%)	1.000[b]	1(1.08%)	10(1.26%)	1.000[b]
Active Smoking		2(3.17%)	33(8.57%)	0.203[b]	10(10.86%)	92(11.61%)	1.000[b]
Immunosuppressive drugs		1(1.58%)	3(0.77%)	0.450[b]	6(6.52%)	8(1.01%)	0.002[b]
Previous use of antibiotics		2(3.17%)	21(5.45%)	0.755[b]	5(5.43%)	44(5.55%)	1.000[b]
Statin use n (%)		50 (79.4%)	310 (80.5%)	0.847b	N\A	N\A	N\A
Euroscore II, Mean ± SD		3.46 (1.54 –	3.32 (2.29 – 4.35)	0.573[c]	4.24 (0.58 – 9.06)	3.12 (2.32 – 3.92)	<0.001[c]

		5.38)					
Laboratory							
Hemoglobin, g/dL	Mean ± SD	11.64±0.60	11.73±1.02	0.521[a]	11.34±0.84	11.43±0.83	0.334[a]
WBC, cells/µL	Mean ± SD	7.42 ± 2.11	7.34 ± 2.09	0.524[a]	7.26 ± 2.08	7.40 ± 2.12	0.446[a]
Total protein, g\l	Mean ± SD	5.54±0.21	5.51±0.46	0.597[a]	2.64±0.80	2.47±0.93	0.103[a]
Albumin, g/l	Mean ± SD	3.58±0.05	3.57±0.25	0.743[a]	2.17±0.56	2.06±0.65	0.121[a]
Platelet, K/µL	Mean ± SD	128.41±39.20	128.08±51.72	0.961[a]	14559.62±45266.41	16523.33±57531.89	0.752[a]
C-reactive protein, mg/L	Mean ± SD	88.42±18.63	88.09±39.57	0.949[a]	100.67±27.78	102.89±30.04	0.499[a]
Creatinine, mg/dL	Mean ± SD	0.89±2.17	1.19±2.69	0.406 [a]	0.94±2.49	1.40±3.26	0.188[a]
Calcium, mg/dL	Mean ± SD	8.50±0.18	8.52±0.30	0.593[a]	8.56±0.36	8.54±0.29	0.449[a]
LDL/HDL ratio	Mean ± SD	3.52±0.78	2.91±0.69	**0.001a**	2.88±0.73	2.65±0.66	**0.034a**

Medication use							
Adrenalin		39(61.90%)	239(62.07%)	1.000[b]	33(35.86%)	334(42.17%)	0.246[b]
Noradrenaline		42(66.66%)	253(65.71%)	0.665[b]	58(63.04%)	498(62.87%)	0.975[b]
Vasopressin		1(1.58%)	7(1.81%)	1.000[b]	2(2.17%)	8(1.01%)	0.280[b]
Dobutamine		0(0.00%)	10(2.59%)	0.370[b]	8(8.69%)	23(2.90%)	0.011[b]
Intra-operative Fentanyl		54(85.71%)	310(80.51%)	0.225[b]	67(72.82%)	587(74.11%)	0.802[b]
Post-operative Fentanyl		16(25.39%)	84(21.81%)	0.511[b]	13(14.13%)	138(17.42%)	0.558[b]
Pethidine		28(44.44%)	170(44.15%)	0.891[b]	27(29.34%)	211(26.64%)	0.620[b]
Morphine		26(41.26%)	137(35.58%)	0.324[b]	40(43.47%)	368(46.46%)	0.587[b]
Procedural parameters							
Pump	Off	4(6.34%)	30(7.79%)	1.000[b]	7(7.60%)	61(7.70%)	1.000[b]
	On	58(92.06%)	356(92.46%)		85(92.39%)	731(92.29%)	

Surgery on the thoracic aorta		1(1.58%)	8(2.07%)	1.000[b]	5(5.43%)	17(2.14%)	0.069[b]
Cardiopulmonary bypass time, min	Mean ± SD	117.82±39.09	121.20±46.31	0.587[a]	117.38±40.48	115.44±43.87	0.686[a]
Aortic cross clamp time, min	Mean ± SD	83.07±35.99	87.20±39.31	0.438[a]	79.52±35.43	82.62±37.51	0.452[a]
Left ventricle ejection fraction, %	Mean ± SD	49.96±7.59	52.21±6.56	0.015[a]	52.92±5.90	52.63±6.61	0.685[a]
Pre-operative hospital stays, days	Mean ± SD	4.05±1.05	4.09±1.60	0.857[a]	4.37±2.20	3.86±2.08	0.09[a]
Post-operative complication							
Post-Operative Receiving a blood transfusion		5(7.93%)	30(7.79%)	1.000[b]	9(9.78%)	49(6.18%)	0.184[b]
Post-operative hospital	Mean ± SD	5.56±0.82	5.85±2.21	0.302[a]	6.26±2.99	5.96±3.17	0.398[a]

stays, days							
Post-operative Ventilation, hours	Median (Q1-Q3)	4.74 (2.98 – 6.50)	6.21 (2.70 – 9.72)	0.030[C]	6.09 (2.03 – 10.15)	5.38 (1.07 – 9.69)	0.309[C]

a. Is tested by in-dependent t-test. b. Is tested by Chi-square test. C. Is tested by Wilcoxon rank-sum (Mann–Whitney) test. BMI = Body Mass Index; LVEF = Left Ventricular Ejection Fraction; CPB = Cardiopulmonary Bypass; SD = Standard Deviation; HIV = Human Immunodeficiency Virus; ICU = Intensive Care Unit; CABG = Coronary Artery Bypass Grafting.

Table 2. Clinical, Procedural, and Risk Score Differences in Patients with and Without Postoperative Auditory Hallucinations Following Cardiac Surgery, Stratified by Lipid Profile Status

Table 2 presents clinical, procedural, and risk score differences in patients who developed postoperative auditory hallucinations compared to those who did not, stratified by lipid status. Among hyperlipidemic patients, auditory hallucinations were associated with a higher LDL/HDL ratio (3.61 ± 0.84 vs. 2.94 ± 0.71, p = 0.002), lower intraoperative fentanyl use (64.7% vs. 82.6%, p = 0.019), and shorter postoperative ventilation duration [4.11 (2.61–5.61) vs. 6.16 (2.73–9.59) hours, p = 0.020]. Additionally, these patients had higher C-reactive protein levels (18.82 ± 7.81 vs. 23.21 ± 12.58, p = 0.046) and more frequent critical preoperative states (26.5% vs. 11.8%, p = 0.028). Among normolipidemic patients, auditory hallucinations were associated with a higher EuroSCORE II [4.86 (1.07–10.79) vs. 3.12 (2.28–3.96), p < 0.001], a higher LDL/HDL ratio (2.91 ± 0.70 vs. 2.68 ± 0.65, p = 0.048), and longer cardiopulmonary

bypass and cross-clamp times (p = 0.031 and p = 0.047, respectively). Postoperative ventilation duration was not significantly different [4.27 (1.52–7.02) vs. 5.54 (1.17–9.91) hours, p = 0.142]. **Detailed subgroup analyses and additional laboratory parameters are provided in eTable 2 of Supplement 1**

Variable	Category	Hyperlipidemia n= 448			Normal lipid n=884		
		Auditory hallucination n= 34	No Auditory hallucination n= 414	P value	Auditory hallucination n= 58	No Auditory hallucination n= 826	P value
Demographic variables							
Age, years	Mean ± SD	57.87 ±9.52	60.79 ±8.62	0.060[a]	56.25 ±11.13	57.61 ±11.70	0.389[a]
BMI, kg/m2	Mean ± SD	24.92 ±4.43	24.34 ±3.92	0.409[a]	23.68 ±3.58	23.76 ±4.17	0.881[a]
Gender	Male	23 (67.6%)	315 (76.1%)	0.300[b]	47 (81.0%)	616 (74.5%)	0.346[b]
Medical History							

Diabetes		23 (67.6%)	253 (61.1%)	0.583[b]	26 (44.8%)	315 (38.2%)	0.330[b]
Hypertension		16 (47.1%)	222 (53.6%)	0.480[b]	16 (27.6%)	263 (31.8%)	0.561[b]
NYHA class	1	29 (85.3%)	368 (88.9%)	0.339[b]	50 (86.2%)	707 (85.6%)	0.92[b]
	2	2 (5.9%)	29 (7.0%)		6 (10.3%)	80 (9.7%)	
	3	2 (5.9%)	15 (3.6%)		2 (3.4%)	33 (4.0%)	
	4	1 (2.9%)	2 (0.5%)		0 (0%)	6 (0.7%)	
Redo surgery		1 (2.9%)	17 (4.1%)	1.000[b]	3 (5.2%)	58 (7.0%)	0.791[b]
Extracardiac arteriopathy		4 (11.8%)	70 (16.9%)	0.630[b]	7 (12.1%)	63 (7.6%)	0.211[b]
Pulmonary disease		3 (8.8%)	41 (9.9%)	1.000[b]	4 (6.9%)	81 (9.8%)	0.645[b]
Active endocarditis		0 (0.0%)	1 (0.2%)	1.000[b]	1 (1.7%)	10 (1.2%)	0.528
Critical preoperative state		9 (26.5%)	49 (11.8%)	0.028[b]	6 (10.3%)	98 (11.9%)	1.000[b]
Recent myocardial infarction		8 (23.5%)	94 (22.7%)	1.000[b]	9 (15.5%)	139 (16.8%)	1.000[b]

Type of Surgery	CABG	28 (82.4%)	339 (81.9%)	1.000[b]	46 (79.3%)	584 (70.7%)	0.179[b]
	Valve surgery	6 (17.6%)	75 (18.1%)		12 (20.7%)	242 (29.3%)	
Renal impairment		1 (2.9%)	11 (2.7%)	1.000[b]	1 (1.7%)	22 (2.7%)	1.000[b]
Hemodialysis-dependent		1 (2.9%)	1 (0.2%)	0.146[b]	1 (1.7%)	9 (1.1%)	0.495[b]
Cirrhosis		0 (0%)	0 (0%)	N/A[b]	0 (0%)	2 (0%)	1.000[b]
HIV		0 (0%)	0 (0%)	N/A[b]	0 (0%)	1 (0%)	1.000[b]
Alcohol abuse		1 (2.9%)	1 (0.2%)	0.146[b]	0 (0.0%)	11 (1.3%)	1.000[b]
Active Smoking		3 (8.8%)	32 (7.7%)	0.741[b]	4 (6.9%)	98 (11.9%)	0.392[b]
Immunosuppressive drugs		1 (2.9%)	3 (0.7%)	0.272[b]	2 (3.4%)	12 (1.5%)	0.233[b]
Previous use of antibiotics		5 (14.7%)	18 (4.3%)	0.023[b]	4 (6.9%)	45 (5.5%)	0.555[b]
Statin use n (%)		26 (76.4%)	330 (79.7%)	0.688b	N\A	N\A	N\A
Euroscore II, Mean ± SD		3.90 (0.91 – 6.89)	3.30 (2.40 –	0.057[C]	4.86 (1.07 –	3.12 (2.28 –	< 0.001[C]

			4.20)		10.79)	3.96)	
Laboratory							
Hemoglobin, g/dL	Mean ± SD	11.53 ± 1.23	11.58 ± 0.96	0.788[a]	11.47 ± 0.58	11.42 ± 0.85	0.712[a]
WBC, cells/µL	Mean ± SD	7.51 ± 2.03	7.39 ± 2.10	0.581[a]	7.29 ± 1.96	7.43 ± 2.15	0.498[a]
Total protein, g/l	Mean ± SD	5.51 ±0.00	5.51 ±0.45	1.000[a]	2.60 ±1.01	2.48 ±0.91	0.342[a]
Albumin, g/l	Mean ± SD	3.52 ±0.39	3.57 ±0.21	0.194[a]	2.10 ±0.73	2.07 ±0.64	0.732[a]
Platelet, K/µL	Mean ± SD	129.53 ± 66.00	130.82 ± 48.73	0.886[a]	126.23 ± 39.61	133.63 ± 50.15	0.271[a]
C-reactive protein, mg/L	Mean ± SD	18.82 ±7.81	23.21 ±12.58	0.046 [a]	32.14 ±7.84	35.07 ±31.34	0.478[a]
Creatinine, mg/dL	Mean ± SD	1.29 ±2.84	1.14 ±2.61	0.738[a]	1.12 ±2.45	1.37 ±3.24	0.571[a]
Calcium, mg/dL	Mean ± SD	8.52 ±0.29	8.52 ±0.29	0.913[a]	8.54 ±0.23	8.54 ±0.30	0.965[a]
LDL/HDL ratio	Mean ± SD	3.61±0.84	2.94±0.71	**0.002a**	2.91±0.70	2.68±0.65	**0.048a**

Medication use							
Adrenalin		17 (50.0%)	261 (63.0%)	0.144[b]	26 (44.8%)	341 (41.3%)	0.680[b]
Noradrenaline		25 (73.5%)	271 (65.5%)	0.451[b]	39 (67.2%)	517 (62.6%)	0.574[b]
Vasopressin		1 (2.9%)	7 (1.7%)	0.471[b]	1 (1.7%)	9 (1.1%)	0.495[b]
Dobutamine		0 (0.0%)	10 (2.4%)	1.000[b]	2 (3.4%)	29 (3.5%)	1.000[b]
Intra-operative Fentanyl		22 (64.7%)	342 (82.6%)	0.019[b]	42 (72.4%)	612 (74.1%)	0.758[b]
Post-operative Fentanyl		7 (20.6%)	93 (22.5%)	1.000[b]	11 (19.0%)	140 (17.0%)	0.718[b]
Pethidine		13 (38.2%)	185 (44.7%)	0.591[b]	14 (24.1%)	224 (27.1%)	0.759[b]
Morphine		11 (32.4%)	152 (36.7%)	0.712[b]	27 (46.6%)	381 (46.1%)	1.000[b]
Procedural parameters							
Pump	Off	12 (35.3%)	131 (31.6%)	0.703[b]	23 (39.7%)	331 (40.1%)	1.000[b]
	On	22 (64.7%)	283 (68.4%)		35 (60.3%)	495 (59.9%)	

Surgery on the thoracic aorta		2 (5.9%)	7 (1.7%)	0.144[b]	4 (6.9%)	18 (2.2%)	0.050[b]
Cardiopulmonary bypass time, min	Mean ± SD	112.47 ±38.01	121.41 ±45.88	0.270[a]	103.71 ±41.08	116.48 ±43.57	0.031[a]
Aortic cross clamp time, min	Mean ± SD	78.69 ±33.71	87.28 ±39.21	0.216[a]	72.90 ±35.59	82.96 ±37.34	0.047[a]
Left ventricle ejection fraction, %	Mean ± SD	53.43 ±5.22	51.78 ±6.85	0.170[a]	53.75 ±5.71	52.58 ±6.59	0.189[a]
Pre-operative hospital stays, days	Mean ± SD	3.73 ±1.13	4.11 ±1.56	0.164[a]	4.16 ±1.98	3.90 ±2.10	0.355[a]
Post-operative complication							
Post-Operative Receiving blood transfusion		4 (11.8%)	31 (7.5%)	0.325[b]	2 (3.4%)	56 (6.8%)	0.421[b]
Post-operative hospital stays, days	Mean ± SD	5.78 ±1.43	5.81 ±2.12	0.938[a]	5.87 ±1.73	6.00 ±3.23	0.767[a]
Post-operative Ventilation,	Median (Q1-	4.11 (2.61 – 5.61)	6.16 (2.73 –	0.020[C]	4.27 (1.52 –	5.54 (1.17 –	0.142[C]

hours	Q3)		9.59)		7.02) [C]	9.91) [C]	

a. **Is tested by in-dependent t-test. b. Is tested by Chi-square test. C. Is tested by Wilcoxon rank-sum (Mann–Whitney) test. BMI = Body Mass Index; LVEF = Left Ventricular Ejection Fraction; CPB = Cardiopulmonary Bypass; SD = Standard Deviation; ICU = Intensive Care Unit; CABG = Coronary Artery Bypass Grafting; HDL = High-Density Lipoprotein.**

Figure 2. Kaplan–Meier Estimates of Visual (A) and Auditory (B) Hallucinations Stratified by Hyperlipidemia

Figure 2A. Kaplan–Meier Estimates of Visual Hallucinations by Hyperlipidemia Status

This Kaplan–Meier plot shows the cumulative incidence of visual hallucinations over the first 7 postoperative days among 448 hyperlipidemic and 884 non-hyperlipidemic patients undergoing cardiac surgery. By day 7, 411 hyperlipidemic and 811 non-hyperlipidemic patients remained at risk. The cumulative incidence of visual hallucinations reached approximately 11.2% in the hyperlipidemia group compared to 10.3% in the non-hyperlipidemia group. Although the curves demonstrate a marginally elevated incidence among hyperlipidemic patients, the trajectories remained parallel, indicating no statistically significant difference between the groups in early postoperative visual hallucination risk.

Figure 2 B. Kaplan–Meier Estimates of Auditory Hallucinations by Hyperlipidemia Status.

This panel presents the 7-day cumulative incidence of auditory hallucinations in the same hyperlipidemic (n = 448) and non-hyperlipidemic (n = 884) cohorts. By the seventh postoperative day, 424 hyperlipidemic and 838 non-hyperlipidemic patients remained at risk. The cumulative incidence was 7.1% for hyperlipidemic and 6.3% for non-hyperlipidemic patients. Both groups displayed closely overlapping trajectories, suggesting no meaningful association between lipid status and early postoperative auditory hallucinations.

Figure 2A. Kaplan–Meier Estimates of Visual Hallucinations by Hyperlipidemia Status

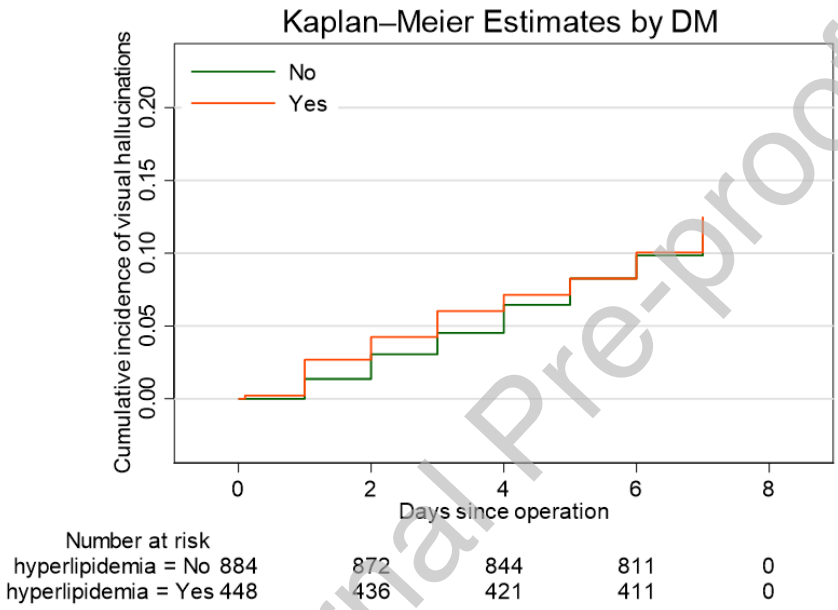
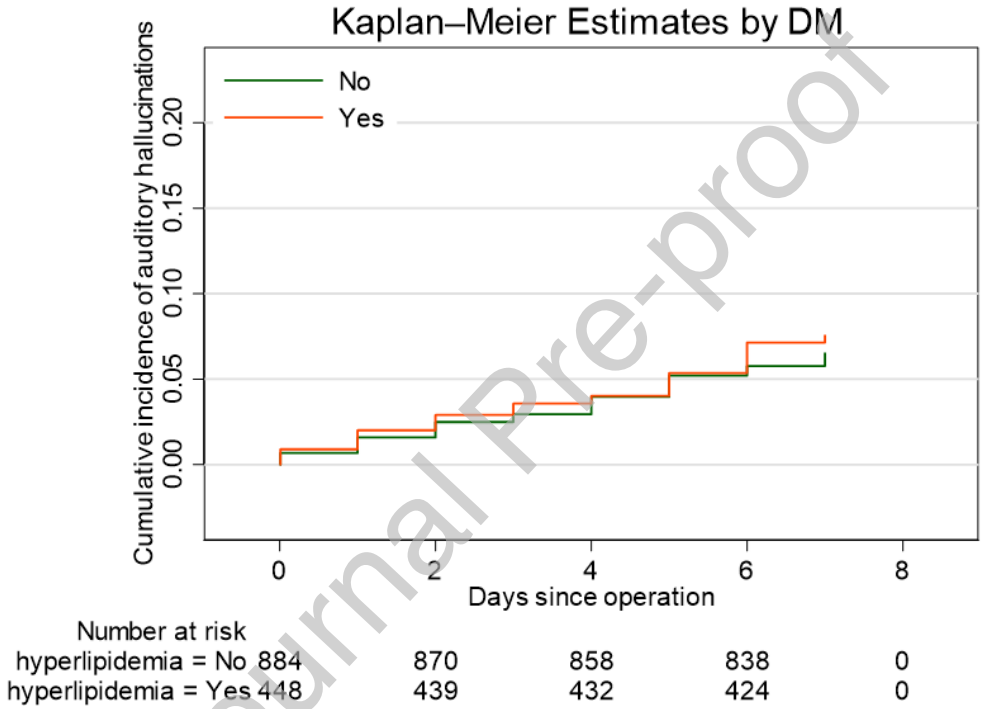


Figure 2 B. Kaplan–Meier Estimates of Auditory Hallucinations by Hyperlipidemia Status



Comprehensive descriptive characteristics of hallucinations, including frequency, duration, emotional valence, distress, and functional impact, **are summarized in eTable 3 of Supplement 1**

Table 3. Multivariate and Univariate Cox Regression Analyses of Predictors of Postoperative Visual and Auditory Hallucinations in Hyperlipidemic Patients Undergoing Coronary Artery Bypass Grafting or Valve Surgery

	Cohort A: Hyperlipidemic Cohort							
	Visual				Auditory			
Predictors	**Crude HR(%95CI)**	**Crude P VALUE**	**adjusted HR(%95CI)**	**adjusted P VALUE**	**Crude HR(%95CI)**	**Crude P VALUE**	**adjusted HR(%95CI)**	**adjusted P VALUE**
Age, years	0.9919 (0.9632–1.0216)	0.590	0.9971 (0.9670–1.0282)	0.855	0.9664 (0.9322–1.0018)	0.063	0.9689 (0.9324–1.0069)	0.107
BMI, kg/m2	0.9788	0.536	0.9494	0.188	1.0343	0.403	0.9797	0.698

	(0.9146–1.0476)		(0.8786–1.0258)		(0.9557–1.1193)		(0.8830–1.0869)	
Gender	1.6161 (0.9294–2.8100)	0.089	1.4964 (0.8077–2.7722)	0.200	1.5134 (0.7377–3.1047)	0.258	1.7519 (0.7973–3.8492)	0.163
Redo surgery	0.8991 (0.2192–3.6878)	0.881	0.8810 (0.2047–3.7907)	0.865	0.7370 (0.1008–5.3888)	0.752	0.6089 (0.0765–4.8443)	0.639
Type of Surgery	1.1189 (0.5787–2.1632)	0.738	1.4478 (0.6878–3.0479)	0.330	0.9777 (0.4048–2.3613)	0.960	1.1799 (0.4467–3.1166)	0.738
Cardiopulmonary bypass time, min	0.9973 (0.9913–1.0033)	0.373	0.9942 (0.9877–1.0007)	0.082	0.9957 (0.9880–1.0035)	0.278	1.0000 (0.9893–1.0109)	0.999
Aortic cross clamp time, min	1.0057 (0.9998–	0.060	**1.0070 (1.0014–**	**0.015**	0.9942 (0.9848–	0.228	0.9956 (0.9831–	0.496

	1.0116)		**1.0127)**		1.0037)		1.0083)	
Left ventricle ejection fraction, %	**1.0592 (1.0098–1.1110)**	**0.018**	1.0469 (0.9990–1.0971)	0.055	1.0411 (0.9823–1.1035)	0.175	1.0300 (0.9740–1.0892)	0.299
Critical preoperative state	0.4957 (0.1793–1.3705)	0.176	0.7168 (0.2548–2.0169)	0.528	**2.4652 (1.1507–5.2815)**	**0.020**	**3.9036 (1.7292–8.8122)**	**0.001**
Previous use of antibiotics	1.5199 (0.5497–4.2025)	0.420	0.8230 (0.2715–2.4950)	0.731	**3.2833 (1.2708–8.4825)**	**0.014**	1.7343 (0.5628–5.3438)	0.338
Intra-operative Fentanyl	**0.4194 (0.2412–0.7293)**	**0.002**	**0.4345 (0.2288–0.8252)**	**0.011**	**0.4109 (0.2034–0.8303)**	**0.013**	**0.3773 (0.1630–0.8736)**	**0.023**
Post-operative Ventilation, hours	**0.8829 (0.8005–**	**0.013**	**0.8430 (0.7529–**	**0.003**	**0.7933 (0.6907–**	**0.001**	**0.7348 (0.6235–**	**<0.001**

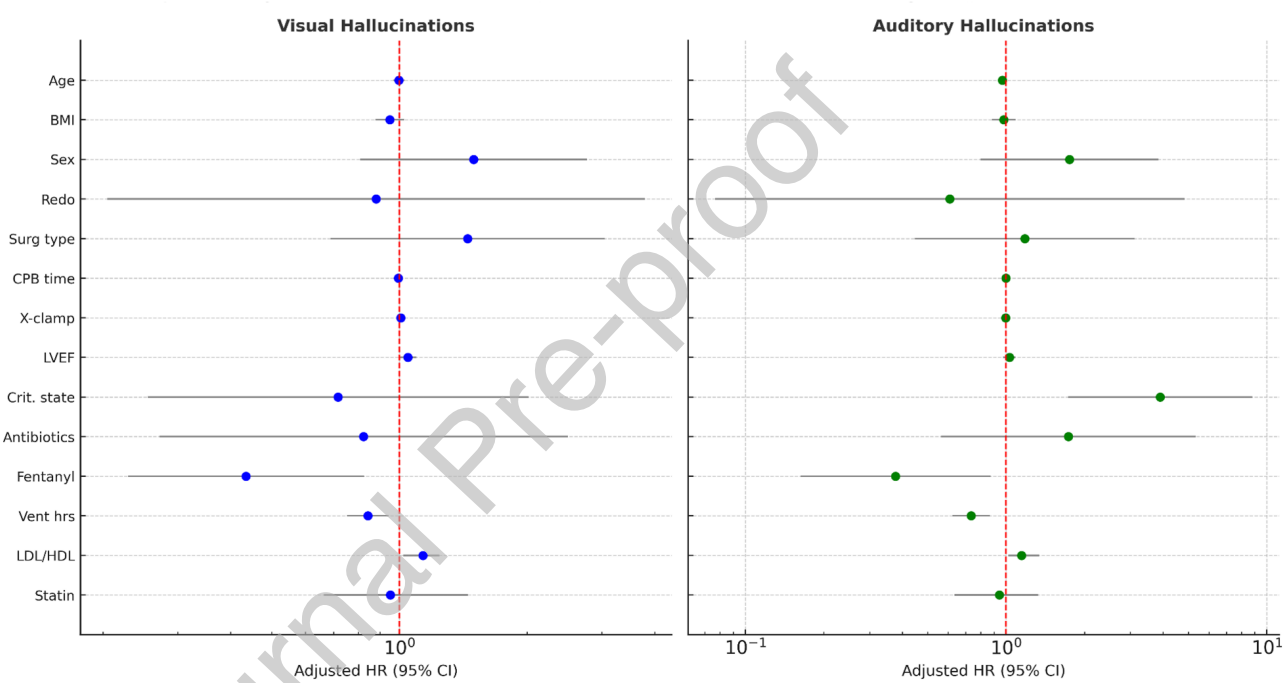
	0.9737)		**0.9439)**		**0.9112)**		**0.8660)**	
LDL/HDL ratio	1.632 (1.0512–1.2649)	**0.003**	1.1364 (1.0211–1.2428)	**0.016**	1.543 (1.0512–1.2749)	**0.002**	1.1464 (1.0211–1.3428)	**0.017**
Statin use	0.9141 (0.6213–1.3442)	0.647	0.9524 (0.6635–1.4496)	0.742	0.9141 (0.6213–1.3442)	0.647	0.9424 (0.6335–1.3296)	0.642

HR = Hazard Ratio; CI = Confidence Interval; BMI = Body Mass Index; CPB = Cardiopulmonary Bypass; LVEF = Left Ventricular Ejection Fraction.

Table 3 and Figure 3 present the results of univariate and multivariate Cox proportional hazards regression analyses evaluating predictors of postoperative visual and auditory hallucinations in hyperlipidemic patients (Cohort A) undergoing coronary artery bypass grafting (CABG) or valve surgery. After adjustment for potential confounders, several variables emerged as significant independent predictors. Notably, longer aortic cross-clamp time was associated with a higher risk of visual hallucinations (adjusted HR 1.007; 95% CI 1.001–1.013; p = 0.015), reinforcing the role of cerebral hypoperfusion in visual sensory disturbances. Intra-operative fentanyl use demonstrated a protective effect against both visual (adjusted HR 0.435; p = 0.011) and auditory hallucinations (adjusted HR 0.377; p = 0.023), suggesting that insufficient analgesia may predispose to postoperative perceptual disturbances. Similarly, longer postoperative mechanical ventilation was independently associated with a lower risk of hallucinations—visual (adjusted HR 0.843; p

= 0.003) and auditory (adjusted HR 0.735; $p < 0.001$), which may reflect smoother recovery dynamics and reduced sedative-related neurotoxicity. Importantly, the LDL/HDL ratio emerged as a robust metabolic predictor. A higher ratio significantly increased the risk of both visual (adjusted HR 1.136; $p = 0.016$) and auditory hallucinations (adjusted HR 1.146; $p = 0.017$), implicating dysregulated lipid balance as a potential biomarker of neuropsychiatric vulnerability in cardiac surgical patients. In contrast, statin use was not significantly associated with either outcome (visual: $p = 0.742$; auditory: $p = 0.642$), suggesting that baseline lipid control, rather than pharmacologic treatment alone, may play a more critical role in perioperative neuroprotection. Redo surgery was included as a covariate in the multivariable Cox models; however, it did not demonstrate an independent association with either visual or auditory hallucinations after adjustment (adjusted $p > 0.05$). Finally, the critical preoperative state remained a strong independent predictor of auditory hallucinations (adjusted HR 3.904; $p = 0.001$), underscoring the additive effect of systemic instability on neurocognitive sequelae. **Associations between visual hallucination severity scores and categorical variables are detailed in eTable 4, while correlations with continuous parameters are shown in eTable 6 of Supplement 1**

Figure 3: Forest Plot for Adjusted Predictors of Postoperative Hallucinations in Hyperlipidemic Patients (Cohort A)



Abbreviations: BMI = Body Mass Index; CPB = Cardiopulmonary Bypass; X-clamp = Aortic Cross-Clamp Time; LVEF = Left Ventricular Ejection Fraction; Crit. state = Critical Preoperative State; Vent hrs = Postoperative Ventilation Hours.

Table 4. Multivariate and Univariate Cox Regression Analyses of Predictors of Postoperative Visual and Auditory Hallucinations in Non-Hyperlipidemic Patients Undergoing Coronary Artery Bypass Grafting or Valve Surgery

	Cohort B: Non-Hyperlipidemic cohort							
	Visual				**Auditory**			
Predictors	**Crude HR(%95CI)**	**Crude P VALUE**	**adjusted HR(%95CI)**	**adjusted P VALUE**	**Crude HR(%95CI)**	**Crude P VALUE**	**adjusted HR(%95CI)**	**adjusted P VALUE**
Age, years	1.0079 (0.9900–1.0261)	0.389	1.0148 (0.9956–1.0343)	0.131	0.9919 (0.9714–1.0128)	0.443	0.9856 (0.9623–1.0094)	0.233
BMI, kg/m2	0.9534 (0.8962–1.0143)	0.131	0.9546 (0.8963–1.0167)	0.148	0.9954 (0.9327–1.0623)	0.889	1.0056 (0.9407–1.0750)	0.870
Gender	0.9535 (0.6021–1.5099)	0.839	0.9524 (0.5850–1.5506)	0.845	0.6886 (0.3571–1.3275)	0.265	0.6770 (0.3308–1.3855)	0.286

Pre-operative hospital stays, days	1.0453 (0.9911–1.1025)	0.103	1.0450 (0.9861–1.1073)	0.137	1.0385 (0.9611–1.1222)	0.339	1.0106 (0.9168–1.1141)	0.832
Type of Surgery	0.9687 (0.6255–1.5002)	0.887	0.9570 (0.5770–1.5870)	0.865	0.6456 (0.3420–1.2186)	0.177	0.6183 (0.2915–1.3118)	0.210
Redo surgery	1.8132 (0.9688–3.3938)	0.063	1.9231 (0.9818–3.7669)	0.057	0.7281 (0.2278–2.3272)	0.592	0.4700 (0.1174–1.8818)	0.286
Renal impairment	2.0959 (0.8525–5.1529)	0.107	0.8113 (0.1076–6.1168)	0.839	0.6558 (0.0908–4.7359)	0.676	0.0787 (0.0027–2.2524)	0.137
Hemodialysis-dependent	4.2511 (1.5629–11.5628)	**0.005**	5.9943 (0.5912–60.7803)	0.130	1.5898 (0.2201–11.4815)	0.646	2.4077 (0.1761–32.8920)	0.492
immunosuppressive drugs	2.9150	**0.036**	1.4322	0.575	2.3709	0.230	2.3888	0.370

	(1.0717–7.9282)		(0.4086–5.0201)		(0.5785–9.7161)		(0.3562–16.0209)	
Euroscore II, Mean ± SD	1.0581 (1.0274–1.0898)	**<0.001**	1.0334 (0.9981–1.0700)	0.064	1.0803 (1.0478–1.1137)	**<0.001**	1.1104 (1.0568–1.1666)	**<0.001**
Dobutamine	0.5546 (0.1368–2.2495)	0.409	0.5674 (0.1367–2.3545)	0.435	1.0048 (0.2452–4.1175)	0.995	1.2149 (0.2930–5.0376)	0.788
Cardiopulmonary bypass time, min	0.9966 (0.9920–1.0013)	0.155	0.9975 (0.9899–1.0052)	0.528	0.9933 (0.9872–0.9994)	**0.031**	0.9967 (0.9867–1.0068)	0.521
Aortic cross clamp time, min	0.9958 (0.9903–1.0012)	0.128	0.9983 (0.9895–1.0072)	0.707	0.9928 (0.9856–1.0000)	**0.049**	0.9958 (0.9840–1.0077)	0.484
Left ventricle ejection fraction, %	0.9899 (0.9613–	0.499	0.9871 (0.9585–	0.388	1.0273 (0.9858–	0.200	1.0230 (0.9803–	0.296

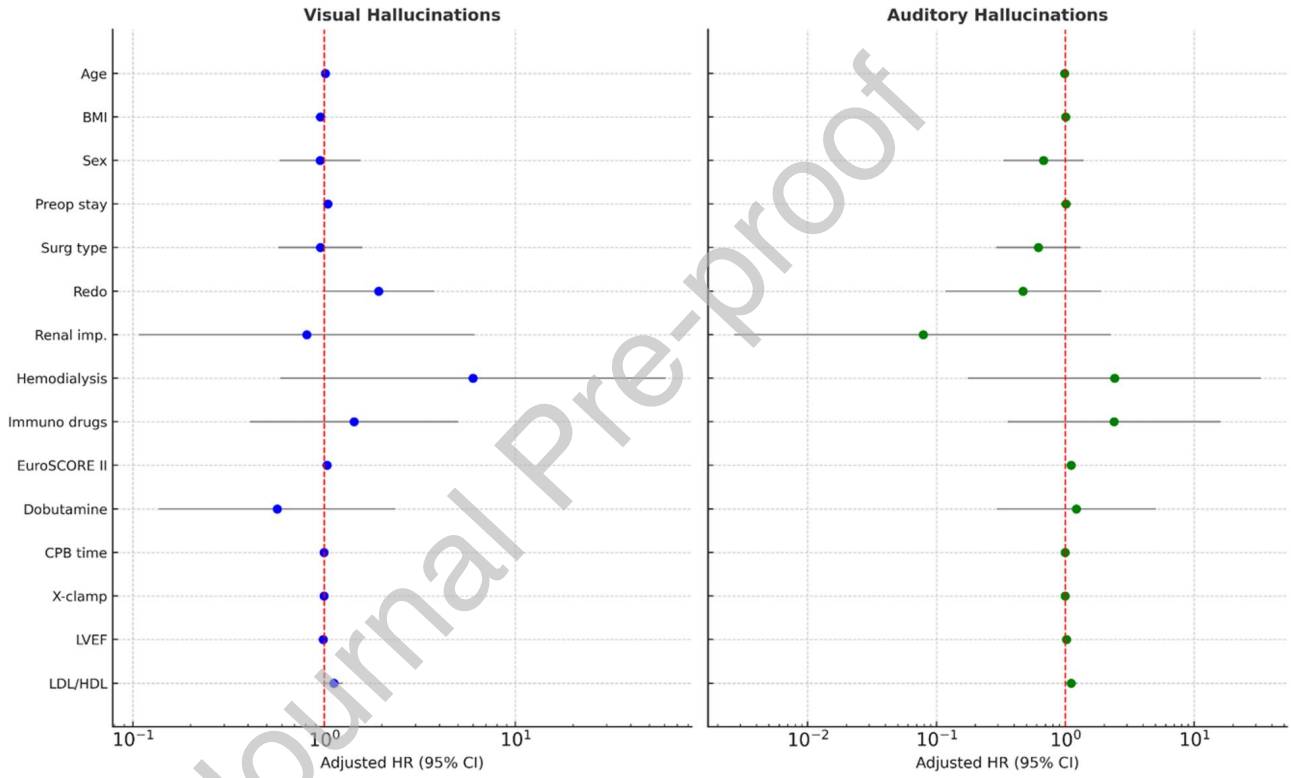
	1.0194)		1.0166)		1.0706)		1.0675)	
LDL/HDL ratio	1.1416 (1.0294–1.2655)	**0.012**	1.1228 (1.0052–1.2546)	**0.038**	1.1289 (1.0173–1.2531)	**0.019**	1.1101 (1.0012–1.2305)	**0.047**

HR = Hazard Ratio; CI = Confidence Interval; BMI = Body Mass Index; LVEF = Left Ventricular Ejection Fraction; CPB = Cardiopulmonary Bypass.

Table 4 and Figure 4 present the results of univariate and multivariate Cox proportional hazards regression analyses assessing predictors of postoperative visual and auditory hallucinations in patients without hyperlipidemia undergoing coronary artery bypass grafting (CABG) or valve surgery. In the crude models, several variables emerged as significant, though many did not retain statistical significance after adjustment. Hemodialysis dependence was strongly associated with visual hallucinations in the univariate model (HR: 4.2511; 95% CI: 1.5629–11.5628; p = 0.005), but this association was attenuated and lost significance in the adjusted analysis. Similarly, immunosuppressive drug use was linked to visual hallucinations in the crude model (HR: 2.9150; p = 0.036), but not after multivariable adjustment (p = 0.575). EuroSCORE II, a composite surgical risk score, demonstrated a robust association with auditory hallucinations in both univariate and multivariate models (adjusted HR: 1.1104; 95% CI: 1.0568–1.1666; p < 0.001), suggesting that higher perioperative risk may predispose individuals to postoperative neuropsychiatric complications. The association with visual hallucinations (adjusted HR: 1.0334; p = 0.064) approached significance but did not meet the threshold. Operative time variables,

including cardiopulmonary bypass (CPB) and aortic cross-clamp times, were inversely associated with auditory hallucinations in the univariate models (CPB time: HR: 0.9933; p = 0.031; cross-clamp time: HR: 0.9928; p = 0.049), though these effects did not persist in adjusted analyses, suggesting potential confounding. Redo surgery was included as a covariate in the multivariable Cox models; however, it did not demonstrate an independent association with either visual or auditory hallucinations after adjustment (adjusted p > 0.05). Importantly, the LDL/HDL ratio emerged as a novel and consistent independent predictor of both visual and auditory hallucinations. In the adjusted models, higher LDL/HDL ratios were significantly associated with increased risk of visual hallucinations (adjusted HR: 1.1228; 95% CI: 1.0052–1.2546; p = 0.038) and auditory hallucinations (adjusted HR: 1.1101; 95% CI: 1.0012–1.2305; p = 0.047). **This finding highlights a potential link between dysregulated lipid profiles, even within a clinically "normal" range, and neurocognitive vulnerability following cardiac surgery. For corresponding analyses of auditory hallucination severity, refer to eTables 5 and 7 in Supplement 1**

Figure 4: Forest Plot for Adjusted Predictors of Postoperative Hallucinations in Non-Hyperlipidemic Patients (Cohort B)



Abbreviations: BMI = Body Mass Index; CPB = Cardiopulmonary Bypass; X-clamp = Aortic Cross-Clamp Time; LVEF = Left Ventricular Ejection Fraction; Crit. state = Critical Preoperative State; Vent hrs = Postoperative Ventilation Hours; EuroSCORE II = European System for Cardiac Operative Risk Evaluation II.

The overall distribution of hallucination severity across lipid groups is illustrated in eFigure 1 of Supplement 1

Discussion

This multicentre prospective cohort study aimed to evaluate the impact of hyperlipidemia on the incidence of postoperative visual and auditory hallucinations in patients undergoing cardiac surgery. Key predictors of hallucinations varied between patients with and without hyperlipidemia. In hyperlipidemic patients, longer aortic cross-clamp time significantly increased the risk of visual hallucinations, While Intraoperative fentanyl use was protective, reducing the risk of visual and auditory hallucinations. The LDL/HDL ratio was a robust metabolic predictor, raising the risk of both hallucination types. A critical preoperative state heightened the risk of auditory hallucinations. In non-hyperlipidemic patients, EuroSCORE II and LDL/HDL ratio remained significant predictors, underscoring lipid imbalance as a key factor in neuropsychiatric vulnerability post-surgery.

Hallucinations Within the Spectrum of Delirium: Conceptual and Diagnostic Overlap

According to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), delirium is classified as a neurocognitive disorder marked by acute disturbances in attention, awareness, and cognition. Perceptual disturbances, most notably visual hallucinations, are included among its core features. These hallucinations are particularly prevalent in the hyperactive subtype of delirium and can be seen in up to 27% of affected individuals, underscoring their diagnostic and clinical relevance(31). While delirium can be triggered by a range of factors, such as alcohol withdrawal or medication effects, hallucinations are not exclusive to delirium and may also present independently in primary psychiatric illnesses like schizophrenia. Thus, while hallucinations may be a component of delirium, they can also occur in isolation, necessitating careful differential diagnosis and contextual evaluation in the postoperative setting.

In this prospective study, we stratified our patients according to their lipid profile, as we hypothesized that lipids may play a role in the pathogenesis of postoperative hallucinations through hypoxia-related mechanisms. We presumed that pathologic lipid states possibly make patients vulnerable to neuropsychiatric disturbances by biologically plausible mechanisms, primarily by amplifying hypoxia-induced neuronal injury. Hyperlipidemia has been associated with impaired cerebral autoregulation, oxidative stress, and microvascular dysfunction, all capable of increasing hypoxic susceptibility postoperatively.

In order to evaluate this hypothesis, we employed Kaplan–Meier survival analysis to track the cumulative incidence of visual and auditory hallucinations over the initial 7 postoperative days. The curves reflected moderately higher rates of both visual (11.2%)

and auditory (7.1%) hallucinations within the hyperlipidemic versus non-hyperlipidemic group (10.3% and 6.3%, respectively). Nevertheless, lines of the Kaplan–Meier curve remained parallel, such that differences were not discovered to be statistically significant early postoperatively. Although no significant difference existed, this trend provides evidence to pursue further investigation into metabolic status and postoperative neurocognitive function. In particular, the slightly elevated incidence in hyperlipidemic patients supports its potential role as a metabolic risk factor for postoperative hallucinations.(32)

Hypoxia has long figured in the description of the pathogenesis of postoperative hallucinations. Girard et al.(33) found that postoperative ICU delirium, traditionally associated with oxygen deficiency, possessed predictive value for long-term cognitive impairment, with an adjusted OR = 9.1 (95% CI: 2.3–35.8); however, they did not report a specific cumulative incidence for hallucinations or delirium. The implicated mechanism entails impaired oxygen delivery to key areas like the occipital cortex and basal ganglia, involved in processing visual information and awareness. (Tschernatsch et al.)(34), however, reported no statistical significance between the duration of mechanical ventilation and hallucinations ($p > 0.05$), uncovering that the duration itself may not be adequate in accounting for hypoxic susceptibility, given that confounders such as the depth of sedation and perfusion pressure were not adjusted for. Nevertheless, these findings reinforce the role of hypoxia, which may be exacerbated in hyperlipidemic patients due to atherosclerosis-related impairment in oxygen delivery.(35)

We stratified patients according to their lipid profiles to explore whether hyperlipidemia increases vulnerability to postoperative hallucinations through specific biological mechanisms. We hypothesize that lipids may amplify hypoxia-induced neurological injury, predisposing patients to perceptual disturbances. Notably, hyperlipidemic patients are more susceptible to hypoxic damage than non-hyperlipidemic individuals due to compounded vascular and metabolic dysfunction.

Mechanistically, three interlinked pathways account for this increased sensitivity. Firstly, cerebral autoregulation is disrupted by atherosclerosis associated with hyperlipidemia, particularly at watershed sites, thus diminishing oxygen supply to brain sites responsible for perception and cognition (Kazmierski et al.) (36). Secondly, hyperlipidemia enhances oxidative stress, producing cytotoxic lipid peroxidation products like 4-hydroxynonenal (4-HNE), which impair mitochondrial activity, diminish ATP synthesis, and evoke neuronal apoptosis—processes that enhance hypoxic damage (Galam et al.)(37). Thirdly, endothelial dysfunction and neuroinflammatory responses associated with hyperlipidemic states further compromise the blood-brain barrier and stimulate glial cells that can further enhance neuronal excitability under hypoxia. Overall, these synergistic actions predispose to postoperative neuropsychiatric symptoms, especially hallucinations.

This hypothesis is supported by IPDACS studies, which found that postoperative hypoxia was an independent risk indicator for delirium with 16.3% cumulative incidence and elevated risk within vulnerable subgroups (38).The oxidative damage caused by 4-

HNE has also been shown to disrupt mitochondrial metabolism under stress conditions with suspected synergism occurring when lipid toxicity is present with hypoxia (37). The findings offer a plausible biological rationale for elevated postoperative hallucinations within hyperlipidemic patients.

Systemic inflammation after cardiopulmonary bypass is yet another important mechanism. Shan et al.(39) revealed that the highest quartile of postoperative NLR significantly increased the risk of delirium (OR = 1.99; 95% CI: 1.41–2.84), with a reported incidence of 27%. This is of particular relevance to hyperlipidemic patients, in whom a chronic pro-inflammatory state is already present prior to surgery(40). The cumulative inflammatory burden, when combined with surgical stress, may act synergistically to potentiate neurocognitive impairment.Chronic low-grade inflammation in hyperlipidemic patients might precondition microglial cells for an excessive cytokine release by reducing the perceptual disturbance threshold(41). Conversely, Staicu et al. (42) reported increased IL-6 and NLR in delirious patients without detecting adjusted statistical significance, highlighting the confounding role of other perioperative factors. Nevertheless, their findings do not preclude the influence of lipid-driven inflammation, particularly when considered in the broader context of chronic metabolic imbalance that primes the central nervous system toward excitability(43). These results represent examples of how preoperative inflammatory conditions, possibly lipid-metabolic in origin, interact with surgical stress to enhance the risk of neurocognitive disturbance.

Lipid toxicity comes in as the third mechanism. Wang et al. (44)suggested that high LDL-C was significantly associated with delirium (OR = 1.47; 95% CI: 1.25–1.73; $p = 3.92 \times 10^{-6}$), suggesting a direct metabolic pathway in the determination of the excitability of the neurons and blood–brain barrier integrity. The reported incidence of delirium was 22%. Importantly, the statistical significance of this association strengthens the argument that hyperlipidemia itself—not just indirect hypoxia—can independently contribute to postoperative neurocognitive dysfunction(45). The mechanism would therefore be through that of oxidative stress, mitochondrial functional defect, and excitotoxicity processes, all germane to the pathogenesis of hallucination. To the contrary, however, Wu et al.(46) suggested that HDL-C was protective (unadjusted OR = 0.71), although after adjustment by multiple variables, this did not achieve significance ($p > 0.05$), perhaps due to confounders such as medication use or burden of comorbid disease. The imbalance between the protective and toxic lipid fractions may thus propel the brain to a fragile place, especially in the added burden of surgery.

By employing a two-cohort approach, we aimed to isolate the effect of hyperlipidemia on the risk of hallucinations. The higher cumulative incidence of hallucinations observed across all three mechanisms in the hyperlipidemic group supports the hypothesis that lipid abnormalities may enhance susceptibility through synergistic physiological insults.

At first, according to Table 3, cardiopulmonary bypass time was marginally associated with visual hallucinations in the adjusted model, but it didn't reach statistical significance. Furthermore, the crude model showed no association with the auditory hallucinations, and no relationship was found. Ottens TH et al. (2)found also that longer cardiopulmonary bypass time was linked to postoperative visual

hallucinations in the univariate model, but the association disappeared in multivariable analyses. However, Brondén et al. reveal that the distribution of lipid microemboli in the blood would affect various organs in the body, including the brain, during cardiopulmonary bypass (CPB) surgeries. This phenomenon depends on the vascular network and capillary morphology and is exacerbated with hyperlipidemia. The brain is found to show lower levels of lipid microemboli compared to other organs. The highest levels are found in the cerebrum, especially in the gray matter that is involved in cognitive functions(47).

Furthermore, Mihalj et al. suggest that cardiopulmonary bypass time marginally affects plasma levels of HDL-C. HDL-C is more influenced by the type of cardiopulmonary bypass system, temperature, and overall surgery time.(48)

An increase in aortic cross-clamp time will slightly increase the risk of visual hallucinations. The reason behind this is likely due to the effect of microemboli, altered cerebral perfusion, and neuroinflammatory damage. Following visual hallucinations, our study found that the increase in Left Ventricular Ejection Fraction was also related, with crude HR=1.059 and p value =0.018, but became non-significant after adjustment (p=0.055). However, Ogawa et al. show that LVEF and cerebrovascular reserve capacity are

related, suggesting that a decline in LVEF might contribute to cognitive dysfunction. Additionally, they noted the effect of elevated aortic cross-clamp time on increased neuroinflammation and fluid shift. Lastly, Ogawa et al. emphasize that the spread of lipid microemboli can induce brain damage, leading us to conclude that these factors could exacerbate the effects of prolonged aortic cross-clamp time and altered LVEF on cognitive function. (49)

Using Fentanyl intraoperatively is found to reduce the risk of visual and auditory hallucinations. Opioids as fentanyl, are highly lipophilic, so they can distribute through the blood-brain-barrier (BBB) and reach the brain faster than hydrophilic drugs, and concentrate there more, then they will lead to a more significant effect than hydrophilic drugs. (Sutcliffe et al.) (50) However, hyperlipidemia affects the pharmacokinetics of lipophilic drugs, as due to increased lipids in the blood, lipophilic drugs as fentanyl can bind to lipids in the blood and this will slow their entry to the brain (prolonged distribution). (De Baerdemaekeret al.) (51).

Post-operative ventilation was also found to raise the risk of both visual and auditory hallucinations. Pei et al. proved that prolonged post-operative mechanical ventilation is an independent risk factor for developing delirium after coronary artery bypass surgeries with an odds ratio (OR) of 9.74 (95% CI: 3.42–27.77, $p<0.001$). They hypothesized that sedative and analgesic use, extended ICU stay, and inflammation are the reasons behind that(52). In addition to that, Liu et al. found that higher SII levels are related to prolonged mechanical ventilation and longer hospital stays(53). From this, we can link it to hyperlipidemia-induced systemic

inflammation, considering it an exacerbating factor to this condition. Following this, Zeng et al. suggest that inflammation contributes to the development of post-operative delirium, especially in patients with hyperlipidemia, as it plays a role in increasing inflammatory markers such as PTGS2, white blood cell counts, and neutrophil counts(54).

Finally, a higher LDL/HDL ratio also increases the risk for both. Lin et al. explore the effects of LDL-C and HDL-C levels on the brain in the context of cardiac surgeries. They found that higher LDL-C levels (a state of hyperlipidemia) are positively associated with post-operative delirium; they also increase levels of Aβ42 and t-Tau deposition in the brain. About HDL-C, it is found to be linked with a lower occurrence of post-operative delirium, in addition to its binding to Aβ, preventing its aggregation. According to that, an increase in LDL-C and a decrease in HDL-C can be defined as an elevation in LDL-C/HDL-C ratio(55). Supporting this, a laboratory study done on mice undergoing laborectomy found that postoperative inflammation remodels HDL proteome, including elevated SAA, decreased apoA-I, and reduced cholesterol efflux capacity. We can hypothesize from this that inflammation induced in cardiac surgeries may disrupt cholesterol transport in the brain. At the end, this can affect neuron membrane fluidity, which is essential for neurotransmitters. When neurotransmitter systems are disrupted, this can affect sensory processing, leading to conditions as hallucinations. (McGillicuddy et al.) (56)

According to table 4, although hemodialysis dependence was strongly associated with visual hallucinations in the crude univariate model, this association was attenuated and lost significance in the adjusted analysis. It is worth noting that while not

directly on hallucinations, Ottens TH et al. (57) found that impaired kidney function was not significantly associated with postoperative hallucinations in cardiac surgery patients. Similarly, immunosuppressive drug use was linked to visual hallucinations in our crude model, but this also lost significance in the adjusted analysis mechanism.

Our study found that EuroSCORE II, a composite surgical risk score, was a robust independent predictor of auditory hallucinations with a trend towards significance for visual hallucinations. This finding aligns with the general understanding that higher perioperative risk, as indicated by scores like EuroSCORE II, can predispose individuals to various postoperative complications, including neuropsychiatric ones. The hypothesis is that higher perioperative risk (as indicated by EuroSCORE II) may predispose individuals to postoperative neuropsychiatric complications, such as auditory and visual hallucinations. This is based on the premise that the physiological stress, inflammatory responses, and potential for cerebral insults associated with high-risk surgical procedures contribute to brain dysfunction leading to these symptoms(58).

Operative time variables, including cardiopulmonary bypass (CPB) and aortic cross-clamp times, were inversely associated with auditory hallucinations in our univariate models. However, these effects did not persist in adjusted analyses, suggesting potential confounding. Tschernatsch M et al. (59) explained a positive correlation between visual hallucinations and aortic clamp time (r=0.175, p=0.018) and extracorporeal circulation time (r=0.146, p=0.048). Li J et al. (60) noted that longer duration of cardiopulmonary bypass was associated with increased delirium in univariate analysis (OR 1.53; 95% CI 1.06–2.21; p=0.022), but not after multivariable adjustment (OR 0.88; 95% CI 0.57–1.36; p=0.566). This is an interesting contrast, as prolonged CPB and aortic

cross-clamp times are generally recognized risk factors for cerebral complications, including postoperative cognitive deficits and delirium, due to increased risk of microemboli and inflammation (61) .

Our study's most notable finding is the emergence of the LDL/HDL ratio as a novel and consistent independent predictor of both visual and auditory hallucinations in patients without hyperlipidemia. This is a significant contribution, especially given the often-conflicting literature on the direct relationship between individual lipid levels and postoperative cognitive dysfunction or delirium. Several studies support the notion that elevated levels of total cholesterol (TC), triglycerides (TG), and low-density lipoprotein cholesterol (LDL-C) are risk factors for postoperative delirium (POD) or postoperative cognitive dysfunction (POCD). Qiu LQ et al. (62) concluded that hyperlipidemia was significantly associated with an increased risk of POD (OR = 1.47; 95% CI 1.13-1.91; P = 0.004). This meta-analysis also found that patients with POD exhibited significantly higher levels of TC, TG, and LDL-C compared to non-POD patients, and significantly lower levels of high-density lipoprotein cholesterol (HDL-C) (62). Specifically, Lin Y et al. (6) found that high concentrations of TC (OR = 3.148; 95% CI 1.858–5.333; P < 0.001), TG (OR = 2.483; 95% CI 1.573–3.918; P < 0.001), and LDL-C (OR = 2.469; 95% CI 1.310–4.656; P = 0.005) were risk factors for POD, and these associations remained stable in sensitivity analyses. Li J et l. (60) identified that higher levels of TC (4.39 ± 1.10 mmol/L vs. 4.24 ± 1.09 mmol/L, P = 0.009) and LDL-C (2.76 ± 0.98 mmol/L vs. 2.65 ± 0.95 mmol/L, P = 0.035) were significantly higher in patients with delirium compared to those without. The literature suggests that elevated LDL-C and TG may promote neuroinflammation by activating

microglia and astrocytes via the NF-κB pathway, leading to increased pro-inflammatory cytokines in the CNS, which can disrupt synaptic plasticity and neurotransmitter balance. They also note that hypertriglyceridemia exacerbates oxidative stress through lipid peroxidation, potentially damaging neuronal mitochondria and impairing cerebral energy metabolism (63). Furthermore, hyperlipidemia can disrupt the blood-brain barrier (BBB), allowing inflammatory factors and harmful substances to enter the CNS (63). Conversely, Lin Y et al. found that high HDL-C concentration has consistently been identified as a protective factor against POD. The underlying mechanism proposed is that HDL-C protects against elevated lipid levels, endothelial dysfunction, oxidative stress, inflammation, and thrombosis. It is also suggested that HDL-C can bind to Aβ, prevent its aggregation, and improve its clearance from the brain, thus decreasing Aβ neurotoxicity. In elderly CABG patients, HDL-C levels ≥ 1.0 mmol/L (OR 0.71) were found to be a protective factor against POD (60). Our finding of the LDL/HDL ratio as a predictor aligns with the idea that the balance of these lipids, rather than isolated values, might be critical.

Strengths

This study, part of the VAACS (Visual and Auditory After Cardiac Surgery) initiative, employed a prospective cohort design, which enhances the credibility of causal inference. The structured temporal data collection minimized recall bias and permitted precise tracking of hallucination onset in relation to perioperative exposures, particularly lipid status and intraoperative factors. A key methodological asset was the use of the Questionnaire for Psychotic Experiences (QPE), a validated psychometric tool that allowed

for accurate, standardized, and consistent evaluation of both visual and auditory hallucinations across centers. This reduced subjective variability and increased the reproducibility of symptom assessment.

The multicenter design, spanning ten high-volume cardiac surgery institutions, considerably boosts external validity. By capturing a diverse patient population and encompassing varied surgical practices, the study's findings become more generalizable and reflective of real-world care patterns across different healthcare settings. Statistical rigor was maintained through the application of Cox proportional hazards models, well-suited for analyzing time-to-event data such as postoperative hallucinations. The inclusion of forest plots further enriched the presentation of results by offering clear visual interpretations of hazard ratios across multiple predictors. Confounding was robustly addressed. Adjustments were made for a comprehensive set of demographics, clinical, intraoperative, and pharmacological variables, thereby enhancing internal validity and ensuring that observed associations, particularly those involving LDL/HDL ratios and fentanyl dosing, were not spurious.

Clinical Significance:

The study provides novel, actionable insights for cardiac surgeons and perioperative teams. It highlights hyperlipidemia as an independent risk factor for postoperative hallucinations, and identifies LDL/HDL ratio and intraoperative fentanyl dose as modifiable predictors. These findings support the inclusion of preoperative lipid profiling and tailored intraoperative opioid strategies in perioperative planning. By doing so, the risk of neuropsychiatric complications can be mitigated, potentially improving patient recovery, reducing ICU burden, and optimizing outcomes in high-risk cardiac surgery cohorts.

Limitations

The study was limited by a relatively short follow-up duration (7 days), which may have resulted in the potential underreporting of later-onset hallucinations. Additionally, residual confounding from unmeasured perioperative variables cannot be entirely excluded, though efforts to standardize assessments and sensitivity analyses were performed to minimize this issue. Findings might not be universally generalizable beyond cardiac surgical contexts. Because all consent was obtained postoperatively, very early hallucinations that may have occurred before capacity was regained could not be captured. This conservative approach prioritizes autonomy and likely led to a modest underestimation rather than exaggeration of the true postoperative incidence.

Although our multivariable models adjusted for redo surgery and other perioperative factors, residual confounding may remain. Patients with prior cardiac operations could have undergone earlier lipid evaluation and treatment initiation, and long-term adherence patterns may differ between groups. Because hyperlipidemia status was defined by the immediate preoperative lipid panel (irrespective of past therapy), unmeasured historical management may still influence risk and cannot be fully excluded. Because multiple predictors were evaluated, p-values are nominal; we mitigated multiplicity by prespecifying endpoints and predictors, using multivariable Cox models, and emphasizing adjusted effect sizes and biological coherence, with secondary analyses interpreted as exploratory.

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Take-Home Message:

Surgeons should recognize elevated LDL/HDL ratios as independent risk factors for postoperative hallucinations, advocate preoperative lipid evaluations, and implement targeted intraoperative and postoperative strategies, such as optimized fentanyl administration and vigilant neuropsychiatric monitoring, to mitigate risks.

Conclusion

In this multicenter prospective study, distinct predictors of postoperative hallucinations emerged between hyperlipidemic and normolipidemic patients. Elevated LDL/HDL ratio consistently correlated with increased hallucination risk across both cohorts, whereas statin use showed no acute protective association. These findings suggest that lipid imbalance may represent a preoperative vulnerability marker for postoperative neuropsychiatric complications rather than an immediately modifiable risk. Future studies should investigate whether long-term lipid optimization affects neurocognitive outcomes following cardiac surgery.

References:

1. Vervoort D, Lee G, Ghandour H, Guetter CR, Adreak N, Till BM, et al. Global Cardiac Surgical Volume and Gaps: Trends, Targets, and Way Forward. Annals of Thoracic Surgery Short Reports. 2024 Jun 1;2(2):320–4.
2. Ottens TH, Sommer IEC, Begemann MJ, Schutte M, Cramer MJ, Suyker WJ, et al. Hallucinations after Cardiac Surgery: A Prospective Observational Study. Medicina 2020, Vol. 56, Page 104. 2020 Mar 2;56(3):104.
3. Nussmeier NA. Neuropsychiatric complications of cardiac surgery. J Cardiothorac Vasc Anesth. 1994 Feb 1;8(1):13–8.
4. Eriksson M, Samuelsson E, Gustafson Y, Åberg T, Engström KG. Delirium after Coronary Bypass Surgery Evaluated by the Organic Brain Syndrome Protocol. Scandinavian Cardiovascular Journal. 2002;36(4):250–5.
5. Evered L, Silbert B, Knopman DS, Scott DA, DeKosky ST, Rasmussen LS, et al. Recommendations for the nomenclature of cognitive change associated with anaesthesia and surgery—2018. Br J Anaesth. 2018 Nov 1;121(5):1005–12.
6. Mailhot T, Cossette S, Côté J, Bourbonnais A, Côté MC, Lamarche Y, et al. A post-cardiac surgery intervention to manage delirium involving families: a randomized pilot study. Nurs Crit Care. 2017 Jul 1;22(4):221–8.

7. Momeni M, Khalifa C, Lemaire G, Watremez C, Tircoveanu R, Van Dyck M, et al. Propofol plus low-dose dexmedetomidine infusion and postoperative delirium in older patients undergoing cardiac surgery. Br J Anaesth. 2021 Mar 1;126(3):665–73.

8. Li X, Yang J, Nie XL, Zhang Y, Li XY, Li LH, et al. Impact of dexmedetomidine on the incidence of delirium in elderly patients after cardiac surgery: A randomized controlled trial. PLoS One. 2017 Feb 1;12(2):e0170757.

9. Mihalj M, Heinisch PP, Huber M, Schefold JC, Hartmann A, Walter M, et al. Effect of Perioperative Lipid Status on Clinical Outcomes after Cardiac Surgery. Cells [Internet]. 2021 Oct 1 [cited 2025 Oct 30];10(10). Available from: https://pubmed.ncbi.nlm.nih.gov/34685697/

10. Smith LE, Smith DK, Yancey PG, Kon V, Remaley AT, Billings FT, et al. Perioperative high-density lipoproteins, oxidative stress, and kidney injury after cardiac surgery. J Lipid Res [Internet]. 2021 [cited 2025 Oct 30]; 62:100024. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC7905072/

11. McKay TB, Graves OK, Mitchell M, Mueller A, Simon C, Patel P, et al. Intraoperative Lipoproteins Associated with Postoperative Delirium in a Prospective Observational Study of Older Adults Undergoing Cardiac Surgery. J Cardiothorac Vasc Anesth [Internet]. 2025 Oct [cited 2025 Oct 30];0(0). Available from: https://www.jcvaonline.com/action/showFullText?pii=S1053077025010006

12. Rehe D, Subashchandran V, Zhang Y, Cuff G, Lee M, Berger JS, et al. Preoperative LDL-C and major cardiovascular and cerebrovascular events after non-cardiac surgery. J Clin Anesth [Internet]. 2025 Mar 1 [cited 2025 Oct 30]; 102:111783. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0952818025000431

13. Reilly MP, McGillicuddy FC, De La Moya ML, Hinkle CC, Joshi MR, Chiquoine EH, et al. Inflammation impairs reverse cholesterol transport in vivo. Circulation [Internet]. 2009 Mar 3 [cited 2025 Oct 30];119(8):1135–45. Available from: https://pubmed.ncbi.nlm.nih.gov/19221221/

14. Barber CN, Raben DM. Lipid metabolism crosstalk in the brain: Glia and neurons. Front Cell Neurosci [Internet]. 2019 May 14 [cited 2025 Oct 30]; 13:452239. Available from: www.frontiersin.org

15. Brondén B, Dencker M, Allers M, Plaza I, Jönsson H. Differential distribution of lipid microemboli after cardiac surgery. Annals of Thoracic Surgery [Internet]. 2006 Feb [cited 2025 Oct 30];81(2):643–8. Available from: https://pubmed.ncbi.nlm.nih.gov/16427867/

16. Staicu RE, Vernic C, Ciurescu S, Lascu A, Aburel OM, Deutsch P, et al. Postoperative Delirium and Cognitive Dysfunction After Cardiac Surgery: The Role of Inflammation and Clinical Risk Factors. Diagnostics (Basel) [Internet]. 2025 Apr 1 [cited 2025 Oct 30];15(7). Available from: https://pubmed.ncbi.nlm.nih.gov/40218194/

17. Libby P. Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol [Internet]. 2012 Sep [cited 2025 Oct 30];32(9):2045–51. Available from: https://pubmed.ncbi.nlm.nih.gov/22895665/

18. Meyer JS, Rogers RL, Mortel KF, Judd BW. Hyperlipidemia is a risk factor for decreased cerebral perfusion and stroke. Arch Neurol [Internet]. 1987 [cited 2025 Oct 30];44(4):418–22. Available from: https://pubmed.ncbi.nlm.nih.gov/3827697/

19. Yehya A, Khaled SM, Sommer IEC, Elhag SF, Hassan MHMO, Woodruff P, et al. The Arabic Questionnaire for Psychotic Experiences in patients with psychotic disorders: a clinical validation. BMC Psychiatry 2023 23:1 [Internet]. 2023 Mar 7 [cited 2025 Oct 30];23(1):1–9. Available from: https://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-023-04649-4

20. Rossell SL, Schutte MJL, Toh WL, Thomas N, Strauss C, Linszen MMJ, et al. The Questionnaire for Psychotic Experiences: An Examination of the Validity and Reliability. Schizophr Bull [Internet]. 2019 Feb 1 [cited 2025 Oct 30];45(45 Suppl 1):S78–87. Available from: https://pubmed.ncbi.nlm.nih.gov/30715541/

21. Rossell SL, Schutte MJL, Toh WL, Thomas N, Strauss C, Linszen MMJ, et al. The Questionnaire for Psychotic Experiences: An Examination of the Validity and Reliability. Schizophr Bull. 2019 Feb 1;45(Suppl 1):S78.

22. Yehya A, Khaled SM, Sommer IEC, Elhag SF, Hassan MHMO, Woodruff P, et al. The Arabic Questionnaire for Psychotic Experiences in patients with psychotic disorders: a clinical validation. BMC Psychiatry. 2023 Dec 1;23(1):141.

23. Yehya A, Khaled SM, Sommer IEC, Elhag SF, Hassan MHMO, Woodruff P, et al. The Arabic Questionnaire for Psychotic Experiences in patients with psychotic disorders: a clinical validation. BMC Psychiatry. 2023 Dec 1;23(1):141.

24. Hyperlipidemia (High Cholesterol): Levels, Causes, Symptoms & Diagnosis [Internet]. [cited 2025 Oct 30]. Available from: https://my.clevelandclinic.org/health/diseases/21656-hyperlipidemia

25. Huang CI, Lin LC, Tien HC, Que J, Ting WC, Chen PC, et al. Hyperlipidemia and statins use for the risk of new-onset anxiety/depression in patients with head and neck cancer: A population-based study. PLoS One [Internet]. 2017 Mar 1 [cited 2025 Oct 30];12(3). Available from: https://pubmed.ncbi.nlm.nih.gov/28362860/

26. Tracey TJ, Steyn FJ, Wolvetang EJ, Ngo ST. Neuronal Lipid Metabolism: Multiple Pathways Driving Functional Outcomes in Health and Disease. Front Mol Neurosci [Internet]. 2018 Jan 23 [cited 2025 Oct 30];11. Available from: https://pubmed.ncbi.nlm.nih.gov/29410613/

27. Ottens TH, Sommer IEC, Begemann MJ, Schutte M, Cramer MJ, Suyker WJ, et al. Hallucinations after Cardiac Surgery: A Prospective Observational Study. Medicina (B Aires). 2020 Mar 2;56(3):104.

28. Zhuang Y, Xu J, Zheng K, Zhang H. Research progress of postoperative cognitive dysfunction in cardiac surgery under cardiopulmonary bypass. Ibrain. 2023 Aug 14;

29. Teller J, Gabriel MM, Schimmelpfennig SD, Laser H, Lichtinghagen R, Schäfer A, et al. Stroke, Seizures, Hallucinations and Postoperative Delirium as Neurological Complications after Cardiac Surgery and Percutaneous Valve Replacement. J Cardiovasc Dev Dis. 2022 Oct 24;9(11):365.

30. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD Statement. BMC Med [Internet]. 2015 Jan 6 [cited 2025 Jul 25];13(1):1–10. Available from: https://bmcmedicine.biomedcentral.com/articles/10.1186/s12916-014-0241-z

31. Diagnostic and Statistical Manual of Mental Disorders (5th ed.) : Free Download, Borrow, and Streaming : Internet Archive [Internet]. [cited 2025 Jul 29]. Available from: https://archive.org/details/APA-DSM-5

32. Zhao Y, Zhang H, Cheng J, Zou Y, Zhang D, Duan X. Association between Dyslipidaemia and Cognitive Impairment: A Meta-Analysis of Cohort and Case-Control Studies. J Integr Neurosci. 2024 Feb 19;23(2):40.

33. Girard TD, Jackson JC, Pandharipande PP, Pun BT, Thompson JL, Shintani AK, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. Crit Care Med. 2010;38(7):1513–20.

34. Tschernatsch M, El Shazly J, Butz M, Lie SR, Yeniguen M, Braun T, et al. Visual Hallucinations following Coronary Artery Bypass Grafting: A Prospective Study. Medicina 2022, Vol 58, Page 1466. 2022 Oct 16;58(10):1466.

35. Meyer JS, Rogers RL, Mortel KF, Judd BW. Hyperlipidemia Is a Risk Factor for Decreased Cerebral Perfusion and Stroke. Arch Neurol. 1987 Apr 1;44(4):418–22.

36. Kazmierski J, Kowman M, Banach M, Fendler W, Okonski P, Banys A, et al. Incidence and predictors of delirium after cardiac surgery: Results from The IPDACS Study. J Psychosom Res. 2010 Aug;69(2):179–85.

37. Galam L, Failla A, Soundararajan R, Lockey RF, Kolliputi N, Galam L, et al. 4-Hydroxynonenal regulates mitochondrial function in human small airway epithelial cells. Oncotarget. 2015 Oct 15;6(39):41508–21.

38. Kazmierski J, Kowman M, Banach M, Fendler W, Okonski P, Banys A, et al. Incidence and predictors of delirium after cardiac surgery: Results from The IPDACS Study. J Psychosom Res. 2010 Aug 1;69(2):179–85.

39. Shan L, Zheng K, Dai W, Wang Y, Hao P. Comparative analysis of inflammatory markers as predictive markers for postoperative delirium in cardiac surgery patients: an observational study. Front Med (Lausanne). 2025 Apr 1;12:1515940.

40. Libby P. Inflammation in atherosclerosis. Arterioscler Thromb Vasc Biol. 2012 Sep;32(9):2045–51.

41. Perry VH, Holmes C. Microglial priming in neurodegenerative disease. Nature Reviews Neurology 2014 10:4. 2014 Mar 18;10(4):217–24.

42. Staicu RE, Vernic C, Ciurescu S, Lascu A, Aburel OM, Deutsch P, et al. Postoperative Delirium and Cognitive Dysfunction After Cardiac Surgery: The Role of Inflammation and Clinical Risk Factors. Diagnostics 2025, Vol 15, Page 844. 2025 Mar 26;15(7):844.

43. Miller AH, Raison CL. The role of inflammation in depression: from evolutionary imperative to modern treatment target. Nature Reviews Immunology 2015 16:1. 2015 Dec 29;16(1):22–34.

44. Long C, Lin D, Zhang L, Lin Y, Yao Q, Zhang G, et al. Association between human blood metabolome and the risk of delirium: a Mendelian Randomization study. Front Endocrinol (Lausanne). 2023 Jan 11;14:1332712.

45. Shen H, Xiong Y, Liang Y, Liu Z, Guo L, Qin Y, et al. The Effects of Hyperlipidemia on Postoperative Cognitive Dysfunction in Patients Undergoing Laparoscopic Gynecological Tumor Surgery. Neuropsychiatr Dis Treat. 2025 Feb 13;21:259–69.

46. Li J, Meng D, Chang C, Fu B, Xie C, Wu Z, et al. Risk factors for delirium after coronary artery bypass grafting in elderly patients. Ann Transl Med. 2021;9(22):1666.

47. Brondén B, Dencker M, Allers M, Plaza I, Jönsson H. Differential distribution of lipid microemboli after cardiac surgery. Annals of Thoracic Surgery. 2006 Feb 1;81(2):643–8.

48. Mihalj M, Heinisch PP, Huber M, Schefold JC, Hartmann A, Walter M, et al. Effect of perioperative lipid status on clinical outcomes after cardiac surgery. Cells. 2021 Oct 1;10(10):2717.

49. Ogawa M, Izawa KP, Satomi-Kobayashi S, Tsuboi Y, Komaki K, Gotake Y, et al. Impact of delirium on postoperative frailty and long term cardiovascular events after cardiac surgery. PLoS One. 2017 Dec 1;12(12):e0190359.

50. Sutcliffe KJ, Corey RA, Alhosan N, Cavallo D, Groom S, Santiago M, et al. Interaction With the Lipid Membrane Influences Fentanyl Pharmacology. Advances in Drug and Alcohol Research. 2022 Mar 21;2:10280.

51. De Baerdemaeker LEC, Mortier EP, Struys MMRF. Pharmacokinetics in obese patients. Continuing Education in Anaesthesia Critical Care & Pain. 2004 Oct 1;4(5):152–5.

52. Pei W, Tan H, Dai T, Liu J, Tang Y, Liu J. Original Article Risk factors for postoperative delirium in adult patients undergoing cardiopulmonary bypass in cardiac surgery. Am J Transl Res. 2024;16(9):4751–60.

53. Liu Q, Zhou Y, Cao X, Wang W, Pan C, YichenXu, et al. The impact of systemic inflammation index on prolonged mechanical ventilation after cardiac surgery: a retrospective study. J Cardiothorac Surg. 2025 Dec 1;20(1):1–9.

54. Daojun Z, Yuling T, Yingzhe X, Kowark A, Coburn M, Yue Z, et al. Effect of parecoxib on postoperative delirium in patients with hyperlipidemia: a randomized, double-blind, single-center, superiority trial. Int J Surg. 2025 Apr 1;111(4):2903–13.

55. Barber CN, Raben DM. Lipid metabolism crosstalk in the brain: Glia and neurons. Front Cell Neurosci. 2019 May 14;13:452239.

56. Reilly MP, McGillicuddy FC, De La Moya ML, Hinkle CC, Joshi MR, Chiquoine EH, et al. Inflammation impairs reverse cholesterol transport in vivo. Circulation. 2009 Mar 3;119(8):1135–45.

57. Ottens TH, Sommer IEC, Begemann MJ, Schutte M, Cramer MJ, Suyker WJ, et al. Hallucinations after cardiac surgery: A prospective observational study. Medicina (Lithuania). 2020 Mar 1;56(3).

58. Yu H, Dong R, Lu Y, Yang X, Chen C, Zhang Z, et al. Short-Term Postoperative Cognitive Dysfunction and Inflammatory Response in Patients Undergoing Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: A Pilot Study. Mediators Inflamm. 2017;2017:3605350.

59. Tschernatsch M, El Shazly J, Butz M, Lie SR, Yeniguen M, Braun T, et al. Visual Hallucinations following Coronary Artery Bypass Grafting: A Prospective Study. Medicina (Lithuania). 2022 Oct 1;58(10).

60. Li J, Meng D, Chang C, Fu B, Xie C, Wu Z, et al. Risk factors for delirium after coronary artery bypass grafting in elderly patients. Ann Transl Med. 2021 Nov;9(22):1666.

61. Vallabhajosyula S, Kanmanthareddy A, Erwin PJ, Esterbrooks DJ, Morrow LE. Role of statins in delirium prevention in critical ill and cardiac surgery patients: A systematic review and meta-analysis. J Crit Care. 2017 Feb 1;37:189–96.

62. Qiu LQ, Song JL, Zhang LC, Fan B, Li Q, Lu B, et al. Association between hyperlipidemia and postoperative delirium risk: a systematic review and meta-analysis. Front Aging Neurosci. 2025 Mar 18;17:1544838.

63. Shaw AL, Teng R, Fasina T, Gonzales AS, Wong A, Schweitzer D, et al. Lipid dysregulation and delirium in older adults: A review of the current evidence and future directions. Brain Res Bull. 2025 May 1;224.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: