The Heart Surgery Forum

Heart Surg. Forum **2026**; 29(11): 52731
https://doi.org/10.31083/HSF52731

Article

Association Between Early Postoperative Absolute Eosinophil Count and Delirium After Cardiac Surgery: A MIMIC-IV Database Study

Weidong Zhang[1,*], Qiyin Cai[2]

[1]Department of Anesthesiology, Beijing Jingmei Group General Hospital, 102300 Beijing, China
[2]Department of Pediatric Intensive Care Unit, Jiangmen Maternity and Child Health Care Hospital, 529000 Jiangmen, Guangdong, China
*Correspondence: a305_zwd@126.com (Weidong Zhang)

Academic Editor: Hitoshi Hirose
Submitted: 8 April 2026 Revised: 29 June 2026 Accepted: 7 July 2026 Published: 3 November 2026

Abstract

Background: Postoperative delirium (POD) is a common and serious neurological complication after cardiac surgery, associated with increased mortality, prolonged intensive care unit (ICU) and hospital stays, and long-term cognitive impairment. Thus, this study aimed to determine whether the early postoperative absolute eosinophil count (AEC) is associated with POD after cardiac surgery and to evaluate the potential utility of AEC for early risk stratification. **Methods:** We performed a retrospective cohort study utilizing data from the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 3.1, data collected 2008–2022) to evaluate the relationship between postoperative AECs and postoperative delirium defined by three complementary data sources including positive Confusion Assessment Method for the ICU (CAM-ICU) screening in adult cardiac surgery ICU patients. After applying prespecified eligibility criteria, we analyzed 1831 patients using multivariable logistic regression and restricted cubic spline (RCS) models. **Results:** POD occurred in 215 patients (11.7%). After multivariable adjustment, each 1-standard deviation (SD) increase in postoperative AEC was associated with a 20% reduction in the odds of POD (adjusted odds ratio (OR), 0.80; 95% confidence interval (CI), 0.67–0.96; $p = 0.016$). Compared with the first quartile (reference), patients in the highest AEC quartile had significantly lower odds of POD (OR, 0.50; 95% CI, 0.32–0.78; $p = 0.002$), with a significant linear trend across quartiles. **Conclusion:** Early postoperative eosinopenia is independently associated with POD following cardiac surgery and may serve as a supportive biomarker to guide early intervention and closer monitoring of high-risk individuals.

Keywords: postoperative complications; delirium; cardiac surgery; surgery; absolute eosinophil count; eosinopenia; intensive care unit; neuropsychological tests

1. Introduction

Cardiac surgical procedures frequently trigger a spectrum of postoperative brain complications, with delirium standing as the most commonly observed adverse neurological event in intensive care unit (ICU) wards. Population-based clinical studies have documented postoperative delirium (POD) occurrence between 26%–51% within cardiac surgical cohorts [1]. This transient brain derangement substantially burdens hospital resources by prolonging inpatient stays [2]. Beyond short-term resource strain, longitudinal clinical follow-ups demonstrate that POD confers lasting damage to patients' cognitive faculties and worsens long-term survival outcomes [3,4].

Although POD carries unequivocally adverse prognostic significance, its precise pathophysiological mechanisms remain incompletely elucidated. The prevailing consensus posits that neuroinflammation occupies a central role in the multifactorial pathogenic pathways of POD [5]. Surgical trauma and cardiopulmonary bypass can provoke a robust systemic inflammatory cascade, compromising blood-brain barrier integrity, subsequently activating resident immune cells in the brain (e.g., microglia), and ultimately culminating in neuronal dysfunction [6]. Notably, postoperative cognitive dysfunction (POCD) and POD exhibit substantial mechanistic overlap and continuity. Both are considered distinct manifestations of perioperative neurocognitive disorders (PNDs), with complex pathogenesis involving multiple interdependent risk factors related to surgery, anesthesia, and patient susceptibility. Among these mechanisms, the surgery-induced inflammatory response is recognized as a critical pathological bridge linking POD and POCD.

Within this inflammatory network, the role of eosinophils is being reassessed. Long confined to roles as effector cells driving allergy and parasitic infection responses, eosinophils have now been shown to exert key functions in immune regulation and tissue remodeling in emerging clinical and preclinical work [7,8]. These leukocytes secrete a diverse panel of immune-modulating and neurotrophic signaling molecules, such as interleukin-4 (IL-4), interleukin-10 (IL-10), interleukin-13 (IL-13), nerve growth factor (NGF), and brain-derived neurotrophic factor (BDNF) [9]. These mediators effectively suppress the production of pro-inflammatory cytokines and can also exert direct neuroprotective effects [10]. The clinical relevance of this anti-inflammatory axis is supported by

Copyright: © 2026 The Author(s). Published by IMR Press.
This is an open access article under the CC BY 4.0 license.

Publisher's Note: IMR Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Glumac et al. [11], who reported that preoperative corticosteroid administration effectively attenuates surgical inflammation, thereby reducing the incidence and severity of POCD. In particular, the anti-inflammatory and neuroprotective properties of IL-10 have been corroborated across multiple studies [12].

Based on the immune pathways outlined above, a drop in eosinophils shortly after surgery carries clear pathological relevance. Rapid postoperative eosinophil loss mirrors the intensity of whole-body inflammatory activation and points to impaired endogenous anti-inflammatory defense and neurotrophic supply. Such immune dysregulation leaves the central nervous system susceptible to unregulated inflammatory injury, raising the odds of delirium and secondary cognitive dysfunction. Prior research also links eosinophil concentrations to clinical outcomes across all subtypes of advanced heart failure [13]. Standard clinical risk screening for delirium mostly depends on general inflammatory biomarkers such as total white blood cell count and C-reactive protein. Yet these assays fail to detect shifts in specialized immune cell subsets or their unique impacts on brain function after surgery [5]. Against this background, we hypothesized that early postoperative absolute eosinophil count (AEC) is independently associated with the occurrence of POD in patients undergoing cardiac surgery. In this study, we utilized the Medical Information Mart for Intensive Care IV (MIMIC-IV, v3.1) large critical care electronic database to explore the relationship, aiming to verify the clinical value of this readily accessible routine blood indicator and to offer supportive evidence for future mechanistic exploration and prospective validation.

2. Materials and Methods

2.1 Data Sources and Ethics Statement

We constructed this retrospective cohort using the open-access critical care dataset MIMIC-IV version 3.1 [14]. The MIMIC-IV database is curated by Beth Israel Deaconess Medical Center and contains de-identified, high-resolution clinical data from ICU admissions (2008–2022), including discharge summaries, laboratory results, medication administration logs, nursing documentation, and diagnostic codes. Cardiac surgery encounters were identified by querying ICD-9 and ICD-10 procedure and diagnosis codes together with relevant clinical fields, and the variables required for analysis were extracted accordingly.

This study adhered to the Declaration of Helsinki and approved by the Ethics Committee of Beijing Jingmei Group General Hospital (approval number: 2025-research-038-01). Because all MIMIC-IV data are anonymized and no identifiable information was accessed, individual informed consent was waived. The investigator Weidong Zhang (Collaborative Institutional Training Initiative [CITI] certification ID: 71122643) completed the CITI program.

2.2 Selection of Study Population

We enrolled adult patients ≥18 years old who received cardiac surgery and subsequent ICU admission at Beth Israel Deaconess Medical Center from the MIMIC-IV v3.1 database. We screened cardiac surgical hospitalizations by extracting procedural codes from ICD-9-CM (International Classification of Diseases, Ninth Revision, Clinical Modification) and ICD-10-PCS (International Classification of Diseases, Tenth Revision, Procedure Coding System). We categorized target cardiac operations and their corresponding diagnostic codes as listed below: Coronary artery bypass grafting (CABG): ICD-9 codes 3611–3614; ICD-10 codes 021009W–02130AW, 021049W–021149W, 02120KW. Cardiac valve repair/replacement: ICD-9 codes 3511–3514, 3596. Aortic surgery: ICD-9 codes 3804, 3814, 3834, 3844, 3922, 3954, 3971; ICD-10 codes 02RX0JZ-02UW4JZ. Patients undergoing other cardiac procedures that did not fall into these predefined categories were not included. We cross-checked all qualifying records against the database's clinical metadata to validate that each hospitalization centered on the target cardiac procedure. All patients in the final cohort underwent index cardiac surgery under general anesthesia via endotracheal intubation. Detailed intraoperative anesthetic management, including anesthetic agents and maintenance strategies, was not available in the MIMIC-IV database.

To improve cohort homogeneity and minimize confounding, selection bias, and information bias, the following exclusion criteria were applied after initial screening: (1) age <18 years at hospital admission; (2) documented preoperative delirium prior to the index surgery; (3) preoperative systemic glucocorticoid use; (4) no ICU admission following the index cardiac surgery; (5) no AEC measurement within 24 hours after cardiac surgery, or missing delirium assessment records between 24 and 72 hours postoperatively; (6) missing data in 20% or more of the key study variables (including core covariates).

Patients who met all inclusion criteria and none of the exclusion criteria comprised the final analytic cohort. The patient screening process and reasons for exclusion were documented in detail to ensure reproducibility, with a corresponding flowchart presented in Fig. 1.

2.3 Data Extraction and Variable Definitions

The analytic dataset was assembled from MIMIC-IV v3.1 using PostgreSQL (v17.2, PostgreSQL Global Development Group) for query execution. Extracted variables included demographics (age, sex, race), admission information, comorbidities, vital signs, laboratory measurements, severity scores (e.g., Simplified Acute Physiology Score II (SAPS II), Acute Physiology Score III (APS III)), comorbidity indices (e.g., Charlson Comorbidity Index (CCI)), and clinical outcomes.

POD, the primary outcome of this study was identified using three complementary data sources within 24 to 72

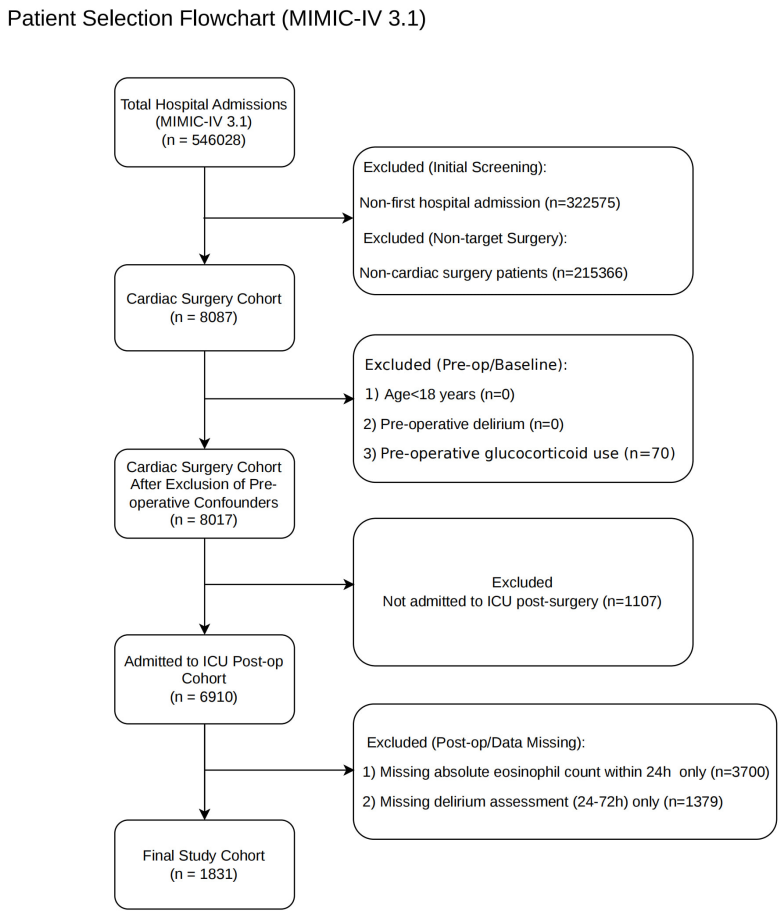


Fig. 1. Patient selection flowchart for the retrospective cohort study. Flowchart of participant inclusion and exclusion criteria for the analysis of early postoperative absolute eosinophil count (AEC) and POD in cardiac surgery patients from the MIMIC-IV v3.1 database (2008–2022). A total of 1831 adult patients who met all inclusion criteria and no exclusion criteria were enrolled in the final analytic cohort. Abbreviations: AEC, absolute eosinophil count; ICU, intensive care unit; MIMIC-IV, Medical Information Mart for Intensive Care IV; POD, postoperative delirium.

hours of ICU admission for cardiac surgical patients. Participants were classified as having POD when they met at least one of the following three criteria: (1) a positive Confusion Assessment Method for the ICU (CAM-ICU) screen formally recorded by bedside ICU nurses; (2) clear clinical narrative notes mentioning delirium symptoms in provider or nurse electronic medical records; or (3) valid ICD-9 and ICD-10 diagnostic codes for delirium linked to the index ICU stay. This multi-source composite identification approach is standard practice in delirium research using large electronic health record datasets, as it minimizes diagnostic misclassification relative to single-variable methods.

The 24–72 hours observation window was prespecified for two primary reasons: First, this timeframe ensures tight temporal alignment between POD events and early postoperative immune shifts, with the initial 24-hours postoperative AEC acting as our core exposure biomarker. Second, this window reduces false-positive classifications that may arise from transient altered mental status or sedation-induced confusion in the immediate 24-hour post-anesthesia phase. These transient states carry minimal pathological relevance and should not be categorized as true POD.

AEC served as the primary exposure. When available, the first AEC recorded within 24 hours of ICU admission was used as the baseline. Repeat measures or values outside the prespecified window were handled according to predefined selection rules. For missing data, variables with ≥20% missing data were excluded, while multiple imputation was applied for the remaining missing entries [15]. In addition to treating AEC as a continuous variable, we also categorized it and explored dose-response relationships using restricted cubic spline. All extraction and preprocessing steps were documented to ensure reproducibility.

2.4 Statistical Analysis

We identified a final analytical sample of 1831 adult cardiac surgical ICU patients extracted from MIMIC-IV version 3.1. Eligibility prerequisites included: routine differential complete blood count recording AEC within

the initial 24 hours of ICU stay, plus at least one formal CAM-ICU screening assessment. The CAM-ICU serves as the guideline-endorsed standard delirium screening instrument for critically ill adults, with all screening assessments scheduled within the 24–72 hour postoperative window.

We designated the first 24-hour postoperative AEC measurement as our main exposure variable, evaluating this marker in two formats: a continuous metric, and categorical quartile groups stratified by its overall sample distribution. Our primary endpoint was postoperative delirium, classified as a binary outcome when patients met at least one of three predefined criteria within the 24–72 hours postoperative monitoring window: positive CAM-ICU screening, clinical notes documenting delirium symptoms, or validated delirium ICD-9/ICD-10 diagnostic codes.

2.4.1 Descriptive Statistics and Group Comparisons

Continuous variables with an approximately normal distribution are expressed as the mean ± standard deviation and compared using the independent two-sample *t*-test for two-group comparisons, or one-way analysis of variance (ANOVA) for comparisons across AEC quartiles. Non-normal (skewed) continuous data are presented as the median (interquartile range) and compared using the Wilcoxon rank-sum (Mann-Whitney U) test for two groups, or the Kruskal-Wallis H test for multi-group comparisons across quartiles. Categorical variables are shown as counts (percentages) and assessed with the chi-square (χ^2) test or Fisher's exact test as appropriate. A two-sided p-value < 0.05 was considered statistically significant.

2.4.2 Covariate Selection

Candidate covariates were predetermined from prior epidemiologic studies, assessed for their clinical relevance for POD following cardiac surgery, and screened using predefined statistical criteria. Variables meeting a relaxed univariate significance threshold ($p < 0.20$) were carried forward into multivariable models, consistent with risk-adjustment practices commonly used in observational cardiac surgery research. This strategy was intended to reduce residual confounding while avoiding model overfitting and retaining clinically meaningful associations with POD.

2.4.3 Assessment of Multicollinearity

Before constructing the models, we evaluated multicollinearity among all covariates considered for multivariable analysis by calculating variance inflation factors (VIFs). A VIF >5 was predefined as indicating problematic collinearity. Covariates exhibiting such high collinearity were either removed from the final models or combined into composite indices to avoid biased effect estimates.

2.4.4 Multivariable Logistic Regression Modeling

To mitigate confounding, we fitted a series of stepwise multivariable logistic regression models using covariates that had been preselected and checked for collinearity: (1) an unadjusted crude model; (2) a model adjusted for age, sex and race; (3) the previous model with additional adjustment for heart rate, systolic blood pressure, body temperature, hemoglobin, platelet count and blood glucose; and (4) a final model that further included the CCI and the SAPS II.

2.4.5 Supplementary and Sensitivity Analyses

To evaluate potential nonlinearity in the relationship between AEC and POD, restricted cubic spline models were fitted with knots positioned at the 25th, 50th, and 75th percentiles of the AEC distribution [16]. When the nonlinearity test reached statistical significance ($p < 0.05$), segmented (piecewise) logistic regression was used to probe for possible threshold effects. For sensitivity analyses, the multivariable models were reconstructed using the original complete-case dataset without imputation to verify the robustness of primary results, given that multiple imputation was used for missing covariates in the main analyses (**Supplementary Table 2**).

All analyses were carried out using R version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and Free Statistics version 2.4 (Beijing Free Clinical Medical Technology Co., Ltd., Beijing, China). Unless stated otherwise, two-sided p-values < 0.05 were considered statistically significant. Reporting adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

3. Results

3.1 Baseline Characteristics

Among 1831 patients undergoing cardiac surgery, the overall incidence of POD within 24–72 hours postoperatively was 11.7% (n = 215). AEC measured within the first 24 hours postoperatively was categorized into quartiles (Table 1). Baseline characteristics across the AEC quartiles differed in terms of sex, systolic blood pressure, respiratory rate, leukocyte count, platelet count, glucose level, diabetes mellitus, chronic kidney disease (CKD), and CCI (all $p < 0.05$). No significant differences were observed for age, race, heart rate, body temperature, serum potassium, SAPS II, and APS III. Although some between-group comparisons reached statistical significance, the absolute differences were small and clinically negligible (Table 1). We also performed baseline comparisons between included patients and those excluded due to missing postoperative AEC measurements (**Supplementary Table 1**). Several variables showed statistically significant differences at the conventional test level ($p < 0.05$); however, the absolute magnitudes of these differences were small.

3.2 Association Between AEC and POD

In unadjusted logistic regression (**Supplementary Table 3**), several variables were associated with POD follow-

Table 1. Baseline clinical characteristics of the study population.

Variables	AEC ($\times 10^9$/L)					*p* value
	Total (n = 1831)	Q1 (<0.05) (n = 376)	Q2 (0.05–0.1) (n = 524)	Q3 (0.11–0.17) (n = 455)	Q4 (≥0.18) (n = 476)	
Demographic characteristics						
Age (years)	68.6 ± 10.4	68.2 ± 11.3	68.7 ± 10.6	69.4 ± 9.7	68.1 ± 9.9	0.204
Sex, n (%)						0.001
Female	408 (22.3)	112 (29.8)	106 (20.2)	90 (19.8)	100 (21.0)	
Male	1423 (77.7)	264 (70.2)	418 (79.8)	365 (80.2)	376 (79.0)	
Race, n (%)						0.354
White	1273 (69.5)	240 (63.8)	373 (71.2)	324 (71.2)	336 (70.6)	
Black	74 (4.0)	15 (4.0)	23 (4.4)	18 (4.0)	18 (3.8)	
Other	484 (26.4)	121 (32.2)	128 (24.4)	113 (24.8)	122 (25.6)	
Physiological parameters						
HR (beats/min)	80.8 ± 9.5	81.7 ± 10.7	80.5 ± 9.3	80.4 ± 8.9	80.8 ± 9.0	0.203
SBP (mmHg)	110.8 ± 7.9	109.7 ± 8.1	110.5 ± 8.0	111.2 ± 7.2	111.6 ± 8.1	0.003
RR (breaths/min)	18.2 ± 2.6	18.5 ± 3.1	18.2 ± 2.6	18.0 ± 2.4	18.0 ± 2.4	0.019
Temperature (°C)	36.7 ± 0.4	36.7 ± 0.5	36.7 ± 0.4	36.7 ± 0.4	36.7 ± 0.3	0.393
Laboratory values						
WBC ($\times 10^9$/L)	17.6 ± 7.3	17.8 ± 11.2	16.4 ± 5.5	17.5 ± 5.6	19.1 ± 6.1	<0.001
Hb (g/dL)	8.9 ± 1.6	8.7 ± 1.8	8.9 ± 1.5	9.0 ± 1.5	9.0 ± 1.6	0.045
PLT ($\times 10^9$/L)	130.9 ± 48.6	122.9 ± 54.5	125.7 ± 49.0	130.0 ± 43.0	143.7 ± 45.7	<0.001
Glucose (mg/dL), mean ± SD	135.4 ± 19.2	139.3 ± 23.3	134.9 ± 17.2	132.9 ± 17.5	135.4 ± 18.8	<0.001
Potassium (mmol/L)	4.7 ± 0.5	4.6 ± 0.6	4.6 ± 0.5	4.7 ± 0.5	4.7 ± 0.6	0.062
Comorbidities						
Diabetes, n (%)						0.003
Yes	344 (18.8)	57 (15.2)	88 (16.8)	84 (18.5)	115 (24.2)	
No	1487 (81.2)	319 (84.8)	436 (83.2)	371 (81.5)	361 (75.8)	
CKD, n (%)						<0.001
Yes	395 (21.6)	61 (16.2)	99 (18.9)	121 (26.6)	114 (23.9)	
No	1436 (78.4)	315 (83.8)	425 (81.1)	334 (73.4)	362 (76.1)	
CCI, score	5.6 ± 2.1	5.6 ± 2.1	5.4 ± 2.0	5.7 ± 2.2	5.8 ± 2.2	0.019
Disease severity						
SAPS II score	38.6 ± 11.3	38.6 ± 11.5	38.0 ± 11.0	38.2 ± 10.8	39.4 ± 11.9	0.217
APS III score	40.5 ± 19.2	42.4 ± 20.2	39.6 ± 19.4	39.3 ± 17.7	41.0 ± 19.6	0.069

Abbreviations: AEC, absolute eosinophil count; HR, heart rate; SBP, systolic blood pressure; RR, respiratory rate; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; CKD, chronic kidney disease; CCI, Charlson Comorbidity Index; SAPS II, Simplified Acute Physiology Score II; APS III, Acute Physiology Score III; IQR, interquartile range. Values are presented as the mean ± standard deviation, number (percentage), or median (interquartile range) unless otherwise stated. Categorical variables were analyzed using the χ^2 test or Fisher's exact test as appropriate; normally distributed continuous variables were analyzed using the independent two-sample *t*-test; non-normally distributed continuous variables were analyzed using the Wilcoxon rank-sum (Mann-Whitney U) test; Comparisons across AEC quartiles were performed using one-way analysis of variance (ANOVA) for normally distributed continuous variables and the Kruskal–Wallis H test for non-normally distributed continuous variables. A two-sided *p*-value < 0.05 was considered statistically significant.

ing cardiac surgery. Increasing age was linked to elevated odds of POD (per 1-year increment: odds ratio (OR) 1.04, 95% CI 1.03–1.06, $p < 0.001$), whereas male sex was associated with lower odds (OR 0.65, 95% confidence interval (CI) 0.48–0.90, $p = 0.009$). No statistically significant differences were observed across racial groups (all $p > 0.05$). For physiological parameters, body temperature, heart rate, systolic blood pressure, and respiratory rate showed no statistically significant associations with POD (all $p > 0.05$). Regarding laboratory markers, higher hemoglobin was associated with reduced odds of POD in unadjusted analysis (per 1-g/dL increase: OR 0.69, 95% CI 0.63–0.77, $p < 0.001$). Platelet count, blood glucose, and serum potassium all demonstrated modest but statistically significant positive associations with POD risk (all $p < 0.05$), while white blood cell count showed no significant correlation ($p = 0.130$). Comorbid conditions including diabetes mellitus, chronic kidney disease, and elevated CCI, as well as higher disease

Table 2. Association between AEC and postoperative delirium: a logistic regression analysis.

Variable	Total (n)	Crude model		Model I		Model II		Model III	
		OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Per 1-SD increase	1831	0.79 (0.66~0.94)	0.008	0.8 (0.67~0.96)	0.015	0.83 (0.70~0.99)	0.042	0.80 (0.67~0.96)	0.016
Quartile of AEC									
Q1	376	1 (Ref)		1 (Ref)		1 (Ref)		1 (Ref)	
Q2	524	0.57 (0.39~0.84)	0.005	0.57 (0.38~0.85)	0.006	0.62 (0.41~0.94)	0.023	0.63 (0.42~0.94)	0.025
Q3	455	0.71 (0.48~1.05)	0.085	0.71 (0.48~1.05)	0.085	0.83 (0.55~1.26)	0.388	0.78 (0.52~1.19)	0.251
Q4	476	0.47 (0.31~0.71)	<0.001	0.48 (0.31~0.74)	0.001	0.54 (0.35~0.84)	0.006	0.50 (0.32~0.78)	0.002
p-value for trend test			0.003		0.005		0.034		0.011

Crude model was unadjusted.

Model I was adjusted for age, sex, and race.

Model II was further adjusted for HR, SBP, temperature, Hb, PLT, and glucose, on the basis of Model I.

Model III was further adjusted for CCI and SAPS II, on the basis of Model II.

All data are presented as OR (95% CI) with corresponding *p*-values.

Abbreviations: AEC, absolute eosinophil count; OR, odds ratio; CI, confidence interval; HR, heart rate; SBP, systolic blood pressure; Hb, hemoglobin; PLT, platelet; CCI, Charlson Comorbidity Index; SAPS II, Simplified Acute Physiology Score II.

severity scores for SAPS II and APS III were consistently associated with increased odds of POD (all $p < 0.01$).

Additionally, we conducted multivariable logistic regression analyses to evaluate the independent association between early postoperative AEC and POD. Before fitting multivariable logistic regression models, we evaluated multicollinearity among all candidate covariates selected for sequential confounder adjustment. No notable multicollinearity was found in the covariates retained for the fully adjusted model (Model III). VIFs ranged from 1.09 to 2.89 (all <5) (**Supplementary Table 4**), indicating that collinearity was unlikely to bias subsequent regression estimates.

Using these pre-screened variables that were assessed for collinearity, we then fitted a series of sequential multivariable logistic models. The inverse relationship between higher AEC and lower risk of POD remained after stepwise adjustment (Table 2). When AEC was treated as a continuous variable (per 1-standard deviation (1-SD) increase), higher values were linked to a significantly lower odds of POD in unadjusted analysis (OR 0.79, 95% CI 0.66–0.94, $p = 0.008$), equivalent to a 21% relative reduction in odds. This protective association persisted across all adjusted models: Model I (adjusted for age, sex, and race), OR 0.80 (95% CI 0.67–0.96, $p = 0.015$); Model II (additional adjustment for heart rate, systolic blood pressure, temperature, hemoglobin, platelet count, and glucose), OR 0.83 (95% CI 0.70–0.99, $p = 0.042$); and the fully adjusted Model III (further adjusted for CCI and SAPS II), OR 0.80 (95% CI 0.67–0.96, $p = 0.016$).

When AEC was examined by quartiles (Q1 as reference), a graded inverse association with POD was observed. In Model III, Q4 was associated with a 50% reduction in adjusted odds (OR 0.50, 95% CI 0.32–0.78, $p = 0.002$) and Q2 with a 37% reduction (OR 0.63, 95% CI 0.42–0.94, $p = 0.025$). Q3 had an OR of <1 (0.78), but this was not significant ($p = 0.251$). A significant linear trend across increasing AEC quartiles persisted in the fully adjusted model (p for trend = 0.011).

3.3 Additional Analyses Assessing Robustness of the Findings

Next, we tested the stability of the early AEC-POD relationship by repeating all analyses in the complete-case (non-imputed) dataset (**Supplementary Table 5**). When AEC was analyzed as a continuous variable (per 1-SD increase), the inverse association remained significant in the unadjusted and minimally adjusted models (unadjusted: OR 0.79, 95% CI 0.66–0.94, $p = 0.008$; Model I: OR 0.80, 95% CI 0.67–0.96, $p = 0.017$). After further adjustment for physiologic and laboratory covariates (Model II) and then for comorbidity and illness severity (Model III), the point estimates remained <1 (Model II: OR 0.90, 95% CI 0.75–1.08, $p = 0.259$; Model III: OR 0.87, 95% CI 0.72–1.05, $p = 0.139$). When AEC was categorized by quartile, a consistent dose-response pattern emerged. Q2 and Q4 showed substantially lower odds of POD relative to Q1 in both crude and Model I analyses (for example, Q2 crude: OR 0.57, $p = 0.005$; Q4 crude: OR 0.47, $p < 0.001$; Model I Q2: OR 0.58, $p = 0.008$; Model I Q4: OR 0.49, $p = 0.001$). In Models II

and III, the protective ORs generally remained <1, but lost statistical significance or became borderline (for instance, Q4 Model III: OR 0.62, 95% CI 0.38–1.01, $p = 0.056$), and trend tests were weakened after full covariate adjustment.

Taken together, the estimates consistently point to a protective association between higher postoperative AEC and reduced POD risk. The loss of significance in the fully adjusted, non-imputed analyses likely reflects the smaller effective sample size and increased model complexity rather than a true reversal of effect, highlighting the need for larger prospective studies to confirm these findings.

3.4 Dose-Response Association Between AEC and POD

We modeled the association between postoperative AEC and POD risk using restricted cubic spline (Fig. 2). Relative to a standardized z-score reference value of –0.2003 for AEC, incrementally elevated eosinophil z-score values correlated with reduced likelihood of POD. The overall association reached statistical significance ($p = 0.024$), and there was no evidence of nonlinearity ($p = 0.305$), consistent with a linear inverse relationship between AEC and POD after cardiac surgery.

3.5 Subgroup-Specific Associations

We conducted prespecified subgroup analyses (Fig. 3) to determine whether the relationship between postoperative AEC and POD varied across 7 predefined groups: sex, age, body temperature, blood glucose, hemoglobin, SAPS II, and CCI. Interaction p-values were adjusted for false discovery rate (FDR) using the Benjamini-Hochberg method (**Supplementary Table 6**).

Across all strata, higher AEC was consistently associated with a lower risk of POD. No significant effect modification was identified, with every FDR-adjusted interaction p-value exceeding 0.05 (range 0.867–0.869).

In sex-specific analyses, a 1-SD rise in AEC was associated with a statistically significant protective effect in men (n = 1423; fully adjusted OR 0.80, 95% CI 0.65–0.98). For women, the estimate was similar in direction but not significant (n = 408; OR 0.81, 95% CI 0.56–1.17, p for interaction = 0.619). With regard to age, patients younger than 65 years showed a significant protective association (OR 0.70, 95% CI 0.49–0.99), while those 65 years or older exhibited a comparable inverse trend that did not reach significance (OR 0.85, 95% CI 0.69–1.05, p for interaction = 0.237).

When stratified by body temperature, a significant protective effect was observed in patients with temperature ≥36.5 °C (n = 1378; OR 0.79, 95% CI 0.64–0.99), whereas those with temperature <36.5 °C showed a consistent inverse trend that did not reach statistical significance (n = 453; OR 0.86, 95% CI 0.62–1.20, p for interaction = 0.772). Significant protective associations were likewise observed in subgroups defined by blood glucose ≥126 mg/dL, hemoglobin ≥7 g/dL, SAPS II score ≥35, and

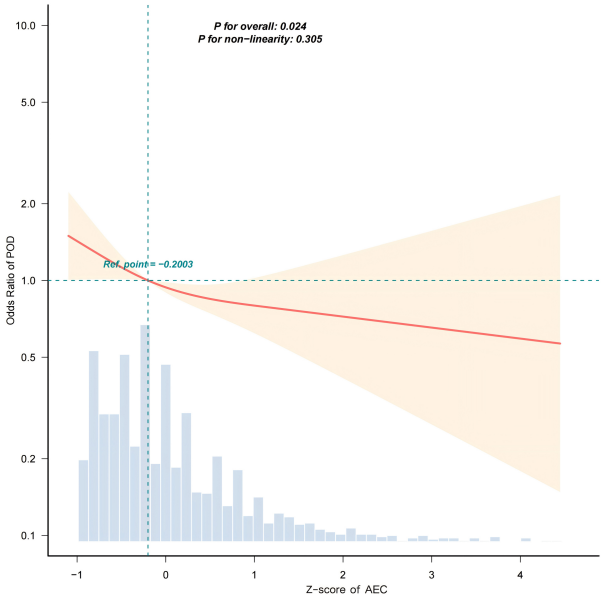


Fig. 2. Dose-response relationship between absolute eosinophil count (AEC) and risk of postoperative delirium (POD). Restricted cubic spline (RCS) regression analysis of the dose-response relationship between early postoperative AEC and POD risk (reference point = –0.2003). The solid line represents the adjusted odds ratio (OR) of POD for each AEC level, and the shaded area indicates the 95% confidence interval (CI). p for non-linearity = 0.305 and p for overall association = 0.024, confirming a linear inverse relationship between AEC and POD risk. Abbreviations: AEC, absolute eosinophil count; POD, postoperative delirium; OR, odds ratio; CI, confidence interval; RCS, restricted cubic spline.

CCI score ≥4 (all $p < 0.05$), without evidence of meaningful effect modification for any of these comparisons.

Overall, these subgroup results reinforce the robustness of the inverse association between postoperative AEC and POD, with no indication of clinically important effect modification across the examined characteristics.

4. Discussion

In this cohort of 1831 cardiac surgery patients from the MIMIC IV database, we found that lower AEC measured within 24 hours of ICU admission was independently associated with higher odds of subsequent POD. This inverse association remained robust across sequential adjustment models and was supported by a monotonic dose-response relationship (p for overall = 0.024; p for non-linearity = 0.305). Stratified analyses showed consistent results across prespecified subgroups (all interactions $p >$ 0.05), with more pronounced significance in men and in patients with higher illness severity, greater comorbidity, and hyperglycemia. These findings suggest that postoperative

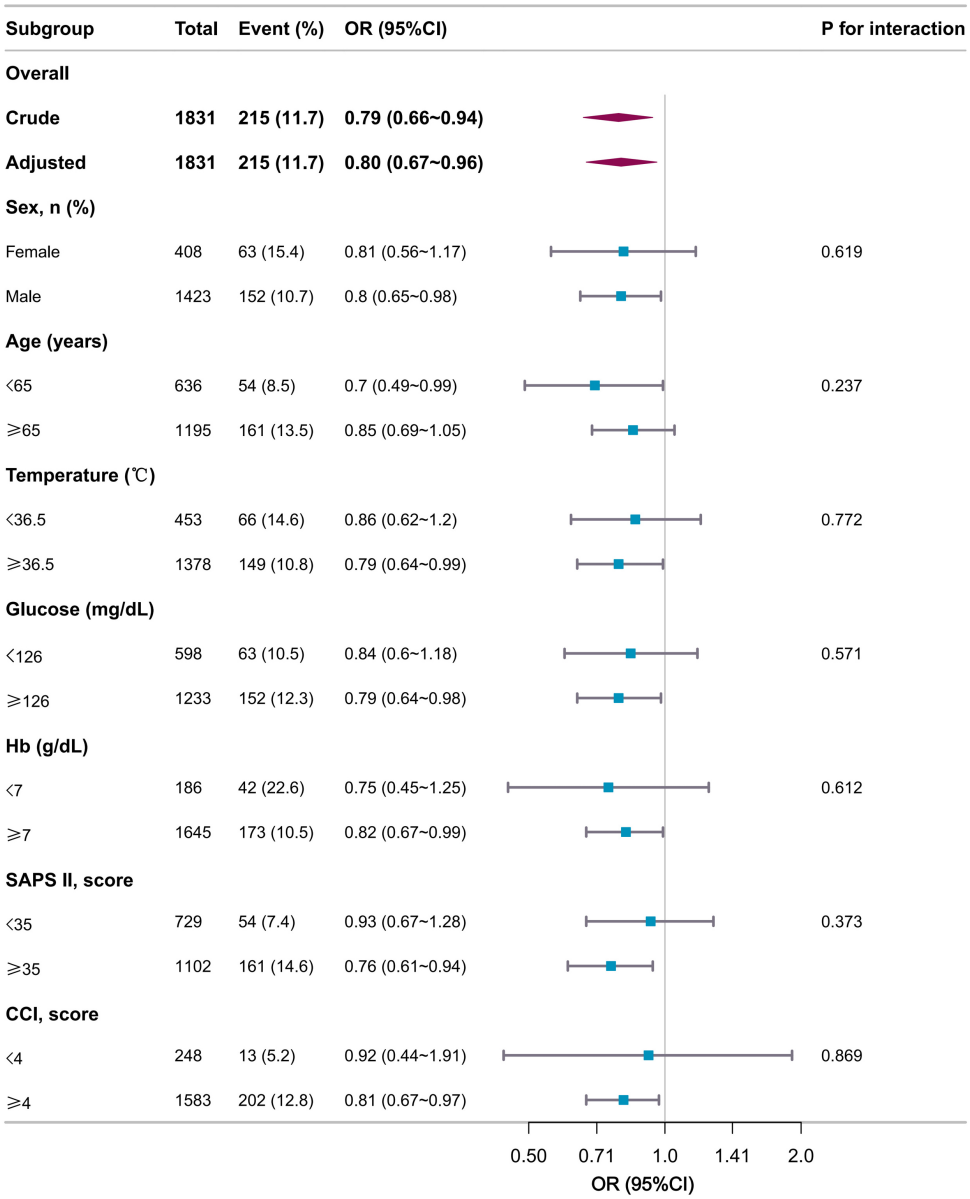


Fig. 3. Subgroup analyses of the association between absolute eosinophil count (AEC) and postoperative delirium (POD). Forest plot showing adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between early postoperative AEC and POD across predefined subgroups. Subgroups were stratified by sex, age (years), temperature, glucose, hemoglobin (Hb), and Simplified Acute Physiology Score II (SAPS II), as well as Charlson Comorbidity Index (CCI). The solid vertical line indicates an OR of 1.0 (no association). No significant interaction effects were detected (all p for interaction >0.05), indicating a consistent association across all subgroups. Abbreviations: AEC, absolute eosinophil count; POD, postoperative delirium; OR, odds ratio; CI, confidence interval; Hb, hemoglobin; CCI, Charlson Comorbidity Index; SAPS II, Simplified Acute Physiology Score II.

eosinopenia may be a potential independent biomarker for cardiac surgery-associated delirium.

POD is a common and severe complication of cardiac surgery [17,18], associated with prolonged ICU stay, increased healthcare costs, persistent cognitive decline, and elevated long-term mortality [19]. One analysis drawing on nationwide Medicare patient records calculated that each delirium event added roughly $8110 to individual inpatient care expenses, and financial burdens grew substantially for patients living with concurrent Alzheimer's disease or other dementia subtypes [20]. This highlights the critical clinical and economic value of early identification and prevention of delirium. Although clinical practice guidelines for the management of ICU delirium are now available [21], the pathogenesis of POD remains incompletely understood. Specific pharmacotherapies targeting postoperative delirium (POD) have thus far yielded only modest clinical benefits. While anti-inflammatory agents such as ulinastatin

exert promising protective effects by modulating perioperative nitric oxide surges, robust high-quality randomized controlled trials (RCTs) are still needed to rigorously validate their real-world clinical efficacy [22]. There is an urgent clinical need for more refined early risk stratification tools and preventive strategies [23]. Accordingly, exploring novel and readily accessible early biomarkers for POD carries substantial clinical significance.

Previous studies have predominantly focused on traditional clinical risk factors or non-specific systemic inflammatory markers, such as C-reactive protein and total leukocyte count. However, these markers are generally elevated after cardiac surgery with cardiopulmonary bypass, making it difficult to isolate genuine signals for delirium risk [5]. Consequently, specific biomarkers capable of reflecting the body's anti-inflammatory capacity or neuroprotective reserve hold substantial clinical value. The study of Wu et al. [24] has additionally tied shifts in perioperative immune cell populations to delirium risk after cardiac procedures. Several recent works uncovered links between postoperative delirium and emerging laboratory markers: fibroblast growth factor 23, triglyceride-glucose index, and fluctuating levels of circulating inflammatory cytokines [25,26,27,28,29]. A pooled meta-analysis of existing clinical trials further validated consistent correlations between POD and key inflammatory mediators such as IL-6, CRP, and IL-8 [30]. Moreover, perioperative redox imbalance has been implicated in delirium after cardiac surgery, suggesting that oxidative stress also constitutes a pathogenic pathway in POD [31]. Among these emerging biomarkers, AEC offers distinct practical advantages: it is routinely measured as part of the complete blood count, inexpensive, and available at the bedside within minutes, making it particularly suitable for early postoperative risk stratification in the ICU setting.

We employed three complementary analytical strategies, all of which yielded convergent evidence supporting an inverse AEC-POD association. Multivariable logistic regression demonstrated an independent association after extensive adjustment for established confounders. Restricted cubic spline modeling confirmed a linear dose-response relationship without evidence of a threshold effect, validating the linear modeling premise. Subgroup analyses further showed consistent protective effects across all pre-specified strata, with no significant interactions. Notably, the association appeared more pronounced in male patients and those with higher SAPS II scores, greater comorbidity burdens, or postoperative hyperglycemia. This pattern may reflect heightened baseline systemic inflammation in these subgroups, creating greater physiological demand for endogenous immunomodulatory mediators such as eosinophils. Together, these three analytical approaches cross-validate one another and provide robust statistical support for an independent association between early postoperative AEC and POD.

Neuroinflammation is now widely recognized as a core mechanism underlying delirium: circulating pro-inflammatory cytokines can penetrate the compromised blood-brain barrier, activate microglia, and induce neurotransmitter imbalance and neuronal dysfunction, ultimately precipitating delirium [5,6]. Anti-inflammatory cytokines tightly regulate this process, with IL-10 playing a particularly pivotal role [10,12]. Eosinophils are important immunomodulatory cells that maintain immune homeostasis through the secretion of two classes of key mediators: type 2 cytokines such as IL-4, IL-13, and IL-10, which suppress excessive inflammatory responses, and neurotrophic factors including nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), which protect neurons and preserve synaptic function [8,9]. Accordingly, a reduction in early postoperative AEC signifies the loss of this critical anti-inflammatory and neuroprotective barrier. On one hand, the amplification of neuroinflammation cannot be effectively restrained, while on the other, insufficient neurotrophic support renders brain cells more vulnerable to surgical stress-induced injury, thereby elevating the risk of POD. Of note, eosinophils exhibit functional plasticity across different disease microenvironments, and their protective roles in tissue repair and immune regulation contrast with reports of pro-inflammatory functions under certain inflammatory conditions [7]. Recent animal research reveals that IL-10 signals through its receptor IL-10R to lower intracellular lipid ROS levels in oligodendrocyte progenitors, blunting ferroptosis and conferring neuroprotection [12], thereby providing experimental evidence for the "eosinophil-IL-10-neuroprotection" axis. Additionally, gut-brain axis dysfunction may contribute to delirium pathogenesis through neuroinflammatory cascades that potentially synergize with eosinophil-mediated immune regulation [32]. Therefore, in the context of the present study, a dose-dependent increase in early postoperative AEC may reflect a more intact anti-inflammatory and neuroprotective system, enabling the brain to better withstand the insult of surgical stress.

Perioperative and ICU sedation practices may exert confounding effects on the assessment of delirium. Sedative agents and the depth of sedation can influence delirium evaluation through multiple mechanisms. Deep sedation blunts patient arousal, making bedside delirium screening tools such as the CAM-ICU unreliable and contributing to underrecognition of hypoactive delirium. On the other hand, emergence from anesthesia or sedation weaning can produce agitation and cognitive fluctuations that may mimic delirium or even precipitate episodes. In the present study, we mitigated these confounders by temporally segregating the exposure and outcome windows. Early AEC was measured within 24 hours of ICU admission, and the occurrence of delirium was assessed between 24 and 72 hours. This approach effectively attenuates the residual impact of intraoperative anesthetic effects on the findings.

5. Limitations

Several limitations of this study should be acknowledged. First, some data were missing from the retrospective MIMIC-IV cohort, and only the first AEC value within 24 hours of ICU admission was analyzed. This precluded the evaluation of longitudinal AEC trends, which is a common constraint of ICU database-based retrospective studies. Second, the delirium incidence of 11.7% was lower than most prior reports, driven largely by our restricted 24–72 hours outcome window (focused on early inflammation-related delirium, and excluding late-onset cases from nosocomial infection, electrolyte disturbances, or prolonged sedation), and the exclusion of patients without valid AEC records. Both factors may have introduced mild selection bias. We compared baseline characteristics across participants with and without postoperative AEC testing. Patients with and without postoperative AEC measurements differed in several recorded baseline variables at the conventional threshold of $p < 0.05$. Although the absolute magnitude of these differences was small, this still suggests that missing AEC data may introduce potential selection bias. Even so, residual selection bias stemming from excluding individuals lacking AEC testing-along with unmeasured confounding differences-cannot be completely ruled out. Additionally, the lack of continuous Richmond agitation-sedation scale (RASS) and precise sedative dosing data prevents full adjustment for sedation-related assessment bias and outcome misclassification. Nonetheless, the tight temporal alignment of exposure and outcome windows means this limitation primarily affects incidence estimates, not the strength of the AEC-delirium association. Third, despite multivariable regression, restricted cubic spline, and subgroup analyses to control for confounding, residual bias remains, and the present observational design cannot confirm a causal relationship between reduced AEC and delirium. Fourth, findings from this single U.S. tertiary center require careful generalization to other ethnic groups, geographic regions, and non-cardiac surgery populations.

6. Conclusion

Early postoperative AEC represents an independent correlate of postoperative delirium among cardiac surgery patients. As a simple, routinely available biomarker, early postoperative AEC enables pre-emptive POD risk stratification, supporting targeted early intervention and intensified clinical monitoring to reduce postoperative neurocognitive complications.

Abbreviations

AEC, absolute eosinophil count; APS III, Acute Physiology Score III; CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; CCI, Charlson Comorbidity Index; CI, confidence interval; CKD, chronic kidney disease; Hb, hemoglobin; HR, heart rate; ICU, intensive care unit; IQR, interquartile range; MIMIC-IV, Medical Information Mart for Intensive Care IV; OR, odds ratio; PLT, platelet; POD, postoperative delirium; RCS, restricted cubic spline; RR, respiratory rate; SAPS II, Simplified Acute Physiology Score II; SBP, systolic blood pressure; SD, standard deviation; WBC, white blood cell.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

WDZ: Conceived and designed the study; participated in data acquisition; performed formal statistical analysis, interpreted study findings, and oversaw the analytical process; drafted the initial manuscript, prepared all figures and tables, and critically revised the manuscript for important intellectual content. QYC: participated in data collection; supervised data analysis work; and critically revised the manuscript for important intellectual content. Both authors have approved the final version of the manuscript for publication and take full responsibility for all aspects of the work. They ensure that any questions related to the accuracy and integrity of the manuscript content will be properly investigated and resolved.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and relevant medical ethics requirements. We used de-identified data from the publicly accessible Medical Information Mart for Intensive Care (MIMIC-IV) database, which has obtained relevant ethical approval and is open to eligible researchers. Since all data have been fully de-identified, the requirement for written informed consent was waived accordingly. This study was also reviewed and approved by the Ethics Committee of Beijing Jingmei Group General Hospital (approval number: 2025-research-038-01).

Acknowledgment

We thank the PhysioNet team for providing access to the MIMIC-IV database, and all staff and patients who contributed to the development of the MIMIC-IV database.

Funding

This work was supported by the Hospital-level Scientific Research Independent Project of General Hospital of Beijing Jingmei Group (Grant No. ZZ2025-13).

Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/HSF52731.

References

[1] Vasilevskis EE, Han JH, Hughes CG, Ely EW. Epidemiology and risk factors for delirium across hospital settings. Best Practice & Research. Clinical Anaesthesiology. 2012; 26: 277–287. https://doi.org/10.1016/j.bpa.2012.07.003

[2] Hshieh TT, Gou RY, Jones RN, Leslie DL, Marcantonio ER, Xu G, et al. One-year Medicare costs associated with delirium in older hospitalized patients with and without Alzheimer's disease dementia and related disorders. Alzheimer's & Dementia: the Journal of the Alzheimer's Association. 2023; 19: 1901–1912. https://doi.org/10.1002/alz.12826

[3] Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK, et al. Cognitive trajectories after postoperative delirium. The New England Journal of Medicine. 2012; 367: 30–39. https://doi.org/10.1056/NEJMoa1112923

[4] Pan S, Wang G. Multimodal brain-gut-sleep phenotypes predict delirium, long-term cognitive decline, and survival after colorectal cancer surgery. Psychoneuroendocrinology. 2026; 187: 107794. https://doi.org/10.1016/j.psyneuen.2026.107794

[5] Cerejeira J, Firmino H, Vaz-Serra A, Mukaetova-Ladinska EB. The neuroinflammatory hypothesis of delirium. Acta Neuropathologica. 2010; 119: 737–754. https://doi.org/10.1007/s00401-010-0674-1

[6] Heffernan ÁB, Steinruecke M, Dempsey G, Chandran S, Selvaraj BT, Jiwaji Z, et al. Role of glia in delirium: proposed mechanisms and translational implications. Molecular Psychiatry. 2025; 30: 1138–1147. https://doi.org/10.1038/s41380-024-02801-4

[7] Rosenberg HF, Dyer KD, Foster PS. Eosinophils: changing perspectives in health and disease. Nature Reviews. Immunology. 2013; 13: 9–22. https://doi.org/10.1038/nri3341

[8] Jacobsen EA, Helmers RA, Lee JJ, Lee NA. The expanding role(s) of eosinophils in health and disease. Blood. 2012; 120: 3882–3890. https://doi.org/10.1182/blood-2012-06-330845

[9] Jesenak M, Diamant Z, Simon D, Tufvesson E, Seys SF, Mukherjee M, et al. Eosinophils-from cradle to grave: An EAACI task force paper on new molecular insights and clinical functions of eosinophils and the clinical effects of targeted eosinophil depletion. Allergy. 2023; 78: 3077–3102. https://doi.org/10.1111/all.15884

[10] Zhou Z, Peng X, Insolera R, Fink DJ, Mata M. Interleukin-10 provides direct trophic support to neurons. Journal of Neurochemistry. 2009; 110: 1617–1627. https://doi.org/10.1111/j.1471-4159.2009.06263.x

[11] Glumac S, Kardum G, Sodic L, Supe-Domic D, Karanovic N. Effects of dexamethasone on early cognitive decline after cardiac surgery: A randomised controlled trial. European Journal of Anaesthesiology. 2017; 34: 776–784. https://doi.org/10.1097/EJA.0000000000000647

[12] Wu W, Luo Z, Shen D, Lan T, Xiao Z, Liu M, et al. IL-10 protects against OPC ferroptosis by regulating lipid reactive oxygen species levels post stroke. Redox Biology. 2024; 69: 102982. https://doi.org/10.1016/j.redox.2023.102982

[13] Guan C, Wang K, Gong A, Zhao Y, Yu H, Zhang S, et al. Association between blood eosinophil levels and prognosis in critically ill patients with different heart failure phenotypes. Scientific Reports. 2025; 15: 6008. https://doi.org/10.1038/s41598-025-90778-7

[14] Liu W, Zeng W, Huang Z, Yuan Q. Association of body mass index changes with short-term mortality risks in ICU patients with sepsis across different admission BMI states: Analysis of the MIMIC-IV database. Frontiers in Immunology. 2025; 16: 1698405. https://doi.org/10.3389/fimmu.2025.1698405

[15] White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Statistics in Medicine. 2011; 30: 377–399. https://doi.org/10.1002/sim.4067

[16] Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. Statistics in Medicine. 2010; 29: 1037–1057. https://doi.org/10.1002/sim.3841

[17] Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. Lancet (London, England). 2014; 383: 911–922. https://doi.org/10.1016/S0140-6736(13)60688-1

[18] Marcantonio ER. Delirium in Hospitalized Older Adults. The New England Journal of Medicine. 2017; 377: 1456–1466. https://doi.org/10.1056/NEJMcp1605501

[19] Inouye SK. Delirium in older persons. The New England Journal of Medicine. 2006; 354: 1157–1165. https://doi.org/10.1056/NEJMra052321

[20] Garcia Morales EE, Umoh ME, Luu K, Oh ES, Reed NS. Additional hospitalization costs associated with delirium among older adults: evidence from the Medicare Current Beneficiary Survey. Frontiers in Public Health. 2026; 14: 1750969. https://doi.org/10.3389/fpubh.2026.1750969

[21] Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Critical Care Medicine. 2018; 46: e825–e873. https://doi.org/10.1097/CCM.0000000000003299

[22] Ran X, Liu J, Tan J, Luo F, Yang P, Xu TT, et al. Ulinastatin attenuates perioperative nitric oxide surge and postoperative delirium in cardiac surgery: a prospective cohort study with molecular docking and experimental validation. International Journal of Surgery (London, England). 2026; 112: 6696–6708. https://doi.org/10.1097/JS9.0000000000004039

[23] Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Audisio R, Borozdina A, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. European Journal of Anaesthesiology. 2017; 34: 192–214. https://doi.org/10.1097/EJA.0000000000000594

[24] Wu J, Cheng Z, Liao X, Yang P, Wu Q, Wang T, et al. Perioperative Profiles of Immune Cells in Patients with Postoperative Delirium After Cardiac Surgery with Cardiopulmonary Bypass. Biomedicines. 2025; 13: 2962. https://doi.org/10.3390/biomedicines13122962

[25] Wiredu K, Qu J, Turco I, McKay TB, Akeju O. Systemic Inflammation and Metabolic Changes After Cardiac Surgery and Postoperative Delirium Risk. Journal of Clinical Medicine. 2025; 14: 4600. https://doi.org/10.3390/jcm14134600

[26] Szczupak M, Kobak J, Ingielewicz A, Wiśniewski J, Krupa-Nurcek S. The Role of C-Reactive Protein as a Biomarker for Postoperative Delirium Following Cardiac and Neurosurgical Surgery: A Retrospective Analysis. Journal of Clinical Medicine. 2025; 14: 8252. https://doi.org/10.3390/jcm14228252

[27] Zeng J, Li N, Ma C, Song Y, Tian W, Gao Y, et al. Association between triglyceride-glucose index and postoperative delirium following cardiac surgery: a multicenter retrospective analysis. Lipids in Health and Disease. 2025; 24: 330. https://doi.org/10.1186/s12944-025-02769-2

[28] Simon C, Kelly Graves O, Williams VE, Turco I, Mueller A, Trigo M, et al. Targeted profiling of the serum proteome associates increased FGF-23 levels with postoperative delirium in cardiac surgical patients. NPJ Dementia. 2026; 2: 31. https://doi.org/10.1038/s44400-026-00084-w

[29] Hansen N, Knopp CM, Esselmann H, Celano CM, Derad C, Asendorf T, et al. Prediction of postoperative delirium after cardiac surgery by the interplay between preoperative plasma p-tau181 and IL-6 and heart-brain axis related factors: results from the prospective observational study FINDERI. Molecular Psychiatry. 2026; 31: 2509–2519. https://doi.org/10.1038/s41380-025-03412-3

[30] Mosharaf MP, Alam K, Gow J, Mahumud RA. Cytokines and inflammatory biomarkers and their association with postoperative delirium: a meta-analysis and systematic review. Scientific Reports. 2025; 15: 7830. https://doi.org/10.1038/s41598-024-82992-6

[31] Arai Y, Koyama Y, Takahashi A, Shimada S, Yoshida T. Temporal Dynamics of Perioperative Redox Balance and Its Association with Postoperative Delirium After Cardiac Surgery. Antioxidants (Basel, Switzerland). 2026; 15: 108. https://doi.org/10.3390/antiox15010108

[32] Ma X, Zhao Y. Gut-brain axis in anesthesia and critical illness: Molecular crosstalk and its impact on delirium and outcome (Review). International Journal of Molecular Medicine. 2026; 58: 188. https://doi.org/10.3892/ijmm.2026.5859