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Clinical Research

Immunological Analysis of Postoperative Delirium after Thoracic Aortic Surgery

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Background: Delirium is a recognized neurological complication following cardiac surgery and is associated with adverse clinical outcomes, including elevated mortality and prolonged hospitalization. While several clinical risk factors for post-cardiac surgery delirium have been identified, the pathophysiology related to the immune response remains unexamined. This study was conducted to investigate the immunological factors contributing to delirium in patients after thoracic aortic surgery.
Methods: We retrospectively evaluated 43 consecutive patients who underwent thoracic aortic surgery between July 2017 and June 2018. These patients were categorized into 2 groups: those with delirium and those without it. All clinical characteristics were compared between groups. Blood samples were collected and tested on the day of admission, as well as on postoperative days 1, 3, 7, and 30. Levels of helper T cells (CD4), cytotoxic T cells (CD8), B cells (CD19), natural killer cells (CD56+CD16++), and monocytes (CD14+CD16–) were measured using flow cytometry.
Results: The median patient age was 71 years (interquartile range, 56.7 to 79.0 years), and 21 of the patients (48.8%) were male. Preoperatively, most immune cell counts did not differ significantly between groups. However, the patients with delirium exhibited significantly higher levels of interleukin-6 and lower levels of tumor necrosis factor-alpha (TNF-α) than those without delirium ($p<0.05$). Multivariate analysis revealed that lower TNF-α levels were associated with an increased risk of postoperative delirium ($p<0.05$).
Conclusion: Postoperative delirium may be linked to perioperative changes in immune cells and preoperative cytokine levels. Additional research is required to elucidate the pathophysiological mechanisms underlying delirium.

Keywords: Intensive care units, Delirium, Aorta, Surgery

Introduction

Delirium is characterized as a disturbance in consciousness, attention, cognition, and perception. According to the "Diagnostic and statistical manual of mental disorders (DSM-5), fifth edition, it may also impact sleep, psychomotor activity, and emotional state [1]. Three types of delirium are recognized: hyperactive, hypoactive, and mixed. Notably, hypoactive delirium presents with negative symptoms such as lethargy, somnolence, and inattention and accounts for nearly 92% of delirium cases in cardiac intensive care units (CICUs) [2]. Tools such as the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are used to diagnose delirium through validated monitoring processes [3].

Delirium following cardiac surgery is associated with decreased functional status, cognitive decline, prolonged hospitalization, increased cost, long-term cognitive impairment, and elevated mortality [4]. A cohort study by Gottesman et al. [5] indicated that delirium after cardiac surgery is a strong predictor of mortality for up to 10 years post-surgery, particularly in younger individuals and those without a history of stroke. In a study on the long-term cognitive outcomes of postoperative delirium, Inouye et al. [6] used the General Cognitive Performance tool and the

Informant Questionnaire on Cognitive Decline in the Elderly to assess patients up to 36 months after surgery. Their findings revealed significantly greater cognitive decline in patients who experienced postoperative delirium compared to those without delirium [6]. Cardiac surgical procedures, including vascular surgery and coronary artery bypass grafting, are associated with a rate of postoperative delirium that is approximately twice as high as that seen with other types of surgery [5].

In a CICU, as in other ICUs, patients (both with and without predisposing risk factors) are susceptible to various precipitating events that can contribute to delirium. These include the use of urinary catheters, vascular access devices, and endotracheal intubation [2]. The utilization of temporary or permanent mechanical ventilation support devices is also associated with delirium. Prior research has identified several markers that are useful in predicting the occurrence of perioperative delirium. A history of delirium, low serum albumin level, and reduced lymphocyte count have all been recognized as valuable predictors of perioperative delirium [7].

The relationship between inflammation, immune cells, and the onset of delirium in patients undergoing cardiac surgery remains poorly understood. Li et al. [8] found that levels of peripheral blood lymphocyte subsets were independently associated with delirium and could predict its occurrence in critically ill patients undergoing cardiac surgery. Furthermore, a pilot study indicated that an increased neutrophil-lymphocyte ratio (NLR) may serve as a marker for delirium during the perioperative period [9].

Variations in cytokine levels have also been implicated in the development of postoperative delirium. The immune response to acute insults is characterized by heightened production of pro-inflammatory cytokines by primed microglia and dysfunction in brain-to-immune-system pathways. Given the complexity of these processes, numerous studies are underway to investigate the potential of cytokines, including interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor-alpha (TNF-α), as biomarkers for predicting delirium [10].

The primary objective of this study was to assess the relationship between immunological changes and the occurrence of postoperative delirium after aortic surgery.

Methods

Patient selection

The research protocol was approved by Institutional Review Board of Chonnam National University Hospital (CNUH-2017-079), and written informed consent was obtained from all legal guardians in accordance with the Declaration of Helsinki. We enrolled consecutive patients who were admitted to the department for elective and emergency aortic surgery between July 2017 and June 2018. The inclusion criteria specified that patients must be older than 30 years and exhibit primary thoracic aortic disease.

Patients were excluded if they had a genetic disorder, aortitis, primary neurological disease, alcohol addiction, or poor communication. A total of 43 patients met these criteria. The enrolled patients were hospitalized with diagnoses of aortic dissection (n=22), intramural hematoma (n=9), and aortic arch aneurysm (n=12).

Perioperative manifestations and surgical procedures

Baseline information such as age, sex, comorbid diseases, and delirium status was collected upon admission. Potential risk factors for delirium, including comorbidities, pain, non-invasive factors (such as instrumental examinations and environmental unfamiliarity), and invasive perioperative interventions (such as vascular catheterization and urinary catheter use), were considered. Flow cytometry and cytokine analysis were performed preoperatively on all patients as part of the immunological study. Laboratory analyses (including biochemical and urine analyses) and diagnostic examinations (such as X-ray, electrocardiography, echocardiography, and computed tomography) were conducted as needed to confirm diagnosis. The European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) instrument was utilized to calculate the predicted operative mortality score. The same analgesics, anticoagulants, sedatives, and antibiotics were administered to all patients preoperatively and postoperatively. All patients received general anesthesia, with the duration of anesthesia corresponding to the type of surgery and lasting at least 5 hours. Intraoperative data, such as the type of surgery, durations of cardiopulmonary bypass (CPB), aortic cross-clamping (ACC), and total circulatory arrest (TCA), and any concomitant procedures, were documented. These factors were also considered potential risk factors for delirium.

Postoperative assessment of delirium

The current diagnostic criteria for delirium are based on the DSM-5, as published by the American Psychiatric Association [1]. The core diagnostic features of delirium in-

clude a sudden onset with a fluctuating course, attention deficits, disturbances in consciousness, and cognitive impairment. Patient assessments were conducted daily using the CAM-ICU and the ICDSC until discharge from the ICU, as part of routine bedside nursing observations. Prior to obtaining the CAM-ICU and ICDSC scores, the Richmond Agitation–Sedation Scale (RASS) was administered to assess the level of sedation. Patients with a RASS score of –5 (unresponsive to physical and verbal stimuli) or –4 (responsive only to physical stimulation) were deemed ineligible for CAM-ICU and ICDSC evaluations at that time and were reassessed later. Consultations with psychiatrists were also arranged for patients who exhibited signs of delirium. Following these assessments, patients were categorized into delirium (n=20) and non-delirium (n=23) groups.

Laboratory measurements

Immune cell distribution

Flow cytometry was conducted using several monoclonal antibodies and reagents. Specifically, allophycocyanin-conjugated anti-CD4 and phycoerythrin-conjugated anti-CD8 antibodies were sourced from Becton Dickinson Pharmingen (San Diego, CA, USA). Additionally, BD Pharm Lyse, a 10× concentrated ammonium chloride-based lysis solution from Becton Dickinson Bioscience, was utilized for erythrocyte lysis. Prior to flow cytometry analysis on a Navios instrument (Beckman Coulter, Brea, CA, USA), the cell preparations were washed with calcium- and magnesium-free phosphate-buffered saline, which was supplied by Lonza (Walkersville, MD, USA).

Cytokine analysis

To examine cytokine levels, plasma samples were prepared by centrifuging whole blood at 1,500 rpm for 15 minutes. The subsequent assay process involved the following reagents: 25 μL of Universal Assay Buffer at 1× concentration, 25 μL of Standard Mix A, 25 μL of 5-plex detection antibody, 50 μL of streptavidin-phycoerythrin, and 120 μL of reading buffer (Bender Medsystems GmbH, Vienna, Austria). Before the application of antibodies, the samples were incubated for 2 hours. The levels of IL-1β, IL-6, and TNF-α were measured using the Luminex xMAP 200 system (EMD Millipore, Burlington, MA, USA).

Statistical analysis

Statistical analysis was performed using MedCalc Statistical Software ver. 22.014 (MedCalc Software Ltd., Ostend, Belgium; https://www.medcalc.org; 2023). Continuous variables were compared using the Mann-Whitney U test, while categorical variables were compared with the Fisher exact test. Multivariate analysis was conducted using logistic regression, incorporating risk factors with p-values of less than 0.02. To compare the sequential immune cell values between the delirium and non-delirium groups, repeated measures analysis of variance (ANOVA) was employed. Categorical variables are presented as frequencies and percentages, and continuous variables are expressed as medians with interquartile ranges (IQRs). In all analyses, p-values of less than 0.05 were considered to indicate statistical significance.

Results

A total of 43 patients (21 male [48.8%] and 22 female [51.1%]) met our selection criteria. The median patient age was 71 years (IQR, 56.7–79.0 years). Hypertension was the most common comorbidity, affecting 55.8% of patients; this was followed by diabetes (9.3%), preoperative acute cerebrovascular accident (CVA) (11.6%), and a distant history of CVA (9.3%). At our center, the EuroSCORE II instrument is employed as a quality control measure to estimate the risk of mortality prior to surgery. The median preoperative EuroSCORE II was 6.5% (IQR, 3.8%–11.6%). The most frequent preoperative diagnoses were aortic dissection (22 patients), intramural hematoma (9 patients), and aneurysm (12 patients) (Table 1). Additionally, 2 patients had previously undergone cardiac surgery.

The overall prevalence of delirium was 46.5%, with a rate of 66.6% among female patients (p=0.032). The patients with delirium tended to be older, with a median age of 74.0 years (IQR, 66.0–80.5 years), as opposed to 61.0 years (IQR, 55.2–75.5 years) in the non-delirium group (p=0.024). We found no significant associations between comorbidities such as diabetes, hypertension, and stroke and the occurrence of delirium. However, the preoperative EuroSCORE II was significantly higher in the delirium group (median, 9.4%; IQR, 4.8%–21.7%) than among those without delirium (median, 5.1%; IQR, 3.0%–7.8%) (p=0.006). Preoperative diagnoses among the patients with delirium included aortic dissection (12 patients), intramural hematoma (6 patients), and aneurysm (2 patients) (Table 1).

A wide range of instrumental and laboratory analyses were conducted preoperatively to rule out any secondary acute and chronic pathologies that would contraindicate surgery. The laboratory results indicated a significantly higher neutrophil count in the patients with delirium com-

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Table 1. Preoperative clinical data

Variable	Total (n=43)	Delirium (n=20)	No delirium (n=23)	p-value
Preoperative characteristics				
Male sex	21 (48.8)	6 (30.0)	15 (65.2)	0.032
Age (yr)	71 (56.7–79.0)	74.0 (66.0–80.5)	61.0 (55.2–75.5)	0.024
Body surface area (m^2)	1.6 (1.5–1.8)	1.6 (1.5–1.6)	1.7 (1.5–1.9)	0.051
Diabetes mellitus	4 (9.3)	2 (10.0)	2 (8.7)	1.000
Hypertension	24 (55.8)	14 (70.0)	10 (43.5)	0.124
Distant history of CVA	4 (9.3)	3 (15.0)	1 (4.3)	0.235
Preoperative acute CVA	5 (11.6)	4 (20.0)	1 (4.3)	0.166
EuroSCORE II (%)	6.5 (3.8–11.6)	9.4 (4.8–21.7)	5.1 (3.0–7.8)	0.006
Aortic dissection	22 (51.1)	12 (60.0)	10 (43.5)	0.364
Type I	9 (20.9)	5 (25.0)	4 (17.3)	0.710
Type II	13 (30.2)	7 (35.0)	6 (26.0)	0.740
Intramural hematoma	9 (20.9)	6 (30.0)	3 (13.0)	0.263
Aneurysm	12 (29.3)	2 (10.0)	10 (43.4)	0.019
Ejection fraction (%)	62.8 (58.5–69.8)	62.5 (60.0–68.7)	62.9 (56.3–70.4)	0.660
Preoperative lab				
Hematocrit (%)	35.3 (32.5–39.4)	33.2 (30.9–39.0)	36.8 (34.1–40.4)	0.030
Blood urea nitrogen (mg/dL)	19.4 (15.1–22.4)	19.7 (15.4–23.4)	18.6 (14.6–21.4)	0.534
Creatinine (mg/dL)	0.8 (0.7–1.0)	0.8 (0.6–1.0)	0.8 (0.7–1.0)	0.836
C-reactive protein (mg/L)	0.6 (0.3–1.3)	0.6 (0.5–2.0)	0.6 (0.2–0.6)	0.358
D-dimer (ng/mL)	7.7 (3.7–24.7)	12.2 (4.9–35.2)	6.5 (3.2–18.9)	0.153
Lactate (mg/dL)	2.4 (2.0–4.4)	2.5 (2.0–5.3)	2.3 (1.8–3.4)	0.327
Platelet count ($10^3/mm^3$)	169.0 (136.7–220.0)	143.5 (136.0–186.0)	192.0 (148.7–251.0)	0.069
Lymphocyte (%)	13.3 (9.3–25.2)	10.4 (8.2–14.8)	19.3 (10.2–26.0)	0.027
Lymphocyte count ($10^3/mm^3$)	1.3 (1.0–1.8)	1.2 (1.0–1.8)	1.4 (1.0–1.7)	0.990
Neutrophil (%)	77.4 (63.9–83.6)	80.1 (74.5–84.4)	71.8 (60.0–80.9)	0.055
Neutrophil count ($10^3/mm^3$)	8.2 (4.0–10.3)	9.5 (5.8–12.0)	8.0 (2.8–8.8)	0.018
NL ratio	5.8 (2.4–8.9)	7.8 (3.6–10.3)	3.7 (2.3–7.6)	0.086

Values are presented as number (%) or median (interquartile range).
CVA, cerebrovascular accident; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; NL ratio, neutrophil-lymphocyte ratio.

pared to the non-delirium group (p=0.018). Conversely, the percentage of lymphocytes was higher among those without delirium (p=0.027). Additionally, the hematocrit level was found to be lower in the delirium group (p=0.03). However, other parameters, including preoperative levels of blood urea nitrogen, creatinine, C-reactive protein, D-dimer, lactate, and platelets, showed no significant differences between the delirium and non-delirium groups (Table 1).

Intraoperative parameters—including durations of CPB, ACC, and TCA—were also recorded for all patients, as we believed that these factors may contribute to an increased risk of delirium. The overall median times for CPB, ACC, and TCA were 195.0 minutes (IQR, 173.0–243.2 minutes), 136.0 minutes (IQR, 114.5–175.0 minutes), and 27.0 minutes (IQR, 19.2–38.2 minutes), respectively. Aortic arch replacement surgery was performed in 26 patients (60.4%), with 9 patients receiving frozen elephant trunk insertion, and 8 patients (18.6%) underwent a Bentall procedure. Four patients underwent concomitant surgical procedures: coronary artery bypass grafting in 1, mitral valve repair in 1, and aortic valve replacement in 2 patients.

Table 2 summarizes the overall hospitalization and postoperative assessments. The median ICU stay among all patients was 46.0 hours (IQR, 33.0–96.2 hours), while the median hospital stay was 18.0 days (IQR, 12.2–22.5 days). Postoperative atrial fibrillation occurred in 12 patients (27.9%). Four patients (9.3%) experienced new neurologic deficits not related to delirium; of these, 2 patients had persistent deficits, while the other 2 had recovered by the time of assessment. Notably, 18 patients (41.8%) exhibited hyperactive delirium during the postoperative stay in the surgical ICU. The bedside nurse was diligent in monitoring for hypoactive or mixed delirium, and 2 cases (4.6%) of hypoactive delirium were identified. Additionally, spontaneous subdural hematoma developed postoperatively in 12 patients (27.9%). One in-hospital death was recorded (2.3%), attributed to heart failure after surgery.

Table 2. Intraoperative and postoperative clinical data

Variable	Total (n=43)	Delirium (n=20)	No delirium (n=23)	p-value
Intraoperative				
Cardiopulmonary bypass time (min)	195.0 (173.0–243.2)	186.5 (174.5–237.0)	196.0 (165.5–243.2)	0.961
Aortic cross-clamp time (min)	136.0 (114.5–175.0)	137.0 (120.5–172.5)	136.0 (112.2–172.5)	0.760
Total circulatory arrest time (min)	27.0 (19.2–38.2)	27.5 (24.5–38.5)	27.0 (2.7–38.2)	0.574
Arch operation	26 (60.4)	12 (60.0)	14 (60.8)	0.755
Hemiarch replacement	11 (25.5)	7 (35.0)	4 (17.4)	0.294
Partial ach replacement	3 (6.9)	1 (5.0)	2 (8.6)	0.589
Total arch replacement	12 (27.9)	4 (20.0)	8 (34.8)	0.327
Concomitant procedures	17 (39.5)	7 (35.0)	10 (43.5)	0.755
Frozen elephant trunk	9 (20.9)	4 (20.0)	5 (21.7)	1.000
Bentall procedure	8 (18.6)	2 (10.0)	6 (26.1)	0.250
Coronary artery bypass grafting	2 (4.6)	1 (5.0)	1 (4.3)	1.000
Mitral valve repair	1 (2.3)	0	1 (4.3)	1.000
Aortic valve replacement	2 (4.6)	0	2 (8.7)	0.490
Postoperative				
Intensive care unit stay (hr)	46.0 (33.0–96.2)	61.5 (36.0–113.0)	42.0 (25.2–52.0)	0.069
Hospital stay (day)	18.0 (12.2–22.5)	18.0 (13.0–21.0)	18.0 (12.2–29.5)	0.741
Postoperative atrial fibrillation	12 (27.9)	7 (35.0)	5 (21.7)	0.497
Newly developed neurologic deficit	4 (9.3)	3 (15.0)	1 (4.3)	0.323
Transient	2 (4.6)	2 (10.0)	0	0.210
Permanent	2 (4.6)	1 (5.0)	1 (4.3)	1.000
Spontaneous subdural hemorrhage	12 (27.9)	6 (30.0)	6 (26.1)	1.000
In-hospital death	1 (2.3)	1 (5.0)	0	0.465

Values are presented as number (%) or median (interquartile range).

Table 3. Preoperative distribution of immune cells and cytokine levels

Variable	Delirium (n=20)	No delirium (n=23)	p-value
Immune cell			
CD4 (%)	2.5 (1.7–4.5)	6.0 (1.7–8.7)	0.064
CD8 (%)	1.1 (0.6–2.1)	2.2 (0.6–4.3)	0.158
CD14+CD16– (%)	3.5 (2.7–4.5)	3.5 (2.7–5.2)	0.662
CD19 (%)	0.5 (0.2–0.7)	0.7 (0.5–1.2)	0.075
CD56+CD16++ (%)	2.9 (1.7–5.2)	2.5 (1.3–4.2)	0.557
Cytokine			
IL-1β (pg/mL)	99.1 (86.3–121.8)	71.7 (52.2–99.5)	0.068
IL-6 (pg/mL)	960.0 (573.4–1442.1)	578.4 (489.1–895.4)	0.016
TNF-α (pg/mL)	121.7 (100.8–248.3)	269.7 (199.2–331.7)	0.004

Values are presented as median (interquartile range).
CD4, helper T cell; CD8, cytotoxic T cell; CD14+CD16–, monocyte; CD19, B-cell; CD56+CD16++, NK cell; IL, interleukin; TNF-α, tumor necrosis factor alpha.

We anticipated that cardiac intraoperative interventions would influence the prevalence of postoperative delirium. However, our findings indicate that intraoperative parameters, such as the durations of CPB, ACC, and TCA, did not differ significantly between the delirium and non-delirium groups. Furthermore, delirium was not associated with any specific type of surgery; as shown in Table 2, the number of each type of operation performed was statistically similar between groups. In addition, the lengths of stay in the ICU and the hospital were comparable between groups, with no significant differences observed (Table 2).

As summarized in Table 3, most immune cell counts displayed no significant difference between the delirium and non-delirium groups in the preoperative flow cytometry analysis. The preoperative assessment of cytokine levels is detailed in Table 3. Relative to the patients with no delirium, delirium was associated with a significantly higher preoperative concentration of IL-6. Conversely, TNF-α

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levels were significantly lower in the delirium group compared to those without delirium (p=0.004) (Table 3).

Repeated measures ANOVA was employed to examine the effects of various immune cell subsets on delirium across 5 time points: the preoperative assessment and postoperative days 1, 3, 7, and 30. Subsets included helper T cells (CD4), cytotoxic T cells (CD8), B cells (CD19), natural killer cells (CD56+CD16++), and monocytes (CD14+CD16–). The analysis revealed significant main effects for helper T cells (CD4) (p=0.019), cytotoxic T cells (CD8) (p=0.023), and monocytes (CD14+CD16–) (p=0.021) (Fig. 1). Specifically, the levels of these immune cell types were consistently lower on average in the patients with delirium compared to those without it across the measured time points.

In the multivariate analysis, variables with p-values of less than 0.02, including EuroSCORE II, neutrophil count, IL-6 level, and TNF-α level, were analyzed. Fig. 2 displays box plots of the variables that yielded p-values of less than 0.02 in the univariate analysis. Lower TNF-α level was identified as a significant risk factor for postoperative delirium in the logistic regression analysis (odds ratio, 0.985; 95% confidence interval, 0.972–0.997; p=0.022) (Table 4).

Discussion

The interaction between the peripheral immune system and the brain primarily occurs through 3 distinct pathways: (1) the passive diffusion of cytokines from the blood

Table 4. Logistic regression analysis of preoperative variables associated with postoperative delirium

Variable	Odds ratio (95% CI)	p-value
EuroSCORE II	1.113 (0.897–1.381)	0.3281
Neutrophil count	1.241 (0.885–1.741)	0.2098
IL-6	1.001 (0.997–1.004)	0.7039
TNF-α	0.985 (0.972–0.997)	0.0226

CI, confidence interval; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; IL, interleukin; TNF-α, tumor necrosis factor-alpha.

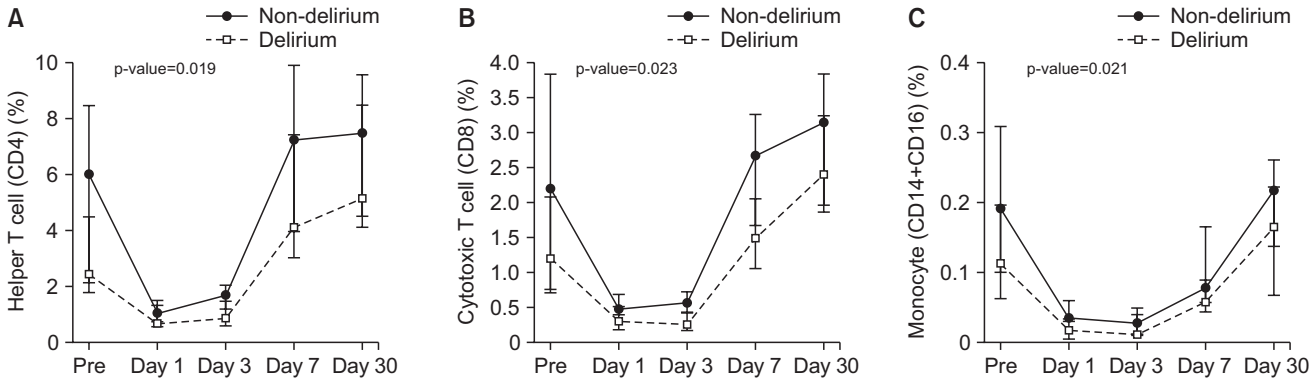

Fig. 1. Changes in immune cell distribution over time in the delirium and non-delirium groups. (A) Comparison of helper T cell (CD4) percentages at 5 time points. (B) Comparison of cytotoxic T cell (CD8) percentages at 5 time points. (C) Comparison of monocyte (CD14+CD16–) percentages at 5 time points. Pre, preoperative; Day, postoperative day.

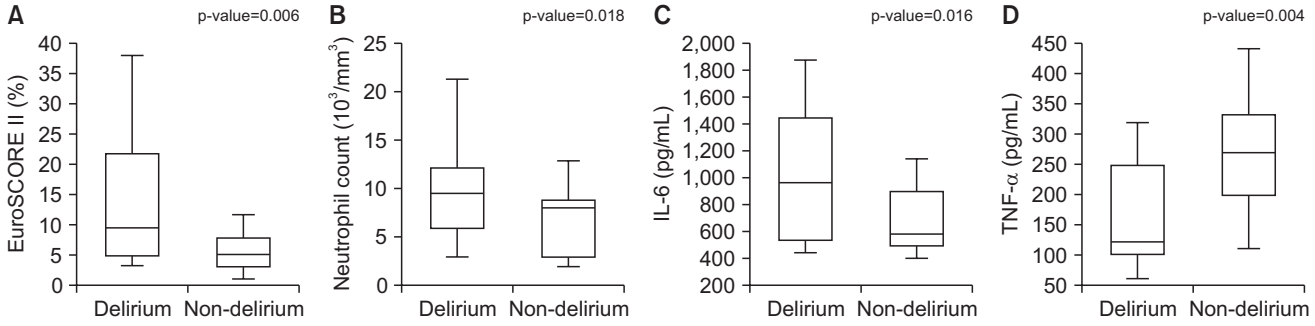

Fig. 2. Box plots illustrating the risk factors with p-values of less than 0.02 in the univariate analysis. (A) European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) (%). (B) Neutrophil count (10^3/mm^3). (C) Interleukin-6 (IL-6) (pg/mL). (D) Tumor necrosis factor alpha (TNF-α) (pg/mL). Delirium, delirium group; Non-delirium, non-delirium group.

into the brain via a leaky blood-brain barrier (BBB), (2) the carrier-mediated active transport of peripheral cytokines into the brain (with an intact BBB), and (3) the de novo production of cytokines following the activation of resident immune cells (microglia) in the brain via vagal afferents in response to peripheral immune signals [11]. Any infection or tissue injury triggers the production of pro-inflammatory mediators both peripherally and within the brain. Activated microglia in the central nervous system are responsible for the acute neuroinflammatory response that leads to the symptoms of delirium. Research has indicated that microglial activation occurs via the signaling of toll-like receptor (TLR) 4. The activation of TLRs in phagocytes and mast cells also triggers the activation of nuclear factor kappa-light-chain-enhancer of activated B cells and interferon regulatory factors. In response to this stimulation, these cells release pro-inflammatory cytokines, notably TNF-α and IL-1, as well as various other inflammatory mediators. This activation induces both morphological and molecular changes in surrounding structures, particularly impacting endothelial cells. Furthermore, pro-inflammatory mediators can readily cross the BBB, thereby exacerbating neuroinflammatory reactions by promoting the production of prostaglandin E2 [12-16].

Lymphocytes play a vital role in the appropriate regulation of the inflammatory response. A decrease in lymphocyte levels is a common reaction to acute stress, but a chronic reduction in lymphocytes—due to increased catecholamine and cortisol levels, redistribution of lymphocytes to lymphatic tissues, and accelerated apoptosis—can lead to an adverse inflammatory state and, ultimately, poor clinical outcomes [17]. The NLR reflects the balance between neutrophils and lymphocytes, combining these immune system components into a single marker. NLR has been shown to be a more robust predictor of adverse outcomes than traditional inflammatory markers, such as total white blood cell count, individual white blood cell subtypes, and C-reactive protein [18]. In this study, the NLR was higher in the delirium group, but this finding did not reach statistical significance (p=0.086), indicating only a trend. The neutrophil count was significantly elevated in the delirium group, which is consistent with previous research findings. A study by Tanaka [7] demonstrated a link between decreased lymphocyte count and a combined outcome of perioperative delirium and acute exacerbation of behavioral and psychological symptoms of dementia. Similarly, Zuliani et al. [19] reported an association between reduced lymphocyte count and subsyndromal delirium. In the present study, the lymphocyte count did not differ significantly between the delirium and non-delirium groups. However, with a larger sample size in future research, statistical significance may be attained.

In individuals with delirium, increased levels of pro-inflammatory cytokines have been observed in both plasma and cerebrospinal fluid [13]. Perry [20] and D'Mello et al. [21] showed that circulating cytokines, including IL-1, IL-6, and TNF-α, can be actively transported across the BBB. This transport allows them to either directly access the brain or interact with receptors on cerebral endothelial cells, ultimately leading to the production of prostaglandin E2 within brain tissue [20-22]. When an individual is healthy, resident microglia remain in a quiescent state, but they possess numerous surface receptors capable of detecting immune signals from the periphery. When activated, these cells initiate a neuroinflammatory response by releasing pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α.

In the present study, TNF-α levels were significantly lower among the patients with delirium, and this reduced level of TNF-α was independently associated with delirium in the multivariate analysis. TNF-α has been repeatedly examined in the context of biomarkers for delirium. Only 1 study has indicated that higher preoperative TNF-α levels may be linked to postoperative delirium, whereas other studies found no significant associations [10]. The discrepancies in these findings could be due to the complex pathophysiology of TNF-α, which can play both neurodegenerative and neuroprotective roles [23]. We hypothesize that patients with delirium may exhibit a dysregulated TNF-α signaling pathway, potentially contributing to the onset of postoperative delirium. However, further research is needed to explore the pathogenesis and to conduct more comprehensive investigations.

This study has several limitations that warrant mention. First, the small sample size and the fact that the study was conducted at a single center may affect the generalizability of the findings to other settings. Furthermore, the retrospective design of the study inherently introduces biases and limitations regarding the collection and analysis of data. An additional limitation is the inconsistency between the neutrophil and lymphocyte counts in the complete blood count and the lymphocyte subset analysis performed using flow cytometry. Although the complete blood count did not reveal statistically significant differences in the NLR or lymphocyte count between the delirium and non-delirium groups, significant differences were noted in the flow cytometry results. This discrepancy may be due to the limited sample size, which poses a challenge for generaliza-

tion.

In conclusion, the objective of this study was to explore the relationship between immunological changes and postoperative delirium in patients who undergo aortic surgery. We propose that postoperative delirium is influenced not only by clinical risk factors, but also by biological elements, including immune cells and cytokines. To build upon these findings, further large-scale studies will be necessary.

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Conflict of interest

No potential conflict of interest relevant to this article was reported.

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