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Original Article

Relationship between neuroinflammatory markers in plasma and cerebrospinal fluid before and after hip arthroplasty and postoperative delirium

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Abstract: Background: Postoperative delirium (POD) is a common complication of total hip arthroplasty (THA), with neuroinflammation playing a critical role in its mechanism. However, the dynamic association between peripheral and central inflammatory markers, as well as their predictive value for POD, remain unclear. This study aims to investigate the perioperative dynamic changes of inflammatory markers in plasma and cerebrospinal fluid (CSF) of THA patients and their relationship with POD. Methods: A total of 280 THA patients were retrospectively enrolled and divided into a delirium group (n = 71) and a non-delirium group (n = 209) according to the Confusion Assessment Method (CAM) assessment 7 days after surgery. The levels of IL-6, TNF-α, and CRP in plasma and CSF were measured before surgery, 1 day after surgery, and 3 days after surgery. Their correlations with the Preoperative Mini-Mental State Examination (MMSE) score and diagnostic efficacy for POD were analyzed. Results: In the delirium group, the plasma levels of interleukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α) increased continuously after surgery, peaking on the 3rd day postoperatively, with significant differences compared with the non-delirium group (all $P < 0.001$). The increases in CSF IL-6 and TNF-α were more significant (IL-6 on the 1st day after surgery: $P < 0.001$), and they were strongly negatively correlated with the MMSE score ($r = -0.62$). The predictive efficacy of CSF IL-6 and TNF-α for POD (AUC = 0.88 on the 3rd day after surgery) was better than that of plasma indicators (AUC = 0.85). In patients over 65 years old, the central inflammatory response occurred earlier ($r = -0.71$ on the 1st day after surgery), and the correlation between inflammatory markers and cognitive impairment was stronger in patients under general anesthesia ($P < 0.01$). CRP in CSF showed no significant predictive value (AUC = 0.60). Conclusion: Postoperative delirium after THA is closely associated with a coordinated increase in peripheral and central IL-6 and TNF-α. Cerebrospinal fluid detection provides a more sensitive early warning signal for POD.

Keywords: Hip arthroplasty, plasma, cerebrospinal fluid, inflammatory markers, postoperative delirium

Introduction

With the global population aging, total hip arthroplasty (THA) has become the primary surgical intervention for end-stage hip disease, markedly improving patients' quality of life [1, 2]. Nonetheless, postoperative complications continue to affect clinical outcomes. In particular, postoperative delirium (POD) has garnered considerable attention due to its high incidence and association with adverse consequences, including cognitive decline, prolonged hospitalization, and increased mortality [3, 4]. Although the precise pathophysiology of POD remains elusive, mounting evidence implicates neuroinflammation as a pivotal driver [5]. Yet, the temporal relationship between peripheral and central inflammatory responses - and their predictive ability for POD - remains controversial.

The neuroinflammation hypothesis posits that surgical trauma activates peripheral immunity, leading to the release of pro-inflammatory cytokines. These mediators cross the blood-brain barrier (BBB), activate microglial, and trigger a central inflammatory cascade that culminates

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in synaptic dysfunction and neuronal injury [6-8]. However, most investigations have relied on single-time-point measurements of peripheral markers, without concurrent assessment of cerebrospinal fluid (CSF) inflammation or longitudinal tracking of cytokine dynamics [9]. This approach may underestimate the true impact of neuroinflammation, as peripheral cytokines must cross the BBB to affect the central nervous system, while CSF markers may more sensitively reflect central immune activity.

The innovation of our study lies in its concurrent quantification of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and C-reactive protein (CRP) in both plasma and CSF of THA patients, and the tracking of their trajectories from the preoperative baseline through 72 hours postoperatively. This multidimensional, dynamic monitoring aims to more precisely identify the critical window of perioperative neuroinflammation compared to previous single-sample or single-time-point designs. Accordingly, this study aims to characterize the perioperative dynamics of IL-6, TNF-α, and CRP in plasma and CSF of THA patients, and evaluate their associations with the development of POD.

Methods

Case collection

This retrospective study was approved by the Medical Ethics Committee of The First People's Hospital of Xianyang. The medical records of 280 patients who underwent THA at Xi'an International Medical Center Hospital and The First People's Hospital of Xianyang from March 2022 to February 2024 were collected. POD was diagnosed according to the Confusion Assessment Method (CAM) [10]. Patients were divided into a delirium group (n = 71) and a non-delirium group (n = 209) according to whether delirium occurred within 7 days after surgery. The CAM assessment makes four-dimensional judgments based on the "4A framework": A1. Acute onset and fluctuating course; A2. Attention disorder; A3. Thinking confusion; and A4. Altered level of consciousness. Delirium is diagnosed if both A1 (acute onset + fluctuation) and A2 (attention disorder) are satisfied, along with either A3 (thinking confusion) or A4 (altered level of consciousness) is met.

Inclusion and exclusion criteria

Inclusion criteria: Age ≥ 18 years; First-time THA; American Society of Anesthesiologists (ASA) grade I - III; Preoperative Mini-Mental State Examination (MMSE) score ≥ 24 (an MMSE score of ≥ 24 indicates normal cognitive function, while a score of < 24 suggests cognitive impairment) [11]; Complete medical records.

Exclusion criteria: Complicated with central nervous system diseases (such as stroke, Alzheimer's disease); Use of immunosuppressants or glucocorticoids within 3 months before surgery; Coagulation disorders; Systemic infections; Complicated with other types of fractures; Communication disorders.

Data collection

Demographic and clinical characteristics were collected, including age, gender, body mass index (BMI), smoking history, years of education, comorbidities (hypertension, heart disease), disease type (femoral neck fracture/avascular necrosis of the femoral head), and surgical method (total hip/hemilateral hip replacement). Perioperative parameters included operating time (from skin incision to suture completion), anesthesia method (general anesthesia/spinal anesthesia) and anesthesia duration, intraoperative hypotensive events (systolic blood pressure < 90 mmHg for > 5 minutes), and ASA grade. The levels of IL-6, TNF-α, and CRP in plasma and CSF were measured before surgery, 1 day after surgery, and 3 days after surgery. Patients were evaluated using the CAM twice a day after surgery for 7 consecutive days. The MMSE score was evaluated on the 7th day after surgery. The total score is 30 points, and a score ≤ 23 points is defined as cognitive impairment [12]. All patients underwent lumbar puncture within 24 hours of admission, on postoperative day 1, and postoperative day 3 under aseptic conditions. Cerebrospinal fluid specimens (0.5 mL) were collected, immediately aliquoted, and stored at -80°C for future use. On the same day of CSF collection, 3 mL of fasting venous blood was drawn from the elbow vein using EDTA-containing vacuum tubes. The bold samples were centrifuged at 3,000 rpm for 10 minutes and stored at -80°C. IL-6 and TNF-α were measured by ELISA (R&D Systems, USA), while CRP

was detected by immunoturbidimetry (Siemens, Germany).

Study outcome measures

Primary outcome: The incidence of POD within 7 days after THA.

Secondary outcomes: Dynamic changes in plasma and CSF levels of IL-6, TNF-α, and CRP; Correlation between inflammatory markers and MMSE scores; Efficacy of biomarkers in diagnosing POD.

Statistical analysis

Categorical variables were expressed as numbers and percentages (n, %) and compared using the chi-square test. Continuous variables were tested for normality via the Shapiro-Wilk test, and data conforming to normal distribution were reported as mean ± standard deviation. Between-group differences were assessed by independent-samples t-test. Longitudinal changes in inflammatory markers were evaluated using repeated-measures analysis of variance (ANOVA), with Bonferroni correction for post hoc comparisons. Pearson correlation coefficients were quantified to assess the associations between inflammatory markers and MMSE scores. Receiver operating characteristic (ROC) curve analysis was used to determine each biomarker's diagnostic utility for POD. All analyses were performed using SPSS 26.0 and GraphPad Prism 9.0. A two-tailed *p* value < 0.05 was considered statistically significant.

Results

Baseline characteristics

Among the 280 patients, 71 (25.4%) developed POD within 7 days post-THA. Compared with the non-delirium group (n = 209), patients who developed POD were older, endured longer operative and anesthesia durations, experienced more intraoperative hypotensive episodes, and had higher ASA grades (all P < 0.05). The choice of anesthesia (general vs. spinal) also differed significantly between the two groups (P < 0.05). Postoperative day 7 MMSE scores were lower in the delirium group (P < 0.05). There were no significant between-group differences in sex, BMI, smoking status, comorbid hypertension or heart disease, surgical indication or approach, or years of education (all P > 0.05) (**Table 1**).

Plasma inflammatory marker dynamics

Preoperatively, serum IL-6, TNF-α, and CRP levels were comparable between groups (P > 0.05). In the delirium cohort, IL-6 rose sharply on postoperative day 1 and peaked on day 3; in contrast, IL-6 in the non-delirium group returned to near baseline by postoperative day 3. Intergroup differences in IL-6 were significant on postoperative day 3 (P < 0.001). TNF-α in the delirium group increased markedly on days 1 and 3, whereas in the non-delirium group it showed only minor, stable elevations; the group differences were significant at both time points (P < 0.001). CRP was likewise significantly higher in the delirium group on days 1 and 3 (P < 0.001) (**Figure 1**).

Cerebrospinal fluid inflammatory marker dynamics

Preoperatively, CSF IL-6 and TNF-α levels were comparable between the two groups but were significantly elevated in the delirium group on postoperative day 1 and day 3 (both P < 0.001), with a gradual decline thereafter. By contrast, CSF CRP showed no between-group differences at any time point (P > 0.05) (**Figure 2**).

Correlation between inflammatory markers and cognitive function

Preoperative plasma marker levels showed no significant correlations with MMSE scores (P > 0.05). Pearson correlation analysis revealed that higher plasma IL-6, TNF-α, and CRP levels on postoperative days 1 and 3 were each significantly associated with lower MMSE scores on postoperative day 7 (IL-6 and TNF-α: P = 0.001; CRP: P = 0.016 on day 1, P = 0.002 on day 3). Similarly, CSF IL-6 and TNF-α on days 1 and 3 were negatively correlated with MMSE scores (both P = 0.001), whereas CSF CRP did not correlate with MMSE at any time point (P > 0.05) (**Figure 3**).

Diagnostic performance of plasma markers for POD

ROC analysis demonstrated that preoperative plasma IL-6, TNF-α, and CRP had poor predictive value for POD (all AUC < 0.65, P > 0.05). On

Table 1. Comparison of baseline data between delirium and non-delirium groups

	Delirium Group (n = 71)	Non-Delirium Group (n = 209)	χ^2/t	P
Age			5.153	0.023
≤ 65 years	28 (39.44)	115 (55.02)		
> 65 years	43 (60.56)	94 (44.98)		
Gender			0.386	0.534
Male	34 (47.89)	109 (52.15)		
Female	37 (52.11)	100 (47.85)		
Body Mass Index			0.764	0.382
≤ 18.4 kg/m^2	31 (43.66)	79 (37.80)		
> 18.5 kg/m^2	40 (56.34)	130 (62.20)		
Smoking History			0.300	0.584
Yes	15 (21.27)	38 (18.18)		
No	56 (78.87)	171 (81.82)		
Hypertension History			0.413	0.520
Yes	33 (46.48)	88 (42.11)		
No	38 (53.52)	121 (57.89)		
Heart Disease History			0.784	0.376
Yes	14 (19.72)	52 (24.88)		
No	57 (80.28)	157 (75.12)		
Operating Time			9.711	0.002
≤ 2.5 h	18 (25.35)	97 (46.41)		
> 2.5 h	53 (74.65)	112 (53.59)		
Disease Type			0.373	0.541
Femoral Neck Fracture	40 (56.34)	109 (52.15)		
Avascular Necrosis of the Femoral Head	31 (43.66)	100 (47.85)		
Surgical Method			1.731	0.188
Femoral Head Replacement	31 (43.66)	73 (34.93)		
Total Hip Replacement	40 (56.34)	136 (65.07)		
Years of Education			0.364	0.546
≤ 9 years	44 (61.97)	121 (57.89)		
> 9 years	27 (38.03)	88 (42.11)		
Intraoperative Hypotension			5.952	0.015
Yes	30 (42.25)	56 (26.79)		
No	41 (57.75)	153 (73.21)		
ASA Grade			10.951	0.004
I	20 (28.17)	60 (28.71)		
II	32 (45.07)	126 (60.29)		
III	19 (26.76)	23 (11.00)		
Anesthesia Method			5.828	0.016
General Anesthesia	50 (70.42)	113 (54.07)		
Spinal Anesthesia	21 (29.58)	96 (45.93)		
Anesthesia Duration (min)	112.72±25.20	120.55±19.90	2.378	0.019
Postoperative MMSE Score	23.87±1.59	26.17±1.96	9.857	< 0.001

ASA: American Society of Anesthesiologists, MMSE: Mini-Mental State Examination.

postoperative day 1, IL-6 (AUC = 0.82, P < 0.001) and TNF-α (AUC = 0.80, P = 0.001) showed good discrimination, whereas CRP did not reach significance (AUC = 0.68, P = 0.052).

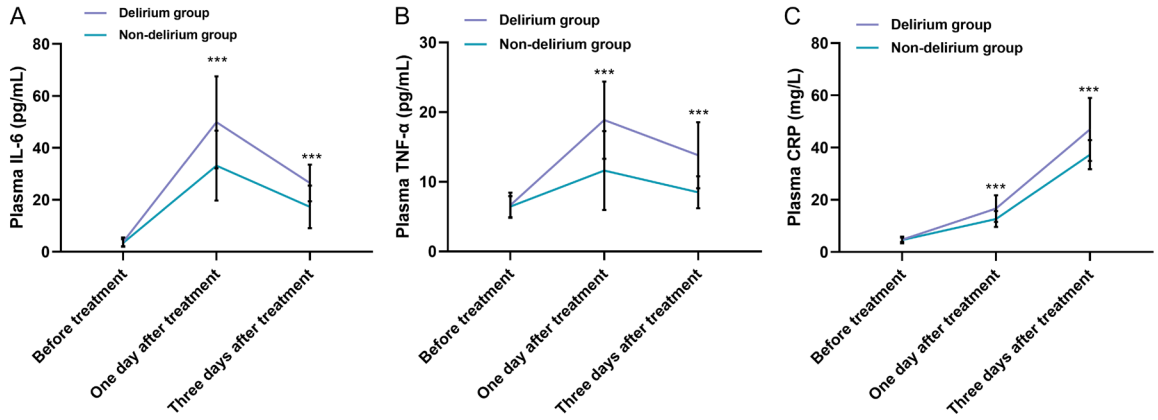

Figure 1. Changes in plasma inflammatory marker levels before and after surgery. A. Changes in plasma IL-6 levels before and after surgery. B. Changes in plasma TNF-α levels before and after surgery. C. Changes in plasma CRP levels before and after surgery. IL-6: interleukin-6, TNF-α: tumor necrosis factor-α, CRP: c-reactive protein. **P < 0.01, compared with the Non-Delirium Group, ***P < 0.01, compared with the Non-Delirium Group.

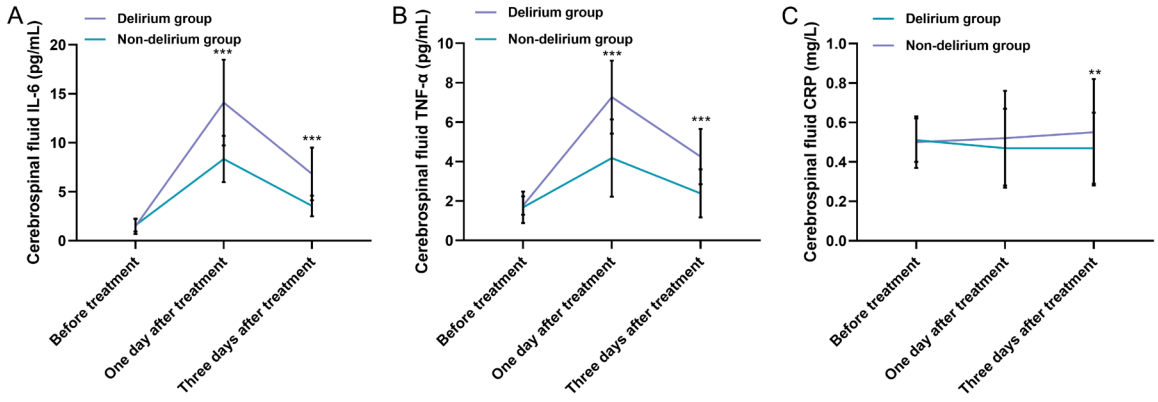

Figure 2. Changes in cerebrospinal fluid inflammatory marker levels before and after surgery. A. Changes in cerebrospinal fluid IL-6 Levels before and after surgery. B. Changes in cerebrospinal fluid TNF-α levels before and after surgery. C. Changes in cerebrospinal fluid CRP levels before and after surgery. IL-6: interleukin-6, TNF-α: tumor necrosis factor-α, CRP: c-reactive protein. **P < 0.01, compared with the Non-Delirium Group, ***P < 0.01, compared with the Non-Delirium Group.

By day 3, IL-6 (AUC = 0.85, P < 0.001) and TNF-α (AUC = 0.83, P < 0.001) further improved, and CRP achieved modest significance (AUC = 0.71, P = 0.012) for discrimination (**Figure 4**).

Diagnostic performance of CSF markers for POD

Preoperative CSF IL-6 and TNF-α levels likewise demonstrated limited predictive power for POD (AUC < 0.65, P > 0.05). On postoperative day 1, CSF IL-6 (AUC = 0.85, P < 0.001) and TNF-α (AUC = 0.82, P < 0.001) outperformed CRP (AUC = 0.63, P = 0.102). By day 3, IL-6 (AUC = 0.88, P < 0.001) and TNF-α (AUC = 0.84, P < 0.001) yielded the highest discriminative values, while CRP remained non-significant (AUC = 0.60, P = 0.215) (**Figure 5**).

Relationship between inflammatory markers and postoperative MMSE at different ages

In patients aged ≤ 65 years, plasma IL-6 (on both the 1st and 3rd days after treatment, P = 0.001) and TNF-α (on the 3rd day, P = 0.018) were significantly negatively correlated with the MMSE score. However, CSF IL-6 was significantly correlated with MMSE on the 3rd day (P = 0.001), and TNF-α was significantly correlated with MMSE on both the 1st and 3rd days after treatment (both P = 0.001). In patients aged > 65 years, plasma IL-6 (both P = 0.001), TNF-α

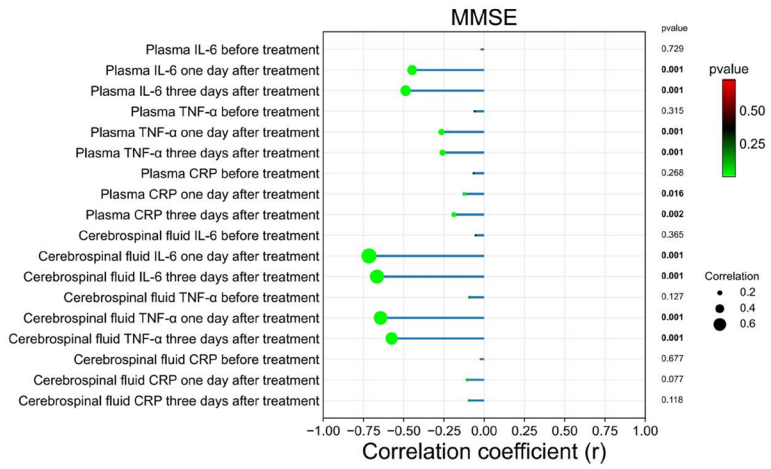

Figure 3. Relationship between inflammatory markers and postoperative MMSE score. MMSE: Mini-Mental State Examination, IL-6: Interleukin-6, TNF-α: Tumor Necrosis Factor-α, CRP: C-Reactive Protein.

(both P = 0.001), and CRP (on the 3rd day, P = 0.005) were significantly negatively correlated with the MMSE score. CSF IL-6 and TNF-α were both significantly associated with MMSE after treatment (both P = 0.001). No significant correlations were found for inflammatory markers measured preoperatively, including both plasma and CSF IL-6, TNF-α, CRP (all P > 0.05) (**Figure 6**).

Relationship between inflammatory markers and postoperative MMSE under different anesthesia methods

Patients under general anesthesia, on postoperative days 1 and 3, had plasma levels of IL-6 (both P < 0.01), TNF-α (P = 0.004 and P = 0.001), and CRP (both P = 0.004); all of which were significantly negatively correlated with the MMSE score. Levels in the CSF for IL-6 (both P = 0.001) and TNF-α (both P = 0.001) were also significantly negatively correlated with MMSE on both postoperative 1st and 3rd days; however, CFS CRP showed no statistical correlation with MMSE at all time points (P > 0.05). In patients under spinal anesthesia, plasma TNF-α on postoperative days 1 (P = 0.019) and 3 (P = 0.043) and CRP on day 1 (P = 0.006) were significantly negatively correlated with MMSE score. However, plasma IL-6 only showed slight negative correlation with MMSE score on postoperative day 1 (P = 0.358) and had no association on the 3rd day (P = 0.976). IL-6 level (on postoperative day 1, P = 0.001) and TNF-α level (on postoperative day 1, P = 0.033, postoperative day 3, P = 0.001) in the CSF were significantly negatively correlated with the MMSE score, while CRP in the CSF did not show a correlation at any time points (P > 0.05). It is worth noting that the negative correlations of plasma IL-6 on postoperative day 3 and CSF IL-6/TNF-α level with MMSE score were stronger in patients under general anesthesia (both P = 0.001). In contrast, the correlation of CSF IL-6 with MMSE in patients under spinal anesthesia was only significant on postoperative day 1 (day 3: P = 0.251). All inflammatory indicators before treatment had no significant associations with MMSE under both anesthesia methods (P > 0.05) (**Figure 7**).

Discussion

This study systematically characterized perioperative trajectories of IL-6, TNF-α, and CRP in both plasma and CSF of patients undergoing THA and analyzed their associations with POD. Our principal findings include: (1) plasma IL-6 and TNF-α levels rose markedly within 24 hours post-surgery and peaked by 72 hours in patients who subsequently developed POD, whereas non-delirious patients exhibited transient or lower-level increases; (2) CSF IL-6 and TNF-α exhibited even greater elevations in the delirium cohort, with stronger negative correlations with day-7 MMSE scores; (3) CSF IL-6 and TNF-α demonstrated superior predictive performance for POD compared with plasma markers, notably reaching AUCs of 0.85-0.88 by postoperative day 3; (4) CRP showed limited predictive value in CSF, despite associations in plasma; (5) age and anesthesia method modulated the timing and strength of inflammatory marker-cognitive associations, with older patients and those under general anesthesia displaying earlier and stronger central inflammatory responses. These findings deepen our understanding of perioperative neuroinflammation in THA and have implications for risk stratification and potential interventions.

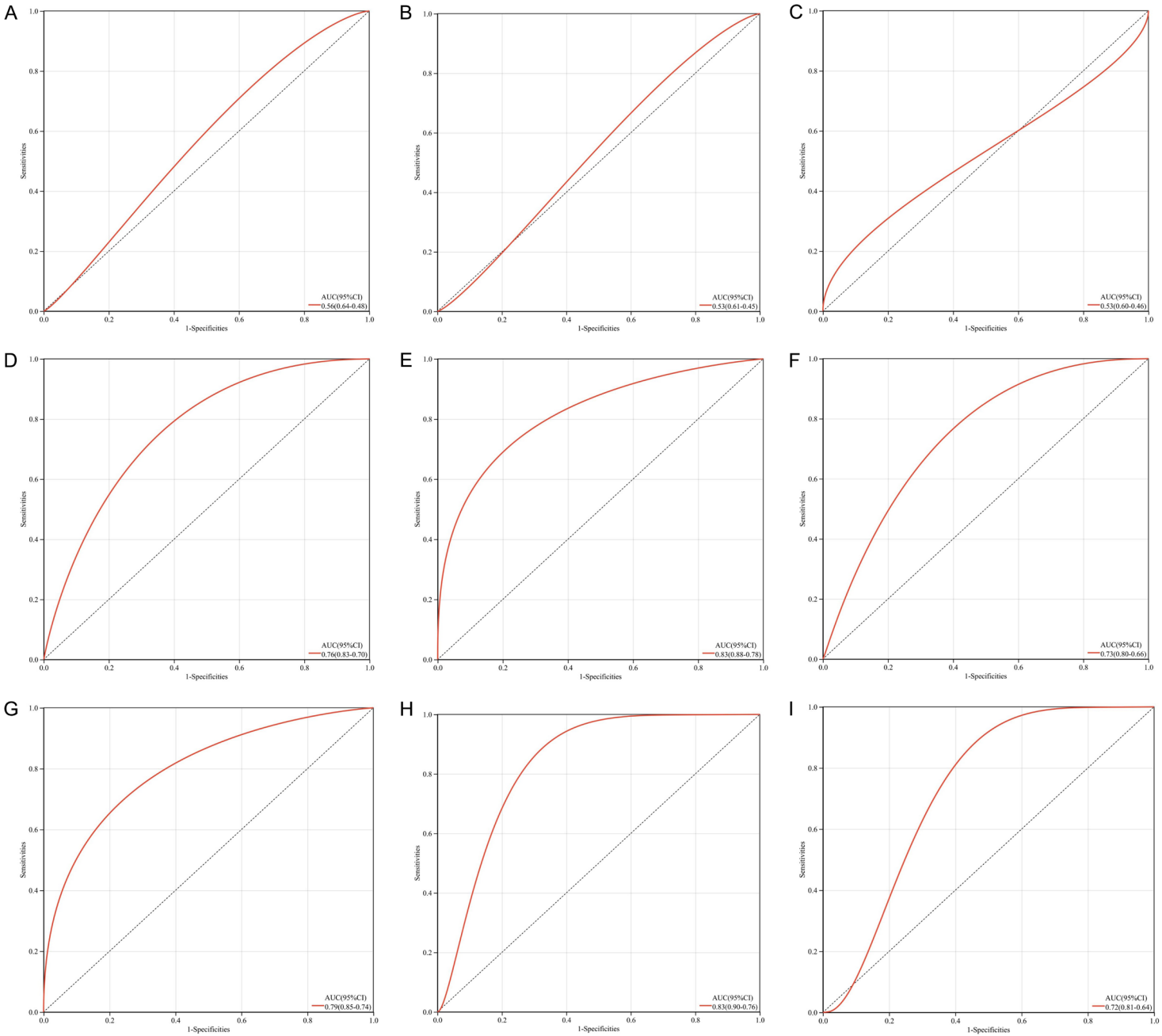
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Figure 4. ROC curve analysis of plasma inflammatory markers for diagnosing postoperative delirium at different time points. A-C. Pretreatment IL-6, TNF-α, CRP; D-F. IL-6, TNF-α, CRP on postoperative day 1; G-I. IL-6, TNF-α, CRP on postoperative day 3. IL-6: interleukin-6, TNF-α: tumor necrosis factor-α, CRP: c-reactive protein.

Our results are consistent with a growing body of evidence indicating that proinflammatory cytokines (such as IL-6 and TNF-α) are closely associated with POD in various surgical settings [13]. Meta-analyses have shown that elevated levels of IL-6 and TNF-α in the postoperative period are significantly correlated with an increased risk of POD [14]. Mechanistic studies have demonstrated that peripheral surgical injury can activate the systemic inflammatory response, releasing large quantities of mediators such as IL-6 and TNF-α. These cytokines can cross the BBB or indirectly activate central immune cells through signal transduction, triggering microglial activation and neuronal dysfunction [15]. The temporal patterns observed in our cohort - an early perioperative surge of IL-6 and TNF-α in plasma, followed by a more pronounced elevation in CSF, particularly in patients who developed POD - align with these mechanisms.

In the delirium cohort, plasma IL-6 and TNF-α surged within 24 hours post-surgery and remained elevated through 72 hours. However, CSF IL-6 and TNF-α exhibited even greater elevations, and their inverse associations with MMSE scores were stronger, indicating that central inflammation may play a more direct role in driving POD. Peripheral cytokines likely penetrate the BBB - compromised by surgical stress or active transport - to initiate central cascades [16-18]. In parallel, resident microglia respond to peripheral damage-associated signals by producing pro-inflammatory mediators, further exacerbating neuronal injury [19-21]. Notably, the higher rates of intraoperative hypotension in delirious patients may exacerbate BBB permeability via cerebral hypoperfusion [22].

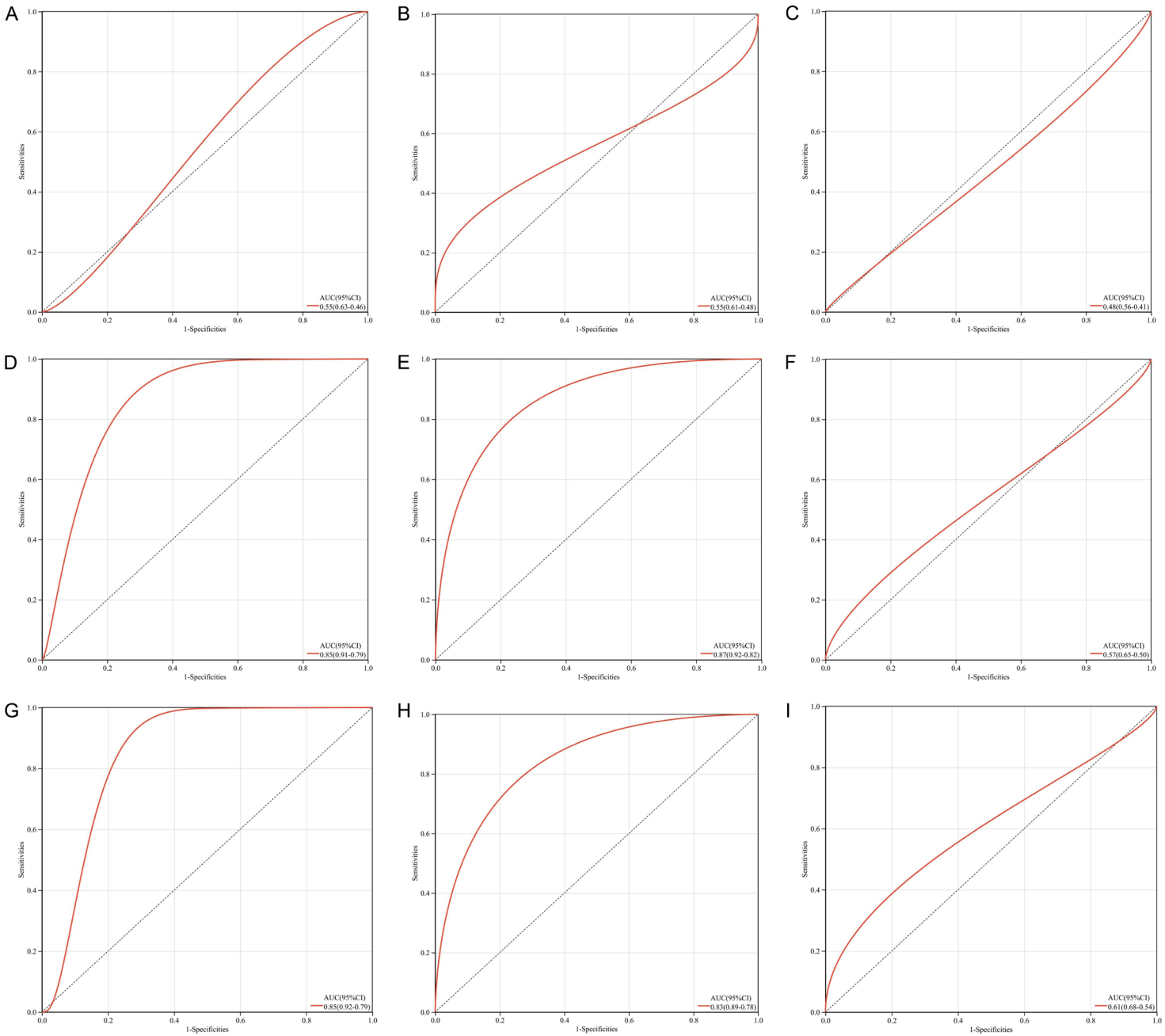
Unlike IL-6 and TNF-α, CSF CRP remained unchanged, despite plasma CRP's association with POD. As a pentameric hepatic acute-phase protein, CRP has limited ability to cross an intact BBB, and its CSF concentration likely reflects local synthesis or minimal leakage [23, 24]. Yan et al. similarly identified plasma CRP > 20.25 mg/L as a POD risk factor but did not measure CSF markers, potentially overestimating the contributions of peripheral markers to neuroinflammation [25]. Our data underscore the necessity of distinguishing marker origin when probing neuroinflammation.

Multi-time-point monitoring pinpointed the first 24 hours after THA as a critical inflammatory window. Plasma IL-6 and TNF-α peaked during this period, offering the highest diagnostic accuracy for POD (IL-6 AUC = 0.82; TNF-α AUC = 0.80). AUCs of CSF IL-6 and TNF-α further improved by postoperative day 3 (up to 0.88 and 0.84, respectively), highlighting the role of sustained central inflammation in delayed POD onset. These insights challenge the limitations of single-time point study designs and emphasize the value of longitudinal assessment for precise risk stratification [26].

Contrary to some reports linking preoperative systemic indices (e.g., SII, CRP) to POD [25], we observed no baseline differences in plasma or CSF markers, suggesting that perioperative insults, rather than chronic inflammation, predominate POD risk in this relatively younger, infection-free cohort. Age-stratified analyses revealed that the negative correlation between CSF IL-6 and the MMSE score emerged at 24 hours in patients > 65 years, but at 72 hours in younger individuals. Age-related BBB breakdown and microglial "priming" toward a pro-inflammatory phenotype likely accelerate central cytokine effects in the elderly [27-30].

Patients under general anesthesia exhibited stronger negative correlations between postoperative plasma IL-6/CSF TNF-α and MMSE than those under spinal anesthesia. Propofol's transient inhibition of NF-κB may suppress early peripheral inflammation but trigger rebound activation after cessation [31], whereas spinal anesthesia attenuates central nociceptive signaling and glial activation [32]. These data favor spinal anesthesia for high-risk THA patients.

Our retrospective design precluded preoperative CSF baselines and assessment of anti-inflammatory mediators (e.g., IL-10) or BBB integrity markers (e.g., S100B), limiting mecha-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AUC(95%CI)
0.61(0.68-0.54)

Figure 5. ROC curve analysis of cerebrospinal fluid inflammatory markers for diagnosing postoperative delirium at different time points. A-C. Pretreatment IL-6, TNF-α, CRP; D-F. IL-6, TNF-α, CRP on postoperative day 1; G-I. IL-6, TNF-α, CRP on postoperative day 3. IL-6: interleukin-6, TNF-α: tumor necrosis factor-α, CRP: c-reactive protein.

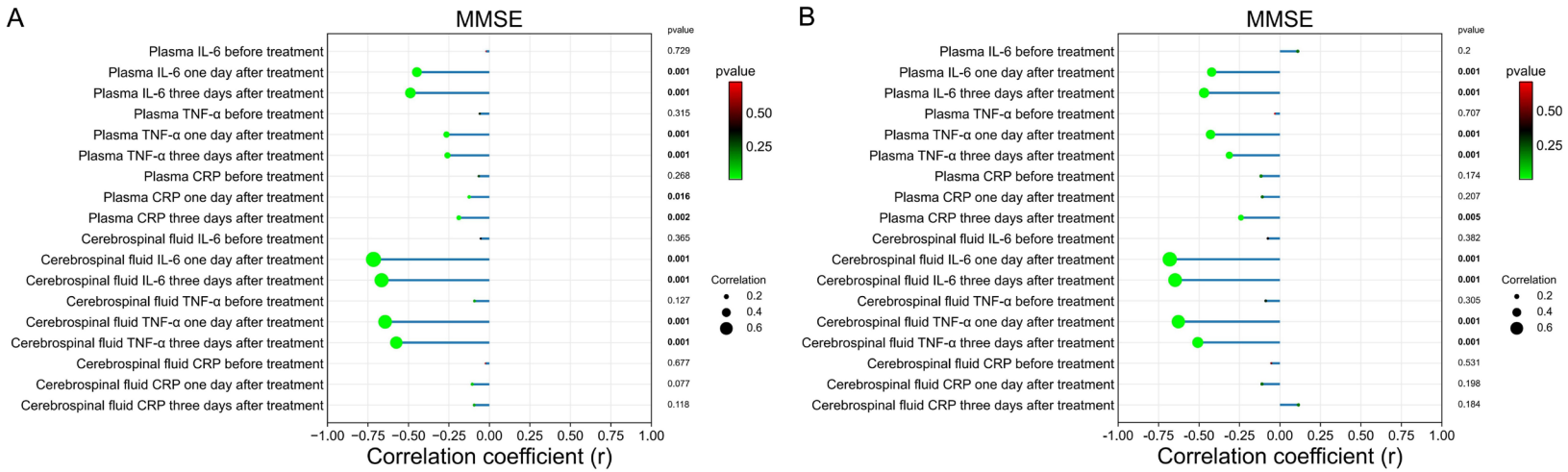

Figure 6. Relationship between inflammatory markers and postoperative MMSE in different age groups. A. Relationship between inflammatory markers and postoperative MMSE in patients aged ≤ 65 Years. B. Relationship between inflammatory markers and postoperative MMSE in patients aged > 65 Years. MMSE: Mini-Mental State Examination, IL-6: Interleukin-6, TNF-α: Tumor Necrosis Factor-α, CRP: C-Reactive Protein.

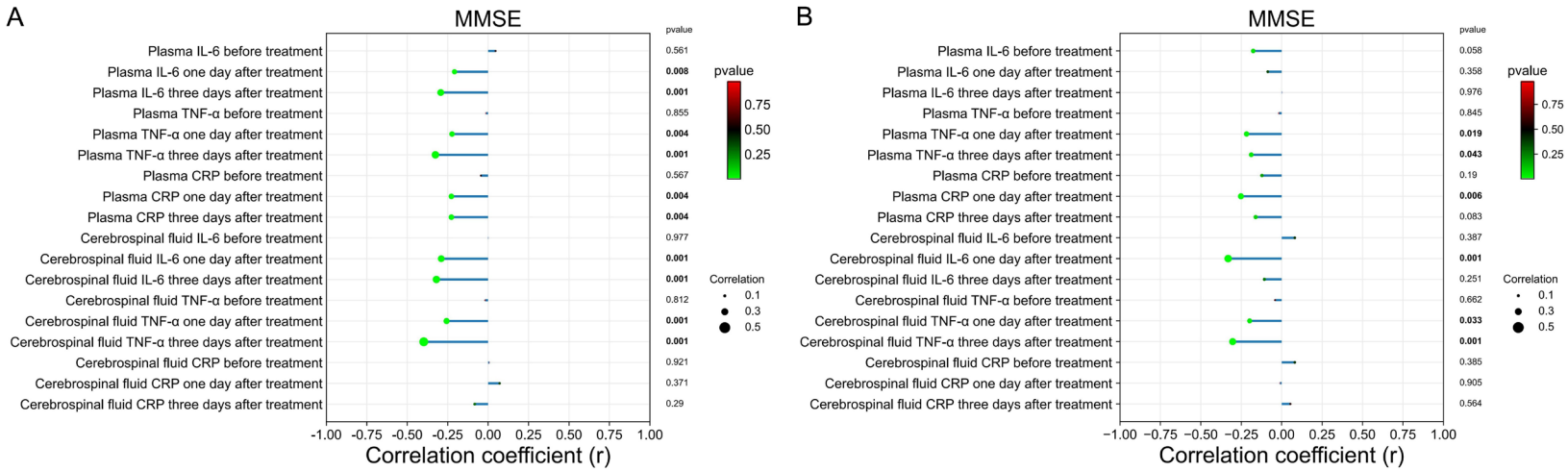

Figure 7. Relationship between inflammatory markers and postoperative MMSE under different anesthesia methods. A. Relationship between inflammatory markers and postoperative MMSE in patients under general anesthesia. B. Relationship between inflammatory markers and postoperative MMSE in patients under spinal anesthesia. MMSE: Mini-Mental State Examination, IL-6: Interleukin-6, TNF-α: Tumor Necrosis Factor-α, CRP: C-Reactive Protein.

nistic insights. Prospective interventional studies are needed to establish the causal roles for IL-6 and TNF-α in POD pathogenesis.

Perioperative surge in peripheral and CSF IL-6 and TNF-α levels is closely linked to POD development following hip arthroplasty. CSF measurements offer a more sensitive early warning signal than plasma alone, providing a rationale for targeted neuroinflammatory interventions.

The innovative aspects of this study are as follows: (1) Quantitative detection of IL-6, TNF-α, and CRP in peripheral blood and CSF at multiple time points (preoperative, 1 day postoperatively, and 3 days postoperatively); (2) Combining dynamic changes in inflammatory levels with the MMSE results on the 7th day postoperatively, the critical inflammatory window within 72 hours after surgery was identified, highlighting the predictive value of central inflammatory peaks in predicting POD; (3) Stratified analysis by age and anesthesia method revealed temporal differences in the inflammation-cognition association among different high-risk subgroups, providing new ideas for individualized perioperative management; (4) Direct comparison of the diagnostic performance of proinflammatory cytokines in plasma and CSF verified the superior sensitivity of CSF indicators, providing an evidence-based rationale for clinical decision-making on lumbar puncture testing.

Conclusion

This study demonstrates that postoperative delirium after THA is driven by a coordinated increase in peripheral and central neuroinflammatory markers (IL-6 and TNF-α). CSF IL-6 and TNF-α provide superior diagnostic sensitivity for POD compared to plasma markers, especially in patients over 65 years or under general anesthesia. These findings support the neuroinflammatory hypothesis of POD and suggest that perioperative monitoring of CSF inflammatory markers may enable early intervention. Future studies should validate IL-6/TNF-α as therapeutic targets for POD prevention in high-risk populations.

Disclosure of conflict of interest

None.

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