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CLINICAL TRIAL REPORT

# Relationship Between Peripheral Serum Adiponectin and Cerebrospinal Fluid TNF-α, IL-1β, Lactic Acid, Pyruvic Acid and Perioperative Neurocognitive Dysfunction in Elderly Patients Undergoing Hip Arthroplasty

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**Background:** Postoperative neurocognitive dysfunction (PND) represents a form of cognitive impairment related to surgery and anesthesia, which may manifest hours or even weeks after the surgical procedure, persist, and potentially progress into Alzheimer's disease. The etiology of PND is intricate, with central nervous inflammation playing a crucial role. The clinical manifestations of PND are not distinctive, no obvious image alterations are observable, and the diagnosis rate is relatively low, thereby influencing prognosis and augmenting postoperative complications and mortality. The optimal treatment approach for PND lies in timely identification and management of the high-risk factors causing PND and implementing early prevention. We hypothesize that the level of peripheral blood adiponectin (APN) is correlated with PND, potentially through inhibiting the central inflammatory response and regulating brain energy metabolism.

**Methods:** Fifty elderly patients undergoing elective hip arthroplasty under continuous epidural spinal anesthesia (CESA) were included. Cognitive function was assessed using the Mini-Mental State Examination (MMSE) preoperatively and postoperatively at 1, 2, 3, and 7 days. Serum APN and CSF levels of TNF-α, IL-1β, lactic acid, and pyruvic acid were measured. The occurrence of PND was recorded, and the patients were divided into a PND group and a non-PND group.

**Results:** PND occurred in 16 patients (34.04%). The PND group had lower serum APN levels and higher cerebrospinal fluid (CSF) concentrations of TNF-α, IL-1β, and lactic acid compared to the non-PND group. CSF TNF-α and IL-1β levels were negatively correlated with serum APN concentration. These biomarkers are associated with PND occurrence and have high diagnostic value.

**Conclusion:** Decreases in serum APN and increases in TNF-α, IL-1β, and lactic acid in CSF may be involved in the pathophysiological process of PND in elderly patients after surgery.

**Keywords:** adiponectin, central inflammation, energy metabolism, perioperative neurocognitive dysfunction

## Introduction

Adiponectin (APN) is a plasma protein secreted by adipocytes, known for its pleiotropic effects.[1] It plays a crucial role in modulating metabolic pathways, enhancing insulin sensitivity, and exerting anti-inflammatory and anti-atherosclerotic effects.[2,3] Recent studies have demonstrated that APN and its receptors are expressed in various brain regions, including the hypothalamus, brainstem, hippocampus, cerebral cortex, and basal nuclei.[4] APN is implicated in the suppression of central



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inflammation and the regulation of brain metabolism, directly influencing critical brain functions. It exhibits neuroprotective and antidepressant effects and is closely linked to cognitive function. An animal study indicated that APN knockout mice exhibited significant neurophysiological and behavioral disturbances resembling symptoms of Alzheimer's Disease (AD), highlighting its association with brain function.[5] Furthermore, within the central nervous system, APN has been shown to effectively inhibit central metabolic dysfunction and enhance brain plasticity.[6–8]

Postoperative neurocognitive dysfunction (PND) represents the most prevalent complication following surgical procedures in the elderly population, contributing to extended hospitalizations and delayed recuperation. The manifestations of PND are predominantly cognitive, including diminished learning and memory capabilities, confusion, anxiety, and inattention, among other symptoms.[9] In severe cases, individuals may experience alterations in personality and a decline in social behavioral competence. Longitudinal research suggests that PND symptoms may persist over an extended period and affect multiple cognitive domains.[10] Recent investigations have indicated that patients with PND exhibit lower serum APN levels, with their scores in immediate memory, visual span, speech function, attention, and delayed memory being significantly inferior to those of control group patients.[11] A positive correlation has been observed between APN levels and the scores on neuropsychological state assessment scales, thereby confirming that serum APN levels are inversely correlated with the severity of cognitive impairment in older patients.[12] Additionally, through research into the correlation between serum APN levels and age-related cognitive decline, scholars have suggested that serum APN is associated with the reduction in general cognitive function and information processing speed observed in elderly patients.[13]

In prior studies, we discovered that postoperative serum APN levels in elderly patients under general anesthesia negatively correlate with the onset of PND.[12,14] To the best of our knowledge, there has been no research establishing a relationship between APN and the central nervous system metabolites lactate and pyruvate in individuals with PND. Additionally, there exists a paucity of studies exploring the associations between adiponectin and the central nervous system inflammatory mediators tumor necrosis factor-alpha (TNF-α) and interleukin-1β (IL-1β) in the context of PND. Therefore, the objective of our study was to evaluate the relationships between serum adiponectin levels and the levels of TNF-α, IL-1β, lactate, and pyruvate in elderly patients diagnosed with PND. Moreover, we sought to investigate the potential confounding effects of biochemical tests in predicting the onset of PND and to explore possible interventions.

# Methods and Design

## Research Design

The study was approved by the ethics committee of Dongguan People's Hospital (KYKT2022-07) and registered at the Chinese Clinical Trial Registry as ChiCTR2100051734, and the reg date is 2021–10-01. Written informed consent was obtained from each subject or their authorized person before evaluation. The study was conducted at Dongguan People's Hospital (The Tenth Affiliated Hospital of Southern Medical University) from October 2021 to September 2024. Study participants included 50 elderly patients scheduled for joint replacement surgery under combined spinal epidural anesthesia. At baseline, American Society of Anesthesiologists Grade II and III patients were involved. The participants ranged in age from 65–85 years and included 15 males and 32 females. The exclusion criteria were any of the following: (1) The score on the Mini-Mental State Examination (MMSE) cognitive assessment less than 24 points one day prior to surgery and a duration of education less than 6 years; (2) Severe visual or auditory impairment, refusal to cooperate with testing, or inability to communicate effectively due to language barriers; (3) Cognitive test form text cannot be recognized; (4) Use of antipsychotics, sedatives, or narcotic analgesics within the previous 2 years; (5) An alcoholism or drug dependency history; (6) Preoperative biochemical examination reveals renal dysfunction, active liver disease, or abnormal coagulation; (7) Coexistence of major diseases in the respiratory, circulatory, liver, kidney, mental and psychological, and central nervous systems. Patients were categorized into PND and non-PND groups based on the presence of PND 7 days post-surgery.

## Study Procedure

Fasting was prescribed for 6 to 8 hours before surgery, and water was forbidden for an hour. Access was established to peripheral upper limb venous system as soon as the patient was identified and entered the operating room. The

multifunctional anesthesia monitor is connected for real-time monitoring of Electrocardiogram (ECG), Pulse Oxygen Saturation (SpO2), Heart Rate (HR), Respiratory Rate (RR), and Blood Pressure (Bp). All of the patients were treated with combined spinal-epidural anesthesia (CSEA) without preoperative medication. Inhaling oxygen via nasal cannula at a flow rate of 2–3 L/min. Peripheral venous blood (5 mL) was collected using a disposable blood collection needle and subsequently centrifuged at 3000 rpm for 5 minutes within a 10-minute timeframe. The supernatant was collected and stored at −80°C. CSEA was performed after 5 minutes. The patient was placed in the lateral decubitus position (the surgical side was on the top), and the pillow was placed under the head to maintain the horizontal position of the spine. The CSEA is established at the L2-3 or L3-4 intervertebral space. Using 2% lidocaine hydrochloride for local infiltration anesthesia, an epidural puncture was performed after the local anesthetic took effect. Local infiltration anesthesia was induced using 2% lidocaine hydrochloride. Following the onset of the local anesthetic effect, a 16-gauge epidural Tuohy needle was inserted into the epidural space via loss of resistance to saline. After confirming the correct placement of the needle in the epidural space, the Spinocath 24G spinal needle was inserted into the subarachnoid space through the Tuohy needle, and 2 mL cerebrospinal fluid (CSF) was collected and stored in the refrigerator at −80°C. After CSF emerged, 1.2 mL to 2.0 mL of 0.5% bupivacaine (Hefeng Pharmaceutical Co., Ltd., Shanghai) was injected into the intrathecal space within 10 seconds. Finally, the spinal needle is withdrawn, and an epidural catheter is inserted into the epidural space approximately 3–4 cm distal to the puncture site. The epidural catheter is then carefully aspirated to assess for any presence of blood or CSF. The lateral decubitus position was maintained for a minimum duration of 5 minutes following subarachnoid injection to optimize surgical area blockade. Intraoperative administration of norepinephrine to augment blood pressure or urapidil to attenuate blood pressure ensures that the patient's intraoperative mean arterial pressure fluctuations remain within 20% of the baseline value.

## Neuropsychological Testing and the Definition of PND (Variables/Data Sources/ Measurement)

The neuropsychological tests were administered by researchers who received specialized training under the supervision of experienced neuropsychologists. A majority of these assessments were conducted by a consistent core group of researchers.

The MMSE, developed by Folstein et al in 1975, is a widely used tool for assessing cognitive function. Its simplicity and ease of use make it suitable for screening for cognitive decline across multiple domains, including orientation, memory, attention and calculation, recall, and language ability. The MMSE is a relatively brief assessment, typically lasting between 5 and 10 minutes, comprising 30 items with a maximum attainable score of 30. Higher scores are indicative of enhanced cognitive capacity. According to Chinese MMSE norms,[15] ≤19 for illiterate individuals, ≤22 for individuals with 1–6 years of education, and ≤ 26 for those with 7 or more years of education.

The same researcher, who remained unaware of the patients' groupings, administered the MMSE to evaluate patients' neuropsychological statuses at multiple time points: 3 days prior to surgery (T0) and on day 1 (T1), day 2 (T2), day 3 (T3), and day 7 (T4) post-surgery. To further investigate the long-term impact of surgery on postoperative neurocognitive dysfunction (PND), the cognitive function of patients was assessed using the TICS-m scale one month postoperatively.

The TICS-m scale possesses several advantages: it is specifically designed for telephone screening and shares a similar structure with the MMSE. The assessment of transient memory and short-term memory encompasses an expanded word count of 10, facilitating ease of operation while promoting early detection of memory disorders; however, this expansion also introduces increased test complexity. Moreover, it demonstrates high sensitivity, as evidenced by a large-scale survey,[16] where its sensitivity reached 99% with a specificity of 86%, making it suitable for early PND screening. Following surgery, patients were contacted via telephone at 10 a.m. one month after the procedure to explain the purpose of the test and obtain their address while ensuring minimal interference by instructing them to turn off any TVs or radios and remove paper and pen from sight. Additionally, measures were taken to ensure that time-displaying objects such as newspapers or calendars were not visible to subjects during testing. Caregivers could be present but were prohibited from providing assistance; however, other questions could be repeated except those related to memory.

## Collection and Testing of Samples

Prior to anesthesia, 5 mL peripheral blood samples were collected from each patient and centrifuged to obtain the supernatant. During anesthesia, 2 mL CSF samples were obtained. The plasma and CSF were stored at −80°C for further analysis. The levels of APN in the serum and TNF-α and IL-1β in the CSF were quantified using a double antibody sandwich enzyme-linked immunosorbent assay kit (Meimian Industrial Co., Ltd., Jiangsu, China). Additionally, the concentrations of lactic acid and pyruvic acid in CSF were determined using a colorimetric method kit (Jiancheng Bioengineering Institute Co., Ltd., Nanjing, China).

## Control Bias

To address potential selection bias, we implemented a fully randomized enrollment process that rigorously adhered to predefined inclusion and exclusion criteria for participant screening. Cognitive function assessments were conducted by a consistent team of professionally trained anesthesiologists. To enhance response rates and reduce attrition, we employed a range of strategies, including multiple reminders and personalized care for participants. In instances of non-response or missed appointments, we reached out to relatives and made several attempts to establish communication as corrective measures.

Furthermore, to minimize information bias, we established stringent, objective, and operational definitions for various indicators and aimed to quantify them effectively. We utilized standardized diagnostic criteria for the occurrence of post-operative neurocognitive dysfunction (PND) and adhered to recognized standards for all indicators. Our study employed standardized instruments, reagents, and methodologies. We provided a comprehensive explanation of the study's objectives, significance, and requirements to secure participant support and cooperation. Data collectors underwent uniform training and assessment, while researchers consistently monitored data quality through established protocols. Throughout the data collection phase and the overall study process, meticulous records were maintained. Data from both the experimental and control groups were collected by the same clinical researchers using identical inquiry methods at consistent time intervals. Clinical data were gathered through blinded methods to eliminate any potential subjective influence from researchers or participants. Additionally, uniform training was implemented to ensure consistency among data collectors, thereby achieving high inter-rater reliability.

## Sample Size Calculation

In this study, the required sample size was calculated using G*Power 3.1 software. The effect size was set at 0.4, with an alpha level of 0.05. The incidence of PND in elderly patients undergoing hip joint surgery ranges from 15% to 55%; for the purposes of this calculation, a rate of 30% was adopted. The results indicated that, to achieve a statistical power of 0.8, a total of 47 patients are needed. Anticipating a dropout rate of 5%, the study actually enrolled 50 subjects.

## Statistical Analysis

SPSS 25.0 software was utilized for the statistical analysis. Mean ± standard deviation(s) was used to describe continuous quantitative data, while analysis of variance was employed for dichotomous and rank variables. Pearson correlation analysis was conducted for normally distributed APN and CSF TNF-α, IL-1β, lactic acid, and pyruvic acid correlations; Spearman correlation analysis was applied for non-normally distributed data. Binary logistic regression analysis was performed to investigate the relationship between PND occurrence and serum APN as well as CSF TNF-α, IL-1β, lactic acid, and pyruvic acid levels; ROC curve analysis was used to evaluate the diagnostic value of these parameters. Statistical significance was set at $P<0.05$.

# Results

## General Characteristics of the Two Groups

From October 2021 to September 2024, 50 patients were recruited, 3 of whom were lost to follow-up (Figure 1). There were no significant differences observed in terms of gender composition, age distribution, BMI, presence of underlying disease (hypertension, coronary heart disease and diabetes), educational background, ASA classification, and preoperative MMSE score between the two groups. ($P>0.05$, Table 1).

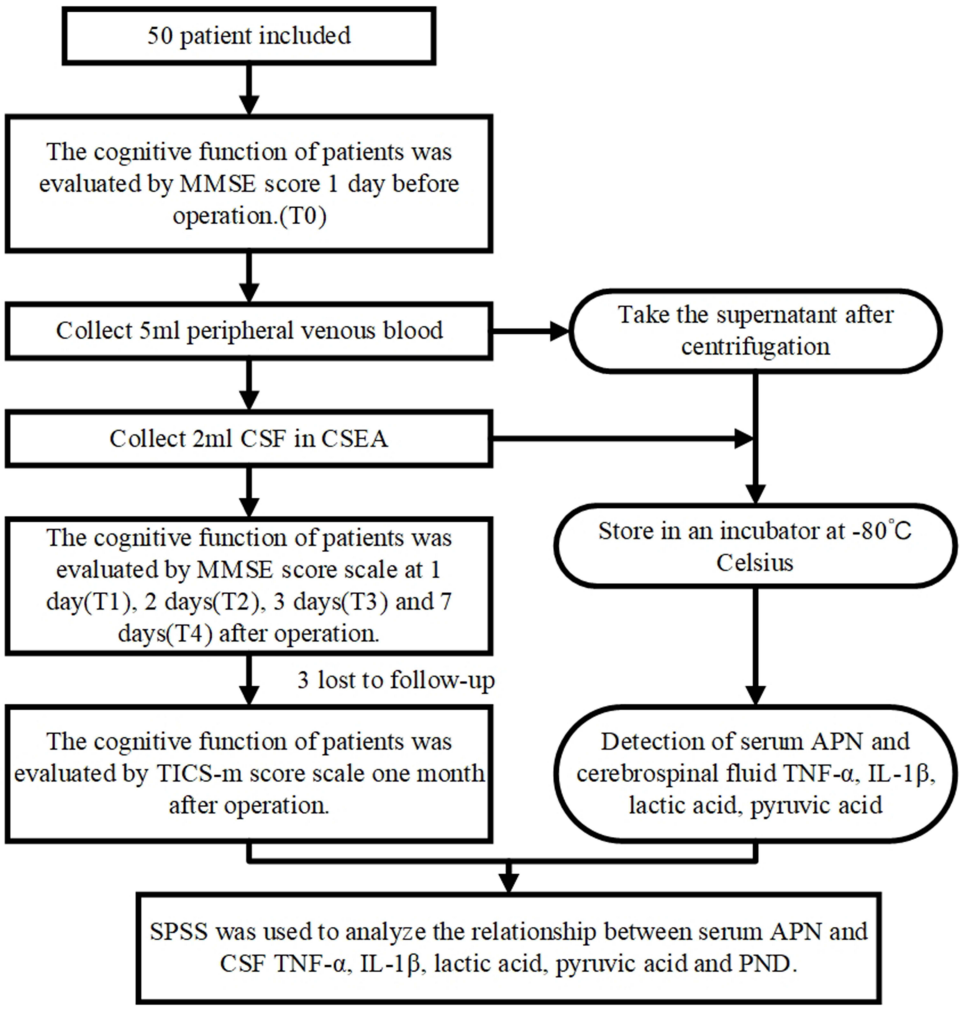


**Figure 1** Flow diagram of the study.

## Intraoperative and Postoperative Data of the Two Groups

The operation time, anesthesia time, and intraoperative blood loss did not show any significant differences between the non-PND group and the PND group (P>0.05). However, the length of stay of the PND group was significantly longer compared to that of the non-PND group, with a statistically significant difference observed (P<0.05, Table 2).

**Table 1** Comparison of General Information Between the Two Groups ($\bar{x} \pm s$)

| Parameters | | Non-PND Group | PND Group | *P* |
|---|---|---|---|---|
| Age (years) | | 72.52±4.92 | 74.69±5.59 | 0.18 |
| Gender | Male | 10(32.3%) | 5(31.3%) | 0.94 |
| | Female | 21(67.7%) | 11(68.8%) | |
| Education (years) | | 7.35±2.30 | 6.38±1.50 | 0.15 |
| BMI | | 22.67±3.69 | 22.82±4.56 | 0.91 |
| Hypertension | | 14(45.2%) | 9(56.3%) | 0.47 |
| Diabetes | | 6(19.4%) | 5(31.3%) | 0.36 |
| Coronary heart disease | | 1(3.2%) | 0(0.0%) | 0.47 |
| ASA II | | 31(100%) | 16(100%) | >0.99 |
| Preoperative MMSE score | | 25.81±1.70 | 25.63±1.36 | 0.71 |

**Note**: Data were presented as the mean±standard deviation or n (%).


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**Table 2** Intraoperative and Postoperative Data of the Two Groups

| Parameters | Non-PND Group | PND Group | *P* |
|---|---|---|---|
| Operation time (min) | 146.23±39.27 | 164.06±106.82 | 0.53 |
| Anesthesia time (min) | 192.90±41.51 | 211.25±104.14 | 0.51 |
| Intraoperative blood loss (mL) | 259.68±175.32 | 262.50±148.89 | 0.96 |
| Length of stay (d) | 11.81±3.56 | 18.13±10.52 | 0.03* |
| TICS-m score | 38.03±2.63 | 28.56±4.24 | <0.01* |

**Note**: *$P<0.05$.

## MMSE Scores of the Two Groups

PND patients' MMSE scores at T0 were not significantly different from those of the non-PND group ($P>0.05$). MMSE scores were significantly lower for patients with PND at T1, T2, T3, and T4 compared to T0 ($P<0.05$, Table 3).

## Serum Levels of APN and CSF Levels of TNF-α, IL-1β, Lactic Acid, and Pyruvic Acid in the Two Groups

The serum APN level in the PND group was significantly lower than that in the non-PND group ($P<0.05$). Compared to those in the non-PND group, the levels of TNF-α, IL-1β, and lactic acid in the CSF were elevated in the PND group ($P<0.05$). The level of pyruvate in the CSF did not exhibit any significant disparity between the two groups ($P<0.05$, Table 4).

## Relationships of Serum APN and CSF TNF-α, IL-1β, Lactic Acid, and Pyruvic Acid

The linear correlation analysis revealed a significant negative association between serum APN levels and CSF TNF-α and IL-1β levels ($P<0.05$). There was no significant correlation between serum APN levels and CSF lactic acid and pyruvic acid levels ($P>0.05$, Table 5, Figures 2 and 3).

## Evaluation of the Diagnostic Potential of Serum APN Levels and CSF TNF-α and IL-1β Levels in PND

Based on the results of binary logistic regression, a significant correlation was observed between the occurrence of PND and serum APN, CSF TNF-α, IL-1β, and lactate ($P<0.05$). However, no significant association was found between the occurrence of PND and CSF pyruvate ($P>0.05$, Table 6).

**Table 3** Comparison of MMSE Scores Between the Two Groups

| Parameters | Non-PND Group | *P* | PND Group | *P* |
|---|---|---|---|---|
| T0 | 25.81±1.70 | / | 25.63±1.36 | / |
| T1 | 25.16±3.28 | 0.34 | 18.06±3.24[a] | <0.01 |
| T2 | 26.26±1.59 | 0.29 | 18.50±3.05[a] | <0.01 |
| T3 | 26.29±1.94 | 0.30 | 19.25±3.72[a] | <0.01 |
| T4 | 26.48±2.10 | 0.17 | 19.63±3.44[a] | <0.01 |

**Note**: Compared with T0, [a]$P<0.05$.

**Table 4** Comparison of the Serum APN and CSF Levels of TNF-α, IL-1β, Lactic Acid, and Pyruvic Acid Between the Two Groups

| Parameters | Non-PND Group | PND Group | *P* |
|---|---|---|---|
| Serum APN (μg/mL) | 6.82±0.73 | 5.97±1.00 | <0.01* |
| CSF TNF-α (pg/mL) | 14.81±0.99 | 16.28±1.34 | <0.01* |
| CSF IL-1β (pg/mL) | 15.15±1.60 | 16.30±1.86 | 0.03* |
| CSF lactic acid (mmol/mL) | 1.44±0.36 | 2.03±0.67 | <0.01* |
| CSF pyruvic acid (μmol/mL) | 0.08±0.08 | 0.09±0.03 | 0.44 |

**Note**: *$P<0.05$.

**Table 5** Correlation Analysis of Serum APN Levels with CSF TNF-α, IL-1β, Lactic Acid and Pyruvic Acid Levels

| Parameters | Correlation Coefficient | *P* |
|---|---|---|
| CSF TNF-α | 0.48 | <0.01* |
| CSF IL-1β | 0.29 | 0.04* |
| CSF lactic acid | 0.26 | 0.08 |
| CSF pyruvic acid | 0.26 | 0.07 |

**Note**: *$P$<0.05.

In the analysis of the receiver operating characteristic (ROC) curve, the area under curve (AUC) for APN was 0.75, while TNF-α in CSF exhibited an AUC of 0.81. Additionally, the CSF concentration of IL-1β had an AUC of 0.68, and lactic acid in CSF showed an AUC of 0.76 (Figure 4).

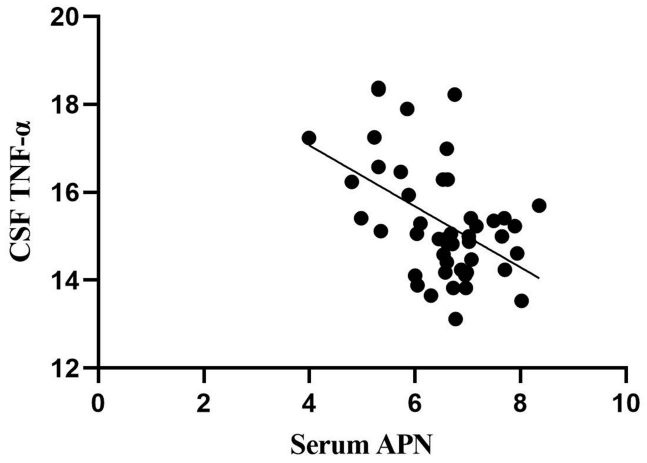


**Figure 2** Title: Correlation between Serum APN Levels and Cerebrospinal Fluid TNF-α Levels.
**Notes**: *Description*: This scatter plot illustrates the relationship between the levels of Serum APN and CSF TNF-α in a study cohort. Each point represents an individual participant, with the x-axis showing the Serum APN levels and the y-axis displaying the corresponding CSF TNF-α levels. The trend line indicates the overall direction of the relationship between these two variables. *Statistical Analysis*: The linear correlation analysis revealed a significant negative association between serum APN levels and CSF TNF-α levels. (P<0.05).

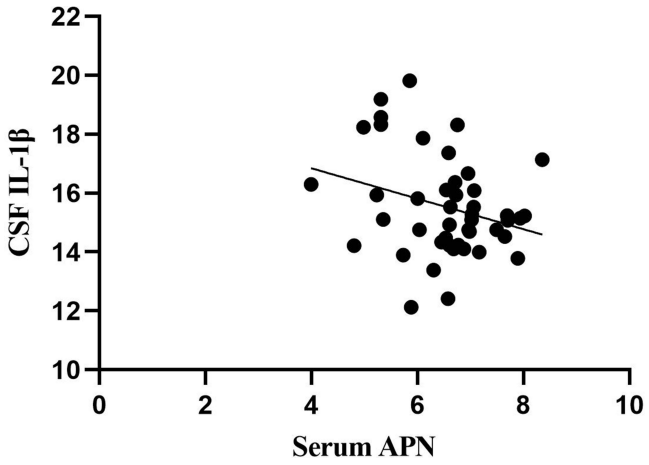


**Figure 3** Relationship between Serum APN Levels and CSF IL-1β Levels.
**Notes**: *Description*: Figure 3 presents a scatter plot depicting the inverse relationship between Serum APN levels and CSF IL-1β levels among study participants. The x-axis represents the concentration of Serum APN, while the y-axis corresponds to the levels of CSF IL-1β. Each data point corresponds to an individual subject, and the trend line is fitted using linear regression to illustrate the overall pattern of association. *Statistical Analysis*: The linear correlation analysis revealed a significant negative association between serum APN levels and CSF IL-1β levels.


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**Table 6** Diagnostic Value of Serum APN Levels and CSF TNF-α, IL-1β, and Lactic Acid Levels in PND

| Parameters | *AUC* | *95% CI* | Sensitivity (%) | Specificity (%) | Yoden Index | *P* |
|---|---|---|---|---|---|---|
| Serum APN | 0.75 | 0.59~0.90 | >99.9 | 43.7 | 0.44 | <0.01* |
| CSF TNF-α | 0.81 | 0.69~0.94 | 68.8 | 80.6 | 0.49 | <0.01* |
| CSF IL-1β | 0.68 | 0.66~0.95 | 62.5 | 77.4 | 0.40 | 0.04* |
| CSF lactic acid | 0.76 | 0.60~0.92 | 62.5 | 93.5 | 0.56 | <0.01* |

**Note**: *$P$<0.05.

## Discussion

The occurrence of PND is a frequently observed complication in elderly patients, particularly in the context of hip surgery, where its incidence is notably high.[17] Previous reports have indicated that PND affects 5–55% of elderly patients undergoing hip surgery.[18,19] In this study, the incidence of PND was 34.04%, which is consistent with previously reported results. The pathogenesis of PND is multifactorial, involving anesthesia, hypoxemia, hypotension, surgical procedure type and anesthetic technique, sleep disorders, and inflammatory responses. However, the precise underlying mechanism remains elusive. Neuroinflammation is the ultimate common pathway for various pathogenesis of PND.[20] Currently, there is no anesthesia technique, drug, or monitoring method that has been proven to effectively reduce the incidence of postoperative cognitive dysfunction. Increasing attention from scholars is being directed toward identifying risk factors and understanding the pathogenesis of PND in order to explore novel approaches for its prevention and treatment.

PND is characterized by postoperative memory impairments; difficulties with attention, logical thinking, and orientation; as well as a decline in self-care and social skills.[21] There is a dearth of specific diagnostic methods for PND in clinical practice, with the majority of clinical studies predominantly relying on neuropsychological scales for diagnosis. Among these scales, the MMSE scale stands out as the most widely employed tool for diagnosing PND.[22] Considering the limited specificity and sensitivity of the MMSE, as well as its high clinical applicability, we excluded patients with significant preoperative cognitive impairment (MMSE score<24). Moreover, acknowledging the potential

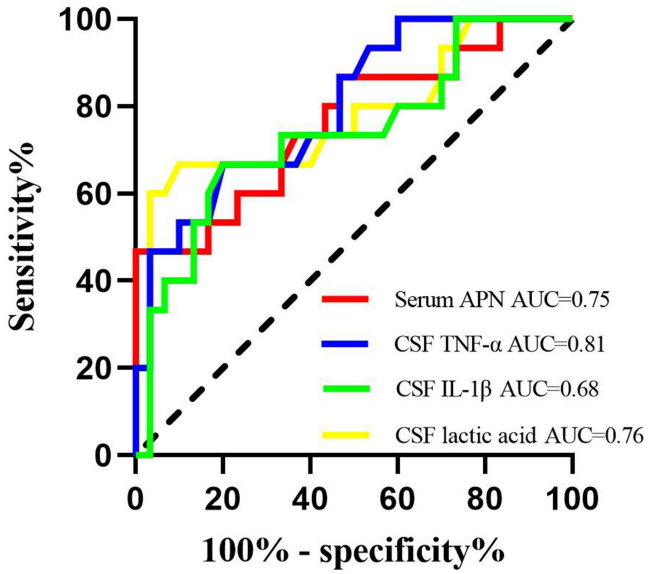


**Figure 4** ROC Curve Analysis of Biomarkers for PND.

**Notes**: *Description*: Figure 4 displays the ROC curves for four different biomarkers used to assess their diagnostic accuracy in detecting PND. The x-axis represents 100% minus the specificity (false positive rate), and the y-axis shows the sensitivity (true positive rate). The ROC curves are shown for Serum APN, CSF TNF-α, CSF IL-1β, and CSF Lactic Acid. Each curve corresponds to a different biomarker, with the AUC provided for each. *Biomarker Performance*: Serum APN with an AUC of 0.75 indicates a moderate level of diagnostic accuracy. CSF TNF-α with an AUC of 0.81 suggests a high level of diagnostic accuracy. CSF IL-1β with an AUC of 0.68 indicates a lower level of diagnostic accuracy. CSF Lactic Acid with an AUC of 0.76 also suggests a moderate level of diagnostic accuracy. The AUC values provide a quantitative measure of how well each biomarker can distinguish between patients with and without PND. An AUC of 1.0 represents perfect accuracy, while an AUC of 0.5 indicates no discriminative ability.

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influence of perioperative anesthetics and pain on cognitive function, we opted to administer the test one day prior to surgery and seven days postsurgery, aligning with previous studies in this field.[23] For patients with depression, psychosis, or hearing impairment, biochemical tests offer a more convenient alternative to questionnaires. Currently, there is no existing biochemical test available for diagnosing PND. Therefore, the development of biomarkers for PND diagnosis holds significant value. In the population of patients with hip fractures, cerebrospinal fluid is readily available at the onset of spinal anesthesia. Cerebrospinal fluid biomarkers have significant value in research to help understand the pathophysiological mechanisms involved.

The recognized risk factors linked to PND damage include age, years of formal education, type of surgical procedure, and insulin resistance. At the same time, several studies have indicated that preoperative cognitive decline also impacts the diagnosis of PND. This could be attributed to factors such as hippocampal atrophy, reduced expression of brain-derived neurotrophic factor, and increased production of inflammatory cytokines.[24,25] In this study, in order to mitigate the impact of patients' general condition on the test results, there were no statistically significant differences in gender composition, years of education, BMI, preoperative MMSE score, and the presence of hypertension, coronary heart disease, and insulin resistance (diabetes) between the two groups. The type of operation was hip replacement. A randomized controlled study indicated that there is a correlation between age and operative time with PND.[26] This correlation may be attributed to brain tissue degeneration, decreased liver and kidney function, as well as the accumulation of anesthetic drugs in elderly patients. Therefore, we carefully controlled for the age and operative time of both patient groups. Statistical analysis revealed that there were no significant differences between the two groups in terms of these factors. This allowed us to minimize the potential influence of risk factors such as age, surgical type, operative duration, and insulin resistance on our findings. In addition, the MMSE scores may be influenced by the patients' level of education, leading to a high false negative rate in highly educated patients and a high false positive rate in those with lower levels of education. Therefore, in this study, we also took into account the difference in years of education between the two groups of patients.

APN is abundant in human plasma and regulated by inflammatory cytokines, reactive oxygen species, transcription factors, and hormones like TNF-α and IL-1β. It suppresses central nervous system inflammation and regulates brain metabolism, enhancing cognitive function and reducing PND risk. Serum APN levels may serve as a biomarker for early cognitive decline detection. Although limited in the brain, APN crosses the blood-brain barrier to bind with AdipoR1 and AdipoR2 receptors, offering neuroprotective and antidepressant effects. It also supports neuronal development, differentiation, and protection in the central nervous system.[4] The findings of this study revealed a significant reduction in preoperative serum APN levels in the PND group compared to the non-PND group, suggesting a higher prevalence of early PND among elderly patients. This reduction in serum APN levels may be implicated in the pathogenesis of PND, indicating that APN could play a role in delaying its onset. Further statistical analysis demonstrated a positive correlation between serum APN levels and MMSE scores, suggesting that APN may function as a protective factor against PND through its anti-inflammatory properties.

Serum APN levels affect cognitive function by modulating systemic factors, especially the inflammatory cascade.[27] Rizzo et al[4] found that APN administration reduced inflammatory markers like C-reactive protein (CRP), IL-6, and TNF-α, while increasing anti-inflammatory IL-10. Animal studies showed APN reduced neuroinflammation in the hippocampus via the AMPK/NF-κB pathway.[28] While peripheral inflammatory factors are linked to PND, less is known about central nervous system mediators. The findings of this study suggest that central nervous system inflammation contributes to PND, examining CSF inflammatory factors in patients to explore their relationship with PND occurrence. The study indicates that patients with PND have higher levels of TNF-α and IL-1β in their CSF compared to those without PND. Statistical analysis confirmed the link between these inflammatory factors and PND occurrence. A negative correlation was found between serum APN and CSF TNF-α and IL-1β, suggesting APN's role in reducing central inflammation. ROC analysis showed that CSF TNF-α and IL-1β levels are effective for diagnosing PND. Overall, higher TNF-α and IL-1β levels in CSF are associated with PND and can help identify individuals at risk.

APN receptor signaling in the central nervous system affects inflammation, energy balance, neuronal activity, and synaptic plasticity, leading to reduced Aβ secretion, enhanced neuroprotection, and glial cell activation. AdipoR1 expression in the hypothalamus and Meynert basal ganglia suggests APN's role in brain energy regulation.[29] Cisternas et al[30] showed APN regulates glucose metabolism in hippocampal neurons, enhancing glucose uptake, glycolysis, and adenosine triphosphate (ATP) production. APN's neuroprotective effects are linked to its impact on nervous system

metabolism.[31] While APN deficiency in mice causes peripheral insulin resistance and diabetes, its effect on brain insulin sensitivity is not fully understood. Our study used linear regression to examine the link between serum APN levels and CSF lactic and pyruvic acid concentrations, finding a weak correlation. Although APN is known to regulate glucose metabolism in the central nervous system, reducing lactic and pyruvic acid levels, our results did not clearly support this association, aligning with existing literature. Future research should consider different methods for detecting these metabolites for more reliable conclusions.

Based on the analysis of lactic acid in CSF, recent studies have expanded our understanding of neuroinflammation in human PND. These studies confirm that changes in lactic acid levels in CSF are associated with the occurrence of PND. It is important to note that anti-inflammatory cytokines are linked to changes in lactic acid and pyruvic acid levels in CSF. This close relationship highlights the known biological mechanism by which lactic acid has an anti-inflammatory effect.[32,33] However, further research is necessary to determine whether the presence of lactic acid in this context indicates a metabolic disorder or signifies a positive response to inflammation suppression and neuronal energy demands. This study detected lactic and pyruvic acid metabolites in CSF and analyzed their relationships. It found higher lactic acid levels in PND patients compared to non-PND, with ROC curve analysis showing its diagnostic value for PND, consistent with previous findings. Lactic acid is vital for glucose metabolism and ATP production via glycolysis and oxidative phosphorylation, serving as a glycolytic end product in the brain. Over 95% of ATP in nerve tissue comes from lactic acid oxidation, highlighting an imbalance with glucose glycolysis.[34] Early studies confirm lactate as the sole energy substrate for activated nerve cells, with any disruption in lactate use by astrocytes affecting neuronal function.[35]

Ivanov et al[36] found that lactate can meet the energy needs of hippocampal slices and boost oxidative phosphorylation. They observed no significant difference in cerebrospinal fluid pyruvate levels between patient groups. Tejero et al[37] showed that methylmalonate inhibits lactate dehydrogenase, reducing lactate conversion to pyruvate and impairing neuron function. Although previous research suggests pyruvate may enhance aerobic metabolism and neuron synaptic integrity, potentially linking it to PND,[38] our study found no significant correlation between pyruvate and PND. After considering various factors, it is important to note that the colorimetric method is not sensitive to the concentration of pyruvate in cerebrospinal fluid. Additionally, we found that freezing the collected cerebrospinal fluid at −80°C and then detecting the specimen after its collection resulted in inaccurate measurements of cerebrospinal fluid content. In future clinical trials, we plan to improve our test procedures by conducting multiple tests and calculating average values in order to obtain more accurate conclusions.

Although our study provides important insights into the interaction between serum adiponectin levels, inflammatory markers, and postoperative neurocognitive dysfunction (PND), its limitations must be acknowledged. Recognizing these limitations is crucial for accurately interpreting our findings and guiding future research efforts. The relatively small sample size of our study may limit the generalizability of our results to larger populations. Larger-scale multicenter studies are needed to validate our results and assess their applicability in different demographic and clinical groups. Second, the cross-sectional design of our study precludes the establishment of causality. Longitudinal studies with repeated measurements over time are necessary to investigate the causal relationship and directionality of the observed associations. Third, our assessment of cognitive function relied on the Mini-Mental State Examination (MMSE) and the Telephone Interview for Cognitive Status - Modified (TICS-m). Although these tools are widely used, they may not cover all aspects of cognitive function, especially in cases of mild cognitive impairment. Fourth, our analysis was limited to a selected few biomarkers. A broader range of inflammatory and metabolic markers could provide a more detailed understanding of the biological mechanisms underlying PND. Fifth, our study was conducted at a single institution and may be subject to variations in surgical and anesthetic practices in different settings, which could affect the incidence and severity of PND. Sixth, the follow-up period was one month. To assess the long-term impact of surgery on cognitive function and determine whether the observed effects are transient or persistent, long-term follow-up is necessary. In conclusion, while our study provides preliminary evidence of the role of adiponectin and inflammation in PND, it is essential to consider these limitations when interpreting the results. Future research should aim to address these limitations and further elucidate the mechanisms promoting the development of PND.

In summary, the findings of this study demonstrate a potential association between serum APN levels, central neuroinflammation, and central nervous system metabolism with the occurrence of PND in elderly patients undergoing hip arthroplasty. APN has potential as a therapeutic target for reducing PND incidence by modulating neuroinflammatory

processes and metabolic regulation. Furthermore, serum APN levels, along with CSF concentrations of TNF-α, IL-1β, and lactate hold diagnostic value for predicting PND occurrence.

## Conclusion

Our findings indicate that serum APN levels, central nervous system inflammation, and metabolic processes within the central nervous system are associated with the incidence of PND following hip replacement in elderly patients. APN may mitigate the occurrence of PND by attenuating neuroinflammation and modulating metabolic pathways. Furthermore, concentrations of TNF-α, IL-1β, and lactic acid in CSF possess diagnostic significance for predicting PND. This study contributes to the growing body of evidence that supports a multifactorial approach to the management of PND, with the ultimate goal of improving postoperative outcomes and quality of life for elderly patients.

## Data Sharing Declaration

The de-identified individual participant data (including data dictionary) will be shared. The data will be available immediately following publication and will be accessible for 5 years. The data will be shared with researchers who provide a methodologically sound proposal. Proposals should be directed to gldeng@foxmail.com. To gain access, data requesters will need to sign a data access agreement. The data will be available at https://www.chictr.org.cn/.

## Ethics Statement

This study was conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 helsinki declaration and its later amendments or comparable ethical standards. For studies involving human participants, informed consent was obtained from all individual participants included in the study. For studies involving animals, ethical approval was obtained from the appropriate ethics committee.

Ethical approval was provided by the Medical Ethics Committee of The Tenth Affiliated Hospital of Southern Medical University, and the study was approved on June 30, 2022. The ethics committee approval number is KYKT2022-027.

Informed consent was obtained from all individual participants included in the study. Additional information can be found in the study protocol.

Any potentially identifying patient details have been anonymized. All authors had access to the study data and played a role in the writing of the manuscript.

## Informed Consent

The subjects from all the cohorts provided written informed consent.

## Statement of Human Rights

All procedures were subjected to approval by the Ethical Committee on Medical Ethics Committee of Dongguan People's Hospital, China (permit number: KYKT2022-027) and performed accordingly.

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An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com).

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in this work.

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