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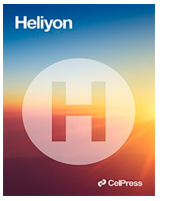

Postoperative serum CHI3L1 level is associated with postoperative cognitive dysfunction in elderly patients after hip fracture surgery: A prospective observational study

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ABSTRACT

Objectives: Postoperative cognitive dysfunction (POCD) is a common postoperative complication in older patients. Chitinase-3-like-1 protein (CHI3L1) is identified as a neuroinflammatory biomarker and impairs cognitive function. This study aimed to evaluate the association between serum levels of CHI3L1 and POCD and explore the levels of interleukin-6 (IL-6), IL-1β and C-reactive protein (CRP) in the elderly after total hip arthroplasty (THA).

Patients and methods: A total of 76 elderly patients undergoing THA were enrolled in the prospective observational study. Serum CHI3L1 levels were measured 1 day before and 1 day after surgery and other perioperative factors were also noted. The correlations between mediators of inflammation in the two groups were compared via Spearman correlation coefficients. The receiver operating characteristic (ROC) curves were implemented to analyze the predictive values of serum CHI3L1 and other inflammatory factors for POCD. And factors associated with POCD were analyzed by univariate and multivariate logistics.

Results: POCD was observed in 31.6% of patients 1 week after surgery. Postoperative serum CHI3L1 levels were higher in POCD patients than in non-POCD patients [1348.26 (778.46–1889.77) VS 2322.86(1686.88–2517.35) ng/ml, $P < 0.001$]. Postoperative serum CHI3L1 level was positively correlated with postoperative IL-6 level ($r = 0.284$, $P = 0.013$). Compared with IL-6, IL-1β, and CRP, postoperative CHI3L1 level has the highest predictive value for POCD with the area under the curve (AUC) value of 0.779 according to the ROC curve. By the multivariate logistic regression analysis, elevated postoperative serum CHI3L1 level was found to be an independent risk factor for POCD 1 week after surgery (odds ratio = 1.204, 95% confidence interval = 1.087–1.332, $P = 0.001$).

Conclusion: Postoperative elevated serum CHI3L1 level was significantly associated with the incident of POCD, and positively correlated with postoperative IL-6 level in the elderly after THA. This biomarker may have potential utility for further elucidating the etiology of POCD.

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1. Introduction

Postoperative cognitive dysfunction (POCD) is a common postoperative complication in older patients, impacting memory, orientation, attention, thinking, executive function, and visuospatial ability [1]. POCD has been combined into a new term "perioperative neurocognitive disorders (PND)" which encompasses cognitive-related changes occurring before and within 1 year after surgery [2]. Considering that this study focused on cognitive decline 1 week after surgery, the expression of POCD was still used. Evidence has reported that the incident of POCD in older patients (>65 years old) was 17–43% after surgery [3,4]. Advanced age, poor physical health, low education level, and invasive surgical procedures are risk factors for POCD. It is crucial for early diagnosis and treatment of POCD in view of decreasing quality of life and increasing the cost of care, the risk of long-term cognitive decline, and even mortality. Reliable and noninvasive biomarkers are important for predicting, preventing, diagnosing, and treating the disease.

Proposed potential mechanisms for POCD are still speculative but include perioperative stress-induced neuroinflammation, oxidative stress, aggregation of amyloid beta (Aβ), and hyperphosphorylation of tau protein [5,6]. Chitinase-3-like-1 (CHI3L1) also known as YKL-40 is a secreted glycoprotein that regulates and controls inflammation, macrophage polarization, and apoptosis. And it has recently been identified as a neuroinflammatory biomarker [7]. CHI3L1 secreted by activated astrocytes and microglia can accelerate macrophage infiltration, angiogenesis, neuroinflammation, and nerve damage [8]. Besides, CHI3L1 levels in astrocytes positively correlated with aggregation of Aβ and tau immunoreactivity [9]. Elevated CHI3L1 levels which may impair cognitive function are commonly discovered in patients suffering from neurodegenerative diseases, including Alzheimer's disease (AD), amyotrophic lateral sclerosis, multiple sclerosis, and Parkinson's disease [10,11]. Meanwhile, CHI3L1 levels have been shown to be significantly increased after major surgery, emphasizing that this protein is involved in the inflammatory process related to surgery [12]. A previous study has identified CHI3L1 as an effective biomarker to predict postoperative delirium [13]. However, no study has focused on the relationship between CHI3L1 and POCD. This study was designed to probe the relationship between serum CHI3L1 and POCD in old patients undergoing total hip arthroplasty (THA) while exploring the levels of interleukin and CRP in order to provide references for further exploration of the probable pathogenesis, clinical diagnosis, and treatment of POCD.

2. Methods

2.1. Participants

This was a single-center, prospective, observational clinical trial. The study was approved by the Medical Institutional Ethics Committee of the Affiliated Hospital of Xuzhou Medical University (XYFY2021-KL202-01). It was prospectively registered at www.chictr.org.cn (ChiCTR2100048826). Between September 2021 and April 2022, we enrolled patients scheduled for elective THA at the Affiliated Hospital of Xuzhou Medical University after obtaining signed informed, and written consent. The inclusion criteria were: (1) patients ≥65 years of age; (2) requiring an elective THA; (3) American Society of Anesthesiologists (ASA) physical status I to III. The exclusion criteria were: (1) preoperative Mini-Mental State Examination (MMSE) score<24; (2) history of schizophrenia, epilepsy, Parkinson's disease, myasthenia gravis, dementia, or clinically evident neurovascular disease; (3) history of bronchial asthma or tumor; (4) dialysis-dependent renal failure, or liver transaminase over 1.5 times normal values; (5) long history of opioid use, or other psychotropic medication; (6) patients who were admitted to ICU after surgery; (7) patients who failed the neurocognitive assessment or refused; (8) loss to follow-up.

2.2. Anesthesia

All patients got the same monitoring system, including electrocardiography, end-expiratory carbon dioxide partial pressure, pulse oximetry, invasive blood pressure monitoring, body temperature, and bispectral index (BIS). The main anesthetic included sevoflurane, propofol, etomidate, rocuronium or cisatracurium, sufentanil, remifentanil, and lidocaine. During the surgery, propofol was adjusted to keep BIS within the range of 40–60. And mechanical ventilation was also administered to 10–14 times/min with a tidal volume of 6–8 ml/kg. Other intraoperative anesthesia management such as the use of vasoactive drugs, and blood pressure targets was at the discretion of the attending anesthesiologist. Patients were treated with postoperative patient control analgesia (Analgesia pump formulation: sufentanil 1.5 μg/kg + dezocine 0.25 mg/kg + tropisetron 6 mg + 0.9% NaCl solution = 100 ml, constant speed 2 ml/h, each additional dose 0.5 ml, locking time 15 min) to relieve pain for 2 days after surgery. When Visual Analogue Scale (VAS) pain score was >4 after surgery, flurbiprofen axetil or parecoxib sodium was injected intravenously to relieve pain.

2.3. Clinical data collection

The following data were gathered and noted: (1) demographics, including age, gender, body mass index (BMI), and education level; (2) clinical characteristics, including smoking and drinking habits, Charlson Comorbidity Index (CCI), ASA physical status, number of previous surgeries, MMSE score, and Montreal Cognitive Assessment (MoCA) score; (3) laboratory tests; (4) other clinical data, including the duration of surgery and anesthesia, estimated blood loss, blood transfusion, liquid infusion volume, urine volume, postoperative nausea and vomiting (PONV), pain level, sleep quality, length of hospitalization.

2.4. Laboratory tests

All enrolled patients had blood samples taken 1 day before and 1 day after surgery. The blood analysis including hemoglobin, white blood cells, serum creatinine, alanine aminotransfease (ALT), aspartate aminotransferase (AST), albumin, interleukin-6 (IL-6), IL-1β, CHI3L1, and C-reactive protein (CRP) was measured. All indicators except IL-6, IL-1β, and CHI3L1 were detected using standard laboratory techniques which are already part of the clinical routine in our hospital. The obtained blood samples were centrifugation for 15 min at 1000×*g* after being clotted for 30 min at room temperature. Then serum samples were separated and stored at −80 °C for further laboratory tests. The levels of serum factors were examined using enzyme-linked immunosorbent assay kits in accordance with the instructions of the manufacturer's procedure: IL-1β (proteintech, Wuhan, China), IL-6 (proteintech, Wuhan, China), and CHI3L1 (R&D Systems, Minneapolis, MN, USA). The obtained serum samples were diluted 50-fold (baseline) or 750-fold (1 day after surgery) before CHI3L1 detection. Repeated measurements were performed and finally averaged by comparing their absorbance with the standard curve. The postoperative day 1-time point was based on the results of the preliminary experiment suggesting that CHI3L1 rises substantially from baseline to postoperative day 1 compared with other time points.

2.5. Assessment of cognitive function

MMSE and MoCA were conducted to evaluate cognitive function at the same time 1 day before surgery, and 1 week after surgery or at discharge. MMSE is the most widely used cognitive function screening scale in clinical application, which is applicable to the assessment of cognitive dysfunction. The test content with a total of 30 points includes memory, attention, orientation, computing ability, executive ability, and drawing ability [14]. Compared with MMSE, MoCA reduces the impact of education level, including 11 items in 8 cognitive fields with a total of 30 points [15]. To minimize the possibility of bias, all the tests were conducted by the same skilled project investigator in a peaceful environment at the same time of day. The evidence of cognitive decline was that both MMSE and MoCA score declined more than 1 standard deviation (SD) after surgery compared with preoperative score [16–18].

2.6. Sleep and pain assessment

A 10-point VAS was used to assess the quality of sleep and severity of postoperative pain once a day over the first week after surgery [19,20]. The patient was asked to score their pain level on a scale of 0–10.0 indicates no pain and 10 indicates the most severe pain. Sleep quality was also evaluated with 0 indicating the worst sleep and 10 the best sleep. The worst pain and sleep scores were recorded over the first postoperative week.

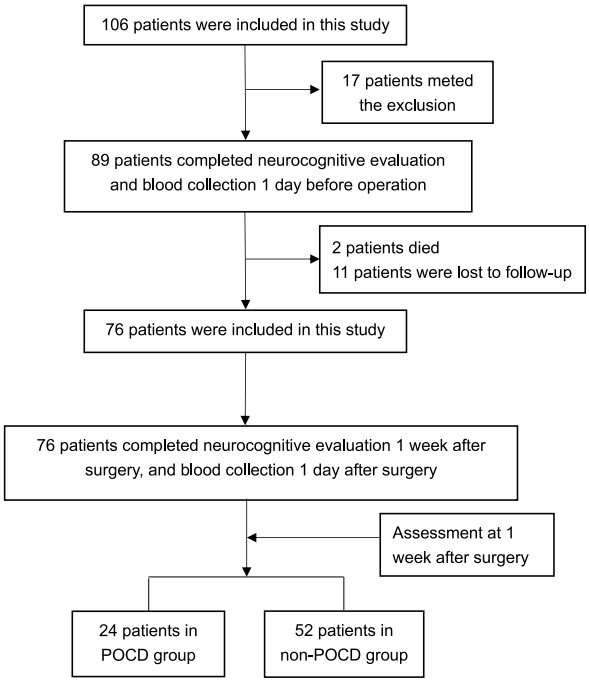

Fig. 1. Study flow chart.

2.7. Statistical analysis

We estimated the sample size using the receiver operating characteristic curve (ROC curve) (Hanley and McNeil approach) [21]. By reference to the results of the preliminary experiment of 20 patients, the sample size was determined with an expected area under the curve (AUC) of CHI3L1 of 0.75 and an expected incidence of POCD of 30% at 1 week after surgery. With a power of 90%, the type 1 error rate of 5% (two-sided), and 20% missing data rates, the calculated sample size was 76 patients.

The normal distribution of data was evaluated using the Shapiro–Wilk test. Normally distributed continuous variables were described as the mean ± standard deviation (mean ± SD), and nonnormally distributed continuous variables were described as the median (interquartile range). Categorical data were expressed as counts (%). We used the Student t-test or the Mann-Whitney *U* test to compare continuous variables between two groups and the χ^2 test or the Fisher's exact test to compare categorical variables as appropriate. The correlations between mediators of inflammation in the two groups were compared via Spearman correlation coefficients. The ROC curve was applied to analyze the predictive values of factors for POCD. AUC, 95% confidence interval (95%CI), optimal cutoff value, specificity, and sensitivity were displayed. Univariate logistic regression models were used to analyze the risk factors for POCD; those variables with a P value < 0.05 or known to be significantly associated with POCD were then analyzed with the multivariate regression analysis. Variance inflation factor (VIF) was used to judge whether multicollinearity existed between variables, and variables with VIF>10 were excluded. In order to adjust for the odds ratio (OR) values and 95% CI of the independent predictors of POCD, multivariable forward stepwise logistic regression models were implemented.

The software of IBM SPSS Statistics 26 (SPSS Inc, Armonk, NY, USA), GraphPad Prism 8.0 (GraphPad Inc, California, USA), and Sigmaplot 14.0 (San Jose, CA) was utilized for the data analysis. Statistics were considered significant when bilateral $P < 0.05$.

3. Results

3.1. Patients

A total of 106 patients were included in this study. 8 patients had preoperative MMSE <24 points, 3 patients had previous history of parkinsonism or myasthenia gravis, 3 patients were admitted to the ICU after surgery, 3 patients refused cognitive function tests, 2 patients died after surgery, and 11 patients were lost to follow-up after surgery. They were all excluded according to the exclusion criteria. Eventually, 76 patients completed the trial (Fig. 1). POCD was diagnosed 1 week after surgery in 24 (31.6%) patients. Individual neurocognitive trajectories are presented in Fig. 2(a, b). The mean age of the enrolled patients was 72.2 years, and it was mainly female (57.9%, 44 of 76). Table 1 displays the demographics and clinical characteristics of the participants. There was no significant difference in age, gender, BMI, ASA grade, CCI, number of previous surgeries, duration of surgery and anesthesia, estimated blood loss, blood transfusion, liquid infusion volume, urine volume, PONV, pain, sleep, and length of hospitalization between two groups ($P > 0.05$). Compared with those without POCD, patients with POCD 1 week after surgery exhibited lower education level ($P = 0.018$). And patients with POCD had significantly lower postoperative MMSE and MoCA scores ($P < 0.001$).

3.2. Laboratory tests

The results of laboratory tests between the two groups are listed in Table 2. There was no significant difference in Hb, ASL, ALT, Albumin, creatinine, and IL-1β between them ($P > 0.05$). Compared with those without POCD, patients with POCD 1 week after surgery showed obviously increased expressions of preoperative CRP ($P = 0.048$) and IL-6 ($P = 0.047$), and postoperative CHI3L1 ($P < 0.001$) and IL-6 ($P = 0.039$) [Table 2 and Fig. 3(a, b)]. Besides, according to the Spearman correlation coefficients, postoperative CHI3L1 was positively associated with postoperative IL-6 ($r = 0.284$, $P = 0.013$) (Fig. 4).

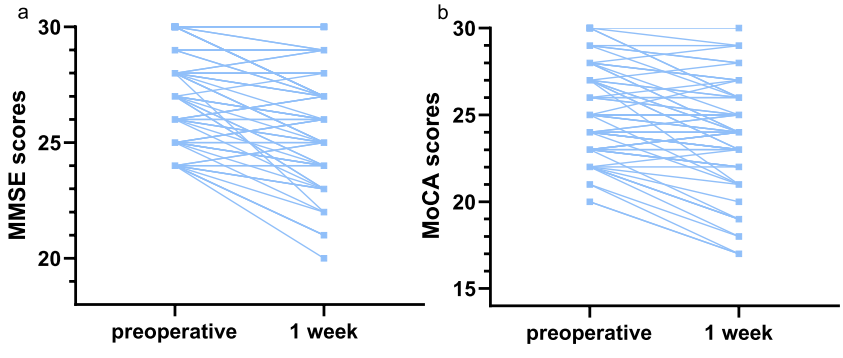

Fig. 2. Individual neurocognitive outcome trajectories 1 week after surgery.

Table 1
The demographic and clinical characteristics of the study participants.

Characteristics	Non-POCD (n = 52)	POCD (n = 24)	*P* value
Preoperative			
Age (years)	70.5(67.0–75.0)	72.5(66.3–77.8)	0.388
Gender (Female, %)	27(51.9)	17(70.8)	0.121
BMI (kg/m^2)	24.15 ± 0.53	23.50 ± 0.78	0.494
Education (years)	4(4–7)	4(0–6)	0.018
ASA physical status II/III, n	35/17	12/12	0.149
CCI	0(0–1)	0(0–1)	0.608
The operation frequency	1(0–1)	1(0–1)	0.957
Smoking, n (%)	10(19.2)	7(29.2)	0.334
Drinking, n (%)	10(19.2)	6(25)	0.566
Hypertension, n (%)	25(48.1)	8(33.3)	0.228
Diabetes, n (%)	7(13.5)	5(20.8)	0.413
Heart Disease, n (%)	10(19.2)	4(16.7)	0.789
MMSE	27(25–28)	27(25–29)	0.928
MoCA	25(24–26)	25(22–28)	0.485
Intraoperative			
Duration of surgery (min)	100(90–111)	100(80–129)	0.875
Duration of anesthesia (min)	125(110–140)	120(110–149)	0.942
Total infusion (ml)	1275(1000–1550)	1500(1213–1688)	0.371
Estimated bleeding loss (ml)	200(100–300)	250(100–300)	0.311
Urine volume (ml)	200(100–300)	225(100–300)	0.259
Blood transfusion, n (%)	1(1.9)	2(8.3)	0.203
Postoperative			
Pain VAS	4.12 ± 0.93	4.52 ± 0.82	0.070
Sleep VAS	6.27 ± 1.16	6.04 ± 1.68	0.494
PONV, n (%)	16(30.8)	7(29.2)	0.888
MMSE	27(25–29)	24(22–27)	<0.001
MoCA	25(23–26)	21(19–24)	<0.001

Data are presented as mean ± SD or median with IQR for continuous variables and as number for categorical variables. The P-value is calculated by the Student t-test or the Mann-Whitney *U* test for continuous variables and by the $\chi 2$ test or the Fisher's exact test for categorical variables.
Abbreviations: POCD, Postoperative Cognitive Dysfunction; BMI, Body Mass Index; CCI, Charlson Comorbidity Index; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PONV, Postoperative Nausea and Vomiting; VAS, Visual Analogue Scale.

Table 2
The laboratory tests of the study participants.

Characteristics	Non-POCD (n = 52)	POCD (n = 24)	*P* value
preoperative			
Hb (g/L)	132.15 ± 2.05	125.83 ± 3.64	0.236
ASL (U/L)	18.65 ± 5.48	18.69 ± 6.81	0.784
ALT (U/L)	15.09 ± 5.97	15.70 ± 7.38	0.622
Albumin (g/L)	40.95(39.45–43.53)	43.15(41.28–45.25)	0.234
Creatinine (umol/L)	56.00(47.75–63.25)	66.00(55.50–75.75)	0.119
CHI3L1 (ng/ml)	139.56(85.06–226.24)	148.87(107.73–239.02)	0.377
IL-1β (pg/ml)	5.93(3.53–7.37)	5.85(5.17–6.53)	0.928
IL-6 (pg/ml)	4.89(1.60–8.91)	10.10(3.98–22.61)	0.047
CRP (mg/ml)	2.25(0.07–6.13)	10.80(1.09–45.90)	0.048
postoperative			
CHI3L1 (ng/ml)	1348.26(778.46–1889.77)	2322.86(1686.88–2517.35)	<0.001
IL-1β (pg/ml)	5.85(3.13–6.91)	5.68(4.65–6.60)	0.585
IL-6 (pg/ml)	73.93(41.99–145.67)	171.82(140.19–424.86)	0.039
CRP (mg/ml)	43.65(24.65–67.83)	71.74(26.89–141.55)	0.187

Data are presented as mean ± SD or median with IQR for continuous variables and as number for categorical variables. The P-value is calculated by the Student t-test or the Mann-Whitney *U* test for continuous variables and by the $\chi 2$ test or the Fisher's exact test for categorical variables.
Abbreviations: Hb, hemoglobin; ASL, aspartate aminotransferase; ALT, alanine aminotransferase; CHI3L1, Chitinase-3-like-1 protein; IL-1β, interleukin-1β; IL-6, interleukin-6; CRP, C-reactive protein.

3.3. Predictive values of inflammatory factors for POCD

According to the ROC curve, postoperative CHI3L1 level could be used to predict POCD occurrence 1 week after surgery with a cut-off value of 1754, a sensitivity of 0.731, a specificity of 0.708, and an AUC of 0.779 (95% CI, 0.675–0.884, $P < 0.001$) (Fig. 5 and Table 3). As shown in Table 3, preoperative IL-6, CRP, and postoperative IL-6 had predictive values for POCD ($P < 0.05$). And the AUC values of IL-6 and CRP are also presented in Fig. 5.

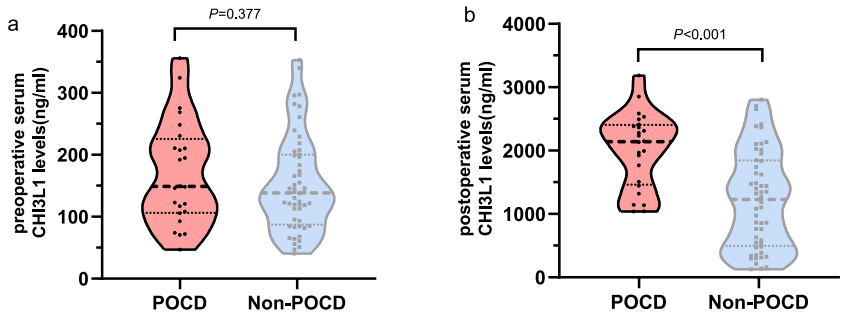

Fig. 3. Comparison of CHI3L1 levels in two groups at different times. (a) Preoperative CHI3L1 levels; (b) postoperative CHI3L1 levels.

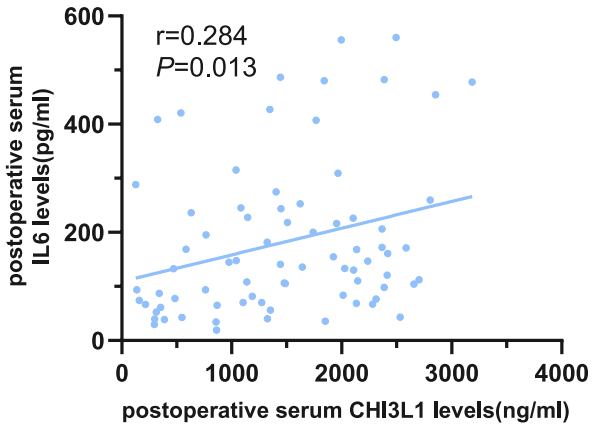

Fig. 4. The correlation of postoperative serum IL-6 and CHI3L1 levels.

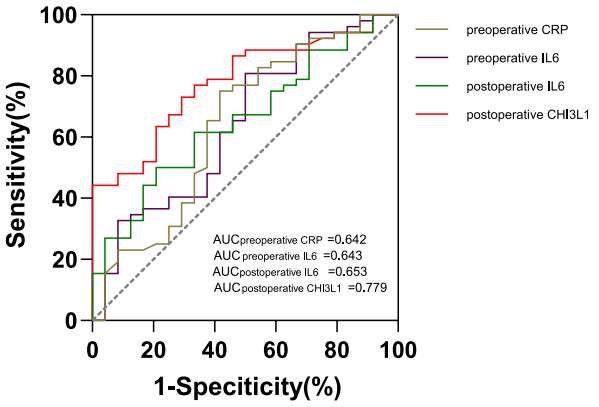

Fig. 5. Predictive values of IL-6、CRP and CHI3L1 for POCD by the ROC curve analysis.

3.4. Independent predictors associated with POCD

When investigating the predictors for the incidence of POCD, univariate analyses were firstly performed to assess the relationship between clinical parameters and patient outcomes. As shown in Table 4, education level (OR = 0.832, 95%CI = 0.709–0.976, P = 0.024), preoperative CRP (OR = 1.032, 95%CI = 1.005–1.060, P = 0.022), and postoperative CHI3L1 (OR = 1.161, 95%CI = 1.070–1.259, $P < 0.001$) were significantly associated with POCD occurrence 1 week after surgery. To ensure whether postoperative CHI3L1 was an independent risk factor of incident of POCD, the multivariable logistic regression analysis was applied. When accounting for the common risks, such as age, ASA physical status, and education level, postoperative CHI3L1 (OR = 1.204, 95%CI = 1.087–1.332, P = 0.001) was the independent factor of POCD occurrence at 1 week after surgery. Meanwhile, education level (OR = 0.478, 95%CI = 0.247–0.927, P = 0.029) and preoperative CRP level (OR = 1.041, 95%CI = 1.002–1.081, P = 0.040) were also

Table 3
Predictive value of inflammatory factors for POCD by ROC curve analysis.

Characteristics	AUC	95%CI	*P* value	cut-off value	Sensitivity	Specticity
preoperative						
CHI3L1	0.563	0.422–0.705	0.377	–	–	–
IL-1β	0.508	0.337–0.680	0.928	–	–	–
IL-6	0.643	0.505–0.781	0.047	13.62	0.500	0.808
CRP	0.642	0.499–0.785	0.048	6.65	0.583	0.750
postoperative						
CHI3L1	0.779	0.675–0.884	<0.001	1753.93	0.708	0.731
IL-1β	0.559	0.359–0.759	0.568	–	–	–
IL-6	0.653	0.526–0.780	0.033	107.26	0.792	0.500
CRP	0.594	0.451–0.737	0.189	–	–	–

Abbreviations: AUC, area under the curve; CHI3L1, Chitinase-3-like-1 protein; IL-1β, interleukin-1β; IL-6, interleukin-6; CRP, C-reactive protein.

Table 4
Univariate analysis results for POCD at 1 week after surgery.

Parameters	OR	95% CI	*P* value
Age (years)	1.058	0.977–1.147	0.165
Gender (male/female)	2.249	0.799–6.329	0.125
BMI (kg/m^2)	0.955	0.839–1.087	0.488
Education (years)	0.832	0.709–0.976	0.024
ASA physical status (II/III)	2.370	0.887–6.331	0.085
Preoperative Hb (g/L)	0.979	0.949–1.010	0.179
Preoperative Albumin (g/L)	0.906	0.803–1.023	0.110
Preoperative IL-6 (pg/ml)	1.027	0.997–1.059	0.081
Preoperative IL-1β (pg/ml)	1.021	0.979–1.065	0.328
Preoperative CRP (mg/ml)	1.032	1.005–1.060	0.022
preoperative CHI3L1 (ng/ml)	1.003	0.997–1.009	0.353
postoperative CHI3L1 (per 100 ng/ml)	1.161	1.070–1.259	<0.001
postoperative IL-6 (pg/ml)	1.003	1.000–1.006	0.055
postoperative IL-1β (pg/ml)	1.151	0.936–1.415	0.182
postoperative CRP (mg/ml)	1.008	0.998–1.017	0.108
postoperative pain VAS	1.669	0.952–2.924	0.074
postoperative sleep VAS	1.230	0.837–1.806	0.292

Abbreviations: POCD, Postoperative Cognitive Dysfunction; OR, Odds Ratio; CI, Confidence Interval; BMI, Body Mass Index; Hb, hemoglobin; CHI3L1, Chitinase-3-like-1 protein; IL-1β, interleukin-1β; IL-6, interleukin-6; CRP, C-reactive protein; VAS, Visual Analogue Scale.

independently associated with the incident of POCD (Fig. 6).

4. Discussion

So far as we know, this is the first time to explore an association between CHI3L1 level in peripheral blood and POCD occurrence in patients undergoing elective THA. In this study, we found that the high CHI3L1 level 1 day after, but not before surgery in elderly patients undergoing elective THA was associated with cognitive decline 1 week after surgery. And after adjusting for the confounders such as age, education, ASA physical status, and other inflammatory factors, the correlation still remains. Our findings suggested that postoperative CHI3L1 level may be associated with the incident of POCD independently and also improve the scientific understanding of the pathobiology of POCD.

CHI3L1 is a 40 kDa glycoprotein combining chitin, heparin, and collagen. CHI3L1 was secreted by a variety of cell types, including macrophages, glial cells, vascular smooth muscle cells, and certain types of cancer cells [8]. Considering the involvement of CHI3L1 in peripheral and central inflammatory response processes, it has recently been identified as a biomarker for neuroinflammation [10]. In recent years, many studies have revealed that CHI3L1 levels in the blood and cerebrospinal fluid (CSF) seem to be positively associated with disease severity and poor prognosis in several neurodegenerative diseases. Laura et al. found that CSF and serum CHI3L1 levels were significantly increased in the acute inflammatory phase of acute disseminated encephalomyelitis and multiple sclerosis, associated with the progression of the disease [22]. A prior research that performed quantitative proteomics analysis of plasma from Parkinson's disease 555 proteins discovered substantial increases in CHI3L1 levels and a positive correlation with the rate of cognitive decline [23]. A prospective cohort study has shown independent associations of CHI3L1 in the peripheral blood with recurrent stroke and poor functional outcome in patients with transient ischemic attack or ischemic stroke [24]. Furthermore, several studies have found that CHI3L1 known as the biomarker of AD predicted progression to AD [25,26]. It indicated that CHI3L1 levels may be beneficial in distinguishing cognitively normal, mild cognitive dysfunction, and AD patients [27]. Meanwhile, previous studies have found neurocognitive-related inflammatory response may influence the relationship of CHI3L1 between blood and CSF [28,29]. CHI3L1 may bring about increased permeability and decreased stability of blood-brain barrier (BBB) in AD patients in turn [30]. The up-regulation of serum CHI3L1 expression can reflect the expression of CHI3L1 in CSF to some extent [31]. Therefore, CHI3L1

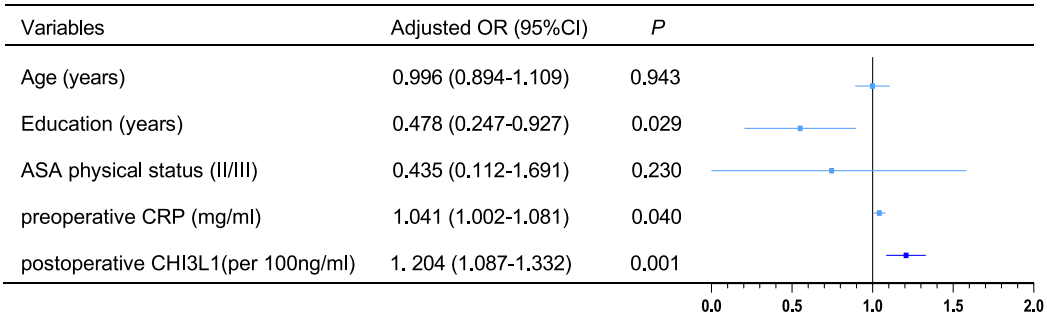

Fig. 6. Forest plots on multivariate analysis results for POCD at 1 week after surgery.

expression in peripheral blood can be used to assess the severity of the neuroinflammatory response and further reflect neurocognitive function damage. We found that the CHI3L1 level was significantly increased compared with the preoperative level and was associated with the incident of POCD. However, we have found there was no association between preoperative CHI3L1 level and POCD. We speculate that it may be due to the exclusion of patients with an MMSE score <24.

CHI3L1 expression is mainly induced by acute inflammation in astrocytes, macrophages, and microglia, and decreases as the inflammation resolves [32,33]. During neurodegeneration, CHI3L1 promotes astrocyte-microglia cross-talk. Increased CHI3L1 levels in astrocytes could contribute to immune cell infiltration and trigger the production of pro-inflammatory cytokines such as IL-6 and IL-1β, which stimulate astrogliosis and CHI3L1 expression in turn [8,34]. Since these inflammatory mediators can cross BBB, the serum levels of CHI3L1, IL-6, and IL-1β may in part reflect the inflammatory state of the CNS. In this study, we found that postoperative serum CHI3L1 was positively correlated with postoperative IL-6 ($r = 0.284$, $P = 0.013$) but there was no relationship between preoperative CHI3L1 and preoperative IL-6. It partly reflected the interaction of CHI3L1 and IL-6 when the inflammatory response occurred to a certain degree after surgical trauma and anesthesia. Studies have shown that central nervous system inflammation is one of the pathophysiological mechanisms of POCD, and perioperative stress can induce POCD by activating peripheral and central nervous system inflammatory responses [35]. Given this complexity, the exact inflammatory mediator of POCD remains a puzzle. Our findings suggest CHI3L1 may be involved in the neuroinflammatory pathological process of POCD. Otherwise, CHI3L1 actively participates in peripheral inflammation and immune regulation. CHI3L1 is also a regulator of T helper 2 cells (Th2) cell response and plays a key role in type 2 immune responses, mediating the change of mature macrophages from monocytes [36]. Our discovery of CHI3L1 may provide new insight into the potential role of type 2 immune activation in the pathogenesis of POCD. Besides, animal experiments have shown that CHI3L1 could bind receptor for advance glycation end product (RAGE), contributing to a variety of cellular responses with increased activation of nuclear transcription factor-kappa B (NF-κB) signaling pathways. Then, NF-κB could reduce transcription factors which regulate β-secretase in brain cells, resulting in the aggregation of Aβ and neuronal cell death [37]. Accumulation of Aβ results in tau protein hyperphosphorylation, synaptic dysfunction, neuronal death, and eventually, loss of cognitive function [38]. Regrettably, we did not evaluate Aβ in blood or CSF. The mechanism underlying the association of high CHI3L1 levels with the incident of POCD is still elusive. We expect more clinical and basic experiments to further elucidate the underlying pathological mechanism of CHI3L1 in POCD.

In this study of 76 patients undergoing elective THA surgery, the occurrence of POCD was 31.6% at 1 week after surgery, which is similar to that of previous reports [3]. The diagnosis of POCD lacks uniform diagnostic criteria and remains controversial. We defined cognitive function decline by MMSE and MoCA scores, which is consistent with many other studies [39,40]. Compared with a series of neuropsychological test groups, MMSE is more suitable for patients with advanced age and low education level, easily accepted by patients [41,42]. However, MMSE alone may not be sufficient for POCD diagnosis due to the ceiling effect. MoCA improved from MMSE is more suitable for patients with higher education level and is more sensitive to mild cognitive impairment than MMSE [41]. Our study has shown that POCD group had lower education level, which was similar to previous studies [43,44]. However, we did not find the difference in age between the two groups, which has been proven to be an independent risk factor of POCD [45]. Different populations and small samples may attribute to the difference. Besides, comparing other inflammatory factors between the two groups, our study has indicated that increased systemic inflammation (high CRP and IL-6) may be potentially involved in POCD, but failed to demonstrate the association between elevated IL-1β and POCD. The finding was comparable with the result of a meta-analysis which has shown a significant increase in preoperative CRP as well as postoperative CRP and IL-6 in POCD patients [46]. However, our results from multivariate logistic analysis only support the predictive value of the preoperative levels of CRP. It may be attributed to the different time of blood collection. And it also reflects that these inflammatory factors may be one of the risk factors for POCD, but they are not highly specific as a predictive marker of POCD due to be affected by a variety of factors. Meanwhile, we also analyzed prognostic values of IL-6 and CRP for POCD by the ROC curve. The results indicated that the AUC values of those were lower than CHI3L1.

The present study has several limitations. First, the sample size was relatively small, which could cause some bias. Considering the size of the sample, we only took several indicators into consideration to perform the multivariable logistic regression for the occurrence of POCD 1 week after surgery as an exploratory analysis. Second, we only focused on the peak serum level of postoperative CHI3L1 and ignored its dynamic changes at multiple time points after surgery. Meanwhile, the CSF levels of CHI3L1 were not tested. It is significant

to analyze potential POCD markers in CSF and their relationship with blood and CSF markers, which has a strength in uncovering the pathobiology mechanisms associated with the occurrence of POCD. Last, the diagnosis of POCD still remains controversial. Only MMSE and MoCA were utilized as diagnostic criteria for POCD.

5. Conclusion

In conclusion, postoperative elevated serum CHI3L1 level was significantly associated with the incident of POCD and positively correlated with postoperative IL-6 level in the elderly after THA. Compared with IL-6, IL-1β, and CRP, postoperative CHI3L1 level has the highest predictive value for POCD. Our results suggested postoperative CHI3LI as a probable useful biomarker for predicting POCD risk. Besides, the relationship between serum levels of postoperative CHI3LI and POCD may provide valuable mechanistic insights into the etiology of POCD. A more detailed description of the pathological mechanism of POCD may give us the opportunity to tailor the treatment strategies and modify the risk factor accurately. More clinical and basic experimental studies are needed to validate our findings and further identify the potential mechanisms of CHI3LI in POCD patients.

Ethics approval and informed consent

The study was approved by the Medical Institutional Ethics Committee of the Affiliated Hospital of Xuzhou Medical University. Patients all signed the written informed consents before taking part into our study. The study project conforms to the ethical guidelines of the Declaration of Helsinki.

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Author contribution statement

Huiwen Zheng: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Qianmin Chen; Chao Liu: Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Jingyue Zhang; Baiqing Ren: Performed the experiments; Analyzed and interpreted the data.

Tianya Liu: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data.

Xiaoye Wang: Contributed reagents, materials, analysis tools or data.

Jingyi Sheng: Performed the experiments.

Zhiping Wang: Conceived and designed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Data availability statement

Data will be made available on request.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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