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Anesthesia and surgery-induced elevation of CSF sTREM2 is associated with early cognitive dysfunction after thoracoabdominal aortic dissection surgery

Kexin Wang, Xuezhao Cao*, Zhe Li*, Sidan Liu, Yongjian Zhou, Lili Guo and Pengli Li

Abstract

Purpose: Soluble triggering receptor expressed on myeloid cells 2 (sTREM2) concentration is increased in cerebrospinal fluid (CSF) in early symptomatic phase of Alzheimer's disease (AD). This study investigated whether CSF sTREM2 has a relationship with early cognitive dysfunction following surgery in cardiac surgery patients.

Methods: A total of 82 patients undergoing thoracoabdominal aortic replacement were recruited in this study. Neuropsychological testing battery was conducted before and after surgery. Postoperative cognitive dysfunction (POCD) was defined as a Z-score > 1.96 on at least 2 different tests or Telephone Interviews for Cognitive Status-Modified (TICS-M) score < 27. The CSF and serum sTREM2, $A\beta_{42}$, T-tau and P-tau were collected and measured by ELISA on day before surgery and postoperative day 3.

Results: Patients were classified into POCD ($n = 34$) and non-POCD ($n = 48$) groups according to Z-score. Compared to non-POCD group, the levels of CSF sTREM2 ($p < 0.001$) and serum sTREM2 ($p = 0.001$) were significantly higher in POCD group on postoperative day 3. The levels of $A\beta_{42}$ ($p = 0.005$) and $A\beta_{42}$/T-tau ratio ($p = 0.036$) were significantly lower in POCD group on postoperative day 3. Multivariate logistic regression analysis revealed that higher value of postoperative CSF sTREM2 (odds ratio: 1.06, 95% confidence interval: 1.02–1.11, $p = 0.009$), age (OR: 1.15, 95%CI: 1.03–1.28, $p = 0.014$) and POD duration (OR: 2.47, 95%CI: 1.15–5.29, $p = 0.02$) were the risk factors of POCD.

Conclusion: This study indicates that anesthesia and surgery-induced elevation of CSF sTREM2 is associated with an increased risk of early cognitive dysfunction following surgery.

Keywords: sTREM2, POCD, $A\beta_{42}$, T-tau, P-tau, $A\beta_{42}$/T-tau ratio

Introduction

Postoperative cognitive dysfunction (POCD) refers to disorders affecting orientation, attention, perception, consciousness, and judgment that develop after cardiac and non-cardiac surgery [1]. It is a common central nervous system complication of anesthesia and surgery, especially in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) [2]. POCD affects up to 65% of cardiac surgery patients at hospital discharge [2], resulting in delayed recovery, prolonged length of hospital stay, and an increased risk of disability and mortality [3, 4]. The International Study of POCD estimated the overall incidence of POCD at 19.5% at 1 week and 9.6% after 3 months in the non-cardiac surgery patients [5]. Although the neurobiological basis of POCD remains unknown, major risk factors, such as advanced age, poor

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education, preexisting cognitive impairment, severity of coexisting illness, duration of anesthesia, respiratory complications and second operation, have been identified [6]. Of these, age has been increasingly reported as the most prominent risk factor for the development of POCD [6]. Owing to elusive pathophysiology and neuropsychological testing battery requirements, POCD diagnosis is usually delayed. Thus, it is necessary to identify reliable and convenient biomarkers for diagnosis and prognosis of POCD.

There is no standard biomarker for POCD prediction and risk stratification. A study by Rasmussen et al. found that there was no relationship between neuron-specific enolase (NSE) or S100β and cognitive decline in elderly patients undergoing abdominal surgery [7]. Similarly, Linstedt et al. revealed an association of S100β but not NSE with early cognitive impairment in the patients undergoing noncardiac surgery [8]. Multiple studies found that the level of tau was increased in the patients who developed POCD [9, 10]. There was significant relationship between perioperative $A\beta_{42}$/T-tau ratio and cognition dysfunction [11, 12]. Thus, it is necessary to find a biomarker with high specificity and sensitivity for POCD predication.

Neuroinflammation plays a crucial role in the progression of POCD [13]. Multiple evidence demonstrated that triggering receptor expressed on myeloid cells 2 (TREM2) inhibited neuroinflammatory responses by repression of microglia-mediated cytokine production [14]. The extracellular domain of TREM2 can be shed by ADAM10/17 cleavage and released in its soluble form into the interstitial fluid of the brain [15–17]. Increased soluble TREM2 (sTREM2) in cerebrospinal fluid (CSF) is related to cognitive impairment in Alzheimer's disease (AD) patients [18, 19]. These data suggest that elevated sTREM2 may involve in early cognitive dysfunction. Therefore, investigating the association between sTREM2 and POCD in surgical subjects might be conducive.

There are no sensitive and specific biomarkers as predictors of POCD. A study by Ferri et al. has indicated the potential application of sTREM2 as a biomarker of cognitive impairment [20]. However, whether sTREM2 can serve as a predictor of POCD in surgical subjects remains unclear. To improve diagnosis and treatment of POCD, the primary objective of this study was to identify the relationship between CSF sTREM2 and POCD.

Materials and methods

Participants

This study protocol was approved by the Ethics Committee of the First Hospital of China Medical University (2020–302-2) and registered in Chinese Clinical Trial Registry Centre (Registration No. ChiCTR2000038634). Between August 2020 and October 2021, the patients with thoracoabdominal aortic dissection were recruited in this study. Informed consent was obtained from all patients. Inclusion criteria was as follows: (1) The age ranges from 30 to 70; (2) The patients undergoing thoracoabdominal aortic surgery under general anesthesia; (3) Lumbar puncture for CSF drainage by L3–4 was performed to prevent paraplegia. Exclusion criteria: (1) Language/communication difficulties; (2) Dementia disorders due to other causes; (3) Contraindications to lumbar puncture; (4) A history of cognitive, psychiatric, or neurological illness; (5) Unavailable for neuropsychological test or refused to participate; (6) MMSE score < 24; (7) A history of cardiovascular surgery or craniotomy.

Anesthesia management and surgical procedures

The lumbar puncture was performed and a catheter was inserted into the subarachnoid space for CSF drainage to confer neurological protection on day before surgery. All participants received routine monitoring, including blood pressure, electrocardiogram, end-tidal carbon dioxide ($ETCO_2$), oxygen saturation, depth of anesthesia by BIS, and temperature on surgery day. Local cerebral oxygen saturation (rSO_2) was also monitored. Midazolam, etomidate, sufentanil, and cisatracurium were administrated for anesthesia induction. Approximately 5 minutes later, the patients were intubated and mechanically ventilated to maintain $ETCO_2$ between 35 and 45 mmHg. Anesthesia was maintained via propofol, sevoflurane, sufentanil, and cisatracurium to adjust BIS values between 40 and 60. All participants underwent CPB with deep hypothermic circulatory arrest. Bilateral anterograde cerebral perfusion was performed to maintain $rSO_2 \geq 50\%$ or within 20% of preoperative value during deep hypothermic circulatory arrest.

Neuropsychological tests

Neuropsychological testing battery was performed to evaluate cognitive function on day before surgery and postoperative days 3 and 7. The tests consisted of Minimental State Examination (MMSE), symbol digit modalities test (SDMT), digit span forward test (DSFT) and digit span backward test (DSBT), Rey auditory verbal learning test (RAVLT), Stroop color-word test (SCWT) and the confusion assessment method - intensive care unit (CAM-ICU). SCWT consists of three tests: a word test (SCWT-A), a color test (SCWT-B), and a word-color interference test (SCWT-C). Telephone Interviews for Cognitive Status-Modified (TICS-M) and score of activities of daily living (ADLs) were conducted to reduce the loss-to-follow-up rate for discharged patients in postoperative months 1, 3 and 6.

CSF and serum collection and storage

CSF (5 ml) and blood (5 ml) samples were collected (8:00–12:00 a.m.) on day before surgery and postoperative day 3. The CSF samples were centrifuged at 2000 g for 10 minutes and the blood samples were centrifuged at 1500 g for 5 minutes at room temperature. The supernatants of CSF and serum were transferred into EP tubes and then stored at -80 °C pending biochemical analysis.

Measurement

Enzyme-linked immunosorbent assay (ELISA) was used to determine sTREM2 (Human TREM2 ELISA kit; Abcam, no. Ab224881), $A\beta_{42}$ (Human $A\beta_{42}$ ELISA kit; JL11012), T-tau (Human T-tau ELISA kit; JL46220) and P-tau (Human P-tau ELISA kit; JL46213). The samples were diluted as recommended by the manufacturer, and a standard curve was used to calculate the concentrations. Briefly, diluted standards, the samples, and antibody were added to the wells. Then, a peroxidase substrate tetramethyl benzidine (TMB) was added for color development. The OD450 was determined using microplate reader and the concentration of the tested substances was calculated by using software ELISACalc.

Calculation of POCD and POD

POCD was defined as a Z-score > 1.96 on at least 2 different tests on postoperative days 3 or 7, or TICS-M score < 27 in postoperative 1, 3 or 6 months [21–24]. Briefly, Z-score was calculated by the following way: ([change score]$_{individual}$-[mean change score])/(standard deviation change score$_{total}$) [25, 26]. The diagnosis of postoperative delirium (POD) employed CAM-ICU on postoperative days 3 and 7 [27, 28].

Statistical analysis

Sample size calculation was performed using PASS software, with 80% power, 0.05 alpha, and the expected OR value is 4. Considering a 20% dropout rate, a total of 100 patients was required.

Data were analyzed with IBM SPSS Statistics Version 26 and submitted to Shapiro-Wilk test for normality evaluation. Continuous variables were expressed as means±SD, medians and interquartile ranges (IQRs) and tested using t-tests or Mann-Whitney U tests. Categorical variables were expressed as percentage and tested using Chi-square tests. Comparison among groups was performed using independent t test for biomarker levels and Mann-Whitney U test for neuropsychological tests. Comparison within groups was performed using paired t test for biomarker and Friedman test for neuropsychological tests. Correlations were analyzed with Spearman correlation test, and multiple comparisons were applied with Bonferroni adjustment method. Univariate and multivariate logistic regressions analyses were performed to identify the risk factors of POCD. A p-value≤0.05 was considered as statistically significant. The figures were made using GraphPad Prism 8.0 software.

Result

Patient characteristics

Characteristics and clinical data of patients were summarized in Table 1. A total of 82 patients undergoing thoracoabdominal aortic replacement were enrolled in this trial. The patients were classified into POCD group ($n = 34$) and non-POCD group ($n = 48$) according to Z-score method. The incidence of POCD was 29.3 and 24.4%, respectively on postoperative days 3 and 7. In 1, 3 and 6 months, the incidence of POCD was 22.0, 17.1 and 11.0%, respectively. The patients who developed POCD were significantly older ($p < 0.001$) and had shorter duration of education ($p = 0.02$) than those without POCD. In addition, a higher incidence of POD and longer POD duration were observed in the patients with POCD ($p < 0.001$ and $p < 0.001$, respectively).

Neuropsychological tests score

The neuropsychological test battery results were presented in Tables 2 and 3. There were no significant differences for preoperative neuropsychological test battery scores in POCD and non-POCD groups. Postoperative test battery scores were significantly decreased compared with group-matched baseline. Furthermore, the lower scores and longer time consumption were found in POCD group compared to non-POCD group (Table 2). The lower TICS-M and ADL scores were also observed in POCD group in 1, 3 and 6 months postoperatively (Table 3).

CSF and serum concentrations of biomarkers

The levels of CSF biomarkers were presented in Fig. 1. CSF sTREM2 was significantly increased compared with baseline in POCD group ($p < 0.001$) and the higher level of CSF sTREM2 was observed in POCD group than that in non-POCD group on postoperative day 3 ($p < 0.001$; Fig. 1A). Postoperative CSF $A\beta_{42}$ was significantly decreased in POCD group ($p = 0.002$). Furthermore, the lower level of CSF $A\beta_{42}$ was observed in POCD group than that in non-POCD group ($p = 0.005$; Fig. 1B). Postoperative CSF P-tau and T-tau were significantly increased in both POCD and non-POCD groups ($p < 0.05$ and $p < 0.05$, respectively). However, no significant differences were found for postoperative CSF P-tau and T-tau between POCD group and non-POCD group (Fig. 1C and Fig. 1)D. Postoperative CSF $A\beta_{42}$/T-tau ratio was significantly decreased in POCD group ($p < 0.001$).

Table 1 Demographics characteristics and clinical data of the study samples

Parameters	POCD ($n=34$)	Non-POCD ($n=48$)	*p*-value
Age (yr), mean ± SD	60.2 ± 6.8	44.1 ± 8.1	< 0.001[a]
Male, n (%)	24 (70.6)	37 (77.1)	0.51
BMI (kg/m^2), mean ± SD	25.4 ± 3.2	25.6 ± 3.3	0.86
Duration of education (yr), median (IQR)	8 (3)	9 (2)	0.02[b]
ASA classification, n (%)			0.77
III	18 (52.9)	27 (56.3)	
IV	16 (47.1)	21 (43.7)	
Smoking, n (%)	17 (50.0)	21 (31.8)	0.58
Drinking, n (%)	14 (41.2)	13 (27.1)	0.18
Hypertension, n (%)	31 (91.2)	42 (87.5)	0.60
Diabetes, n (%)	5 (14.7)	6 (12.5)	0.77
Sleep duration (h), median (IQR)	7 (2)	7 (1)	0.10
Duration of surgery (h), median (IQR)	6.5 (0.9)	6.5 (1.7)	0.58
CPB duration (min), mean ± SD	153.4 ± 25.5	153.3 ± 29.4	0.98
Aortic cross-clamp duration (min), mean ± SD	103.8 ± 26.00	108.8 ± 23.2	0.37
Circulatory arrest duration (min), median (IQR)	17 (4)	16 (4)	0.87
Perfusion pressure (mmHg), median (IQR)	180 (30)	180 (30)	0.85
Perfusion volume (ml), median (IQR)	1950 (1200)	2000 (800)	0.64
Deep hypothermic duration (min), mean ± SD	54.7 ± 7.8	51.4 ± 8.6	0.08
Minimum temperature (°C), median (IQR)	21.7 (0.9)	21.4 (1.5)	0.38
Midazolam (mg), median (IQR)	5 (4.3)	5 (4.8)	0.98
Sufentanil (ug), median (IQR)	70 (40)	70 (35)	0.55
Propofol (mg), mean ± SD	1221.3 ± 493.8	1250.5 ± 509.6	0.80
Mechanical ventilation time (h), median (IQR)	47 (32)	38 (30)	0.08
ICU length of stay (d), median (IQR)	7.5(4.0)	6.0 (4.8)	0.08
POD, n (%)	23 (67.6)	9 (18.8)	< 0.001[c]
POD duration (d), median (IQR)	2 (3)	0 (0)	< 0.001[d]
Length of hospital stay (d), median (IQR)	24 (9)	22 (13)	0.41

Data are shown as count n (%), median and interquartile range (IQR) or mean ± SD. *POCD* postoperative cognitive dysfunction, *BMI* Body Mass Index, *ASA* American Society of Anesthesiologists, *CPB* cardiopulmonary bypass, *ICU* intensive care unit. Duration of deep hypothermic: nasopharyngeal temperature < 28 °C; *POD*, postoperative delirium; [a] t test; [b,d] Mann-Whitney U test; [c] $\chi 2$ test.

Additionally, lower CSF $A\beta_{42}$/T-tau ratio was observed in POCD group compared to non-POCD group on postoperative day 3 ($p=0.036$; Fig. 1E).

The levels of serum biomarkers were presented in Fig. 2. Postoperative serum sTREM2 was significantly increased in POCD group ($p=0.007$) and the higher level of serum sTREM2 was observed in POCD group than that in non-POCD group ($p=0.001$; Fig. 2A). There were no significant differences in serum $A\beta_{42}$, P-tau, T-tau and $A\beta_{42}$/T-tau ratio on postoperative day 3 compared to baseline in both groups. Additionally, no significant differences in serum $A\beta_{42}$, P-tau, T-tau and $A\beta_{42}$/T-tau ratio were observed between POCD and non-POCD groups on postoperative day 3 (Fig. 2B-E).

Analyses of the correlation of postoperative CSF sTREM2 values and other factors were showed in Table 4. Postoperative CSF sTREM2 was positively correlated with postoperative serum sTREM2 (Spearman $r=0.381$, $p<0.05$) and age (Spearman $r=0.459$, $p<0.05$) and time taken ($p<0.05$), and negatively correlated with the correct numbers of postoperative neuropsychological tests ($p<0.05$) and score of TICS-M ($p<0.05$).

Univariate and multivariate logistic regression analysis

Seven potential risk factors of POCD were identified by univariate logistic regression analysis, including postoperative CSF sTREM2, $A\beta_{42}$, $A\beta_{42}$/T-tau ratio, serum sTREM2, age, duration of POD and education (Table 5). The relationship between POCD and risk factors was determined by multivariable logistic regression analysis. After adjustment of potential factors, postoperative CSF sTREM2 (odds ratio: 1.06, 95% confidence interval: 1.02–1.11, $p=0.009$), age (OR: 1.15, 95%CI: 1.03–1.28, $p=0.014$) and POD duration (OR: 2.47, 95%CI: 1.15–5.29, $p=0.020$) were the risk factors of POCD (Table 5).

Table 2 Score for neuropsychological tests

Tests	Baseline	Postoperative day 3	Postoperative day 7
DSFT (n)			
POCD	8 (1)	3.5 (3) **,a	4 (2) **,a
Non-POCD	8 (1)	6 (1) a	7 (1) a
DSBT (n)			
POCD	6 (1)	3 (0) **,a	3 (1) **,a
Non-POCD	5 (2)	4 (1) a	4 (1) a
RAVLT (n)			
POCD	27.5 (6)	14.5 (6) **,a	18 (3) **,a
Non-POCD	30 (6)	21.5 (8) a	25 (7) a
SDMT (n)			
POCD	42.5 (15)	8.5 (5) **,a	16.5 (9)**,a
Non-POCD	39 (9)	20.5 (15) a	26 (10) a
SCWT-A (s)			
POCD	46 (9)	88 (24) **,a	86.5 (23) *,a
Non-POCD	44.5 (9)	67 (15) a	53.5 (11) a
SCWT-B (s)			
POCD	42.5 (15)	93.5 (17) **,a	87 (20) **,a
Non-POCD	45 (15)	67.5 (11) a	59 (13) a
SCWT-C (s)			
POCD	51.5 (16)	130.5 (59) **,a	116 (47) **,a
Non-POCD	54 (10)	88.5 (22) a	73 (12) a

Test results are either number of correct answer (n) or time consumption (s). Data are presented as median (IQR); *POCD* postoperative cognitive dysfunctionm, *DSFT*, Digit Span Forward Test, *DSBT* Digit Span Backward Test, *RAVLT* Rey Auditory Verbal Learning Test, *SDMT* Symbol Digit Modalities Test, *SCWT* Stroop Color Word Test, * $p < 0.05$ compared with the non-POCD group (Mann-Whitney U test); ** $p < 0.001$ compared with the non-POCD group (Mann-Whitney U test); a $p < 0.001$ compared with baseline (Friedman test).

Table 3 The TICS-M score and ADL score between the two group patients

Tests	Postoperative month 1	Postoperative month 3	Postoperative month 6
TICS-M			
POCD	26 (6) **	29 (7) **	35 (11) *
Non-POCD	34 (4)	37 (2)	39 (2)
ADLs			
POCD	33 (20) **	53 (16) **	75 (15) *
Non-POCD	45 (10)	75 (10)	80 (5)

Data are presented as median (IQR); *POCD* postoperative cognitive dysfunction, *TICS-M* Telephone Interview for Cognitive Status-Modified, *ADLs* score of Activities of Daily Living, * $p < 0.05$ compared with the non-POCD group (Mann-Whitney U test); ** $p < 0.001$ compared with the non-POCD group (Mann-Whitney U test).

Discussion

Our study investigated the relationship between sTREM2 and POCD in the patients undergoing thoracoabdominal aortic surgery. This study demonstrated that the level of CSF sTREM2 was significantly increased in the subjects who developed POCD on postoperative day 3. Elevated CSF sTREM2 was associated with an increased risk of POCD in the patients with cardiac surgery.

Despite improvements in surgical and anesthetic techniques, POCD in cardiac surgery patients is still highly prevalent. Relander et al. reported that POCD was observed in 71% of patients 1 week postoperatively and in 47% of elderly patients 3 months after cardiac surgery [29]. Our study illustrated that the incidence of POCD was 24.4% on postoperative day 7 and 17.1% at 3 months in the patients undergoing thoracoabdominal aortic surgery. The difference for the incidence of POCD in these studies is probably due to the diverse neuropsychological tests and the statistical methodology, as well as the fact that to date there is no universally accepted definition of POCD. Previous studies indicated an association between POD and subsequent POCD in elderly patients undergoing orthopedic surgery [30] and cardiac surgery [31]. A higher incidence and a longer duration of POD were observed in the patients who developed POCD in this study.

There is no internationally accepted definition for POCD. Neuropsychological testing battery is required to evaluate postoperative cognitive function reliably. The precise and inclusive neuropsychological tests were applied in this study, including MMSE, SDMT, DFST, DSBT, RAVLT, SCWT, CAM-ICU, TICS-M and ADLs, which allowed to detect slight changes in cognitive function characteristic of POCD. Consistent with previous studies, the definition of POCD was based on Z-score in this study [21, 23, 24].

The present study demonstrated that elevated level of CSF sTREM2 was correlated with an increased risk of developing POCD in the patients undergoing thoracoabdominal aortic surgery. A growing number of studies demonstrated that CSF sTREM2 was increased in the late-onset AD [32, 33] and early-onset familial AD [34]. The upregulation of CSF sTREM2 was associated with the increased risk of dementia [35]. A study by Tanaka et al. reported that elevated sTREM2 was related to cognitive impairment in non-obese diabetic patients [36]. This study indicated that CSF sTREM2 was associated with cognitive impairment after thoracoabdominal aortic replacement surgery. These findings indicate that elevated CSF sTREM2 may be a potential therapeutic target of POCD.

The underlying mechanism for the relationship between sTREM2 and POCD remains unknown. One explanation is that CSF sTREM2 elevation reflects sTREM2-mediated microglial activation and acute neuroinflammation. Microglial activation and subsequent neuroinflammatory response are frequently accompanied by the early progress of Aβ accumulation, tau pathology,

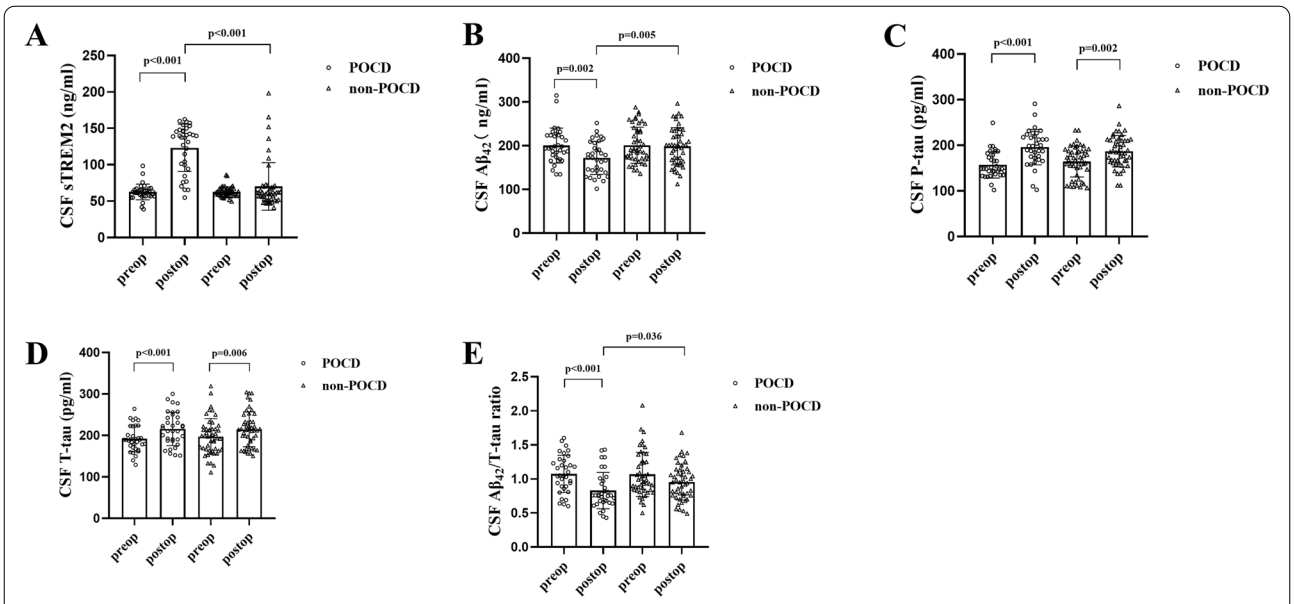

Fig. 1 The levels of CSF biomarkers. The levels of CSF sTREM2, $A\beta_{42}$, P-tau, T-tau, and $A\beta_{42}$/T-tau ratio in POCD and non-POCD group. **(A)** CSF sTREM2 was significantly increased on postoperative day 3 and the higher level of CSF sTREM2 was observed in POCD group than that in non-POCD group ($p < 0.001$ and $p < 0.001$, respectively). **(B)** The lower level of CSF $A\beta_{42}$ was observed in POCD group than that in non-POCD group ($p = 0.005$). **(C)** CSF P-tau was significantly increased in both groups ($p < 0.05$ and $p < 0.05$, respectively) on postoperative day 3. **(D)** Postoperative CSF T-tau was significantly increased in both groups ($p < 0.05$ and $p < 0.05$, respectively). **(E)** Lower CSF $A\beta_{42}$/T-tau ratio was observed in POCD group compared to non-POCD group on postoperative day 3 ($p = 0.036$). Abbreviation: CSF, cerebrospinal fluid; sTREM2, soluble triggering receptor expressed on myeloid cells 2; $A\beta_{42}$, β-amyloid 42; P-tau, phosphorylated tau; T-tau, total tau; POCD, postoperative cognitive dysfunction

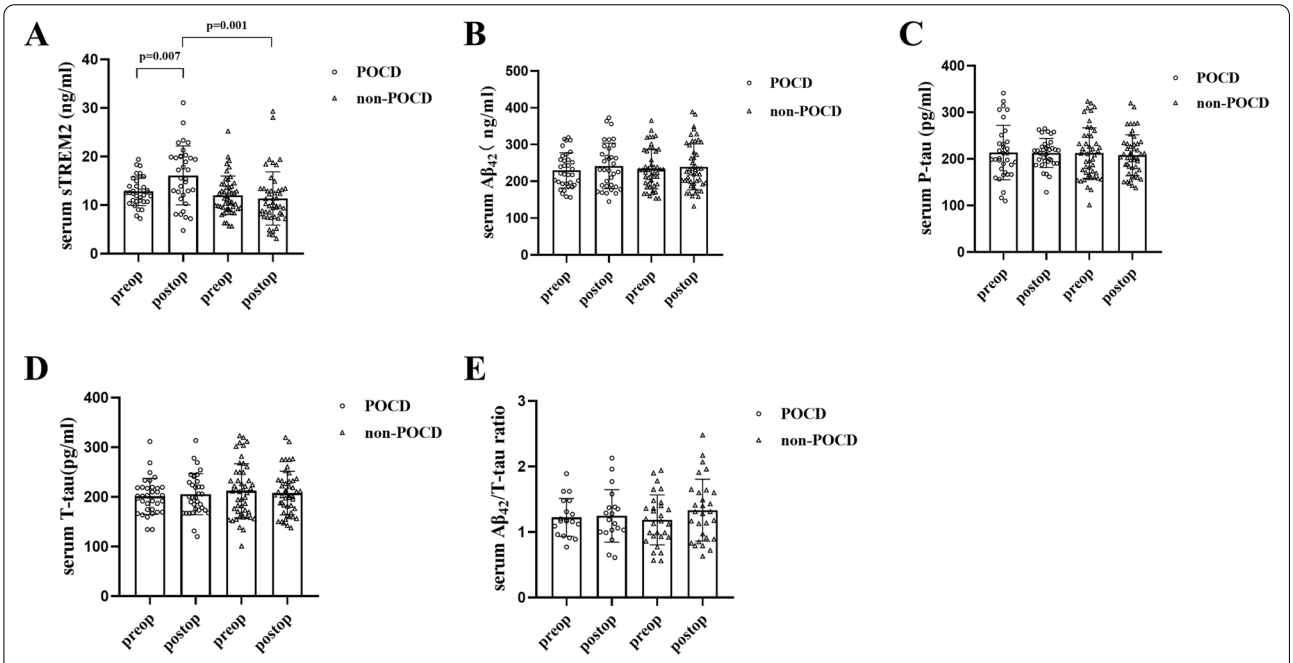

Fig. 2 The levels of serum biomarkers. The levels of serum sTREM2, $A\beta_{42}$, P-tau, T-tau, and $A\beta_{42}$/T-tau ratio in POCD and non-POCD group. **(A)** Postoperative serum sTREM2 was significantly increased in POCD group ($p = 0.007$) and the higher level of serum sTREM2 was observed in POCD group than that in non-POCD group ($p = 0.001$). **(B-D)** No significant differences were observed for serum $A\beta_{42}$, P-tau and T-tau between POCD and non-POCD groups on postoperative day 3. **(E)** There was no significant difference in $A\beta_{42}$/T-tau ratio between POCD and non-POCD groups on postoperative day 3. Abbreviation: CSF, cerebrospinal fluid; sTREM2, soluble triggering receptor expressed on myeloid cells 2; $A\beta_{42}$, β-amyloid 42; P-tau, phosphorylated tau; T-tau, total tau; POCD, postoperative cognitive dysfunction

Table 4 Factors associated with postoperative CSF sTREM2 values

Factors	Correlation Coefficient	*p*-value
CSF $A\beta_{42}$ postop (ng/ml)	−0.219	>0.05
CSF P-tau postop (pg/ml)	0.204	>0.05
CSF T-tau postop (pg/ml)	−0.040	>0.05
CSF $A\beta_{42}$/T-tau ratio postop	−0.181	>0.05
CSF sTREM2 preop (pg/ml)	0.055	>0.05
Serum sTREM2 postop (pg/ml)	0.381	**<0.05**
Age (yr)	0.459	**<0.05**
Duration of education (yr)	−0.271	>0.05
Duration of POD (d)	0.442	>0.05
DSFT preop (n)	0.004	>0.05
DSFT postop 3d (n)	−0.377	**<0.05**
DSFT postop 7d (n)	−0.403	**<0.05**
DSBT preop (n)	0.066	>0.05
DSBT postop 3d (n)	−0.356	**<0.05**
DSBT postop 7d (n)	−0.403	**<0.05**
RAVLT preop (n)	−0.288	>0.05
RAVLT postop 3d (n)	−0.383	**<0.05**
RAVLT postop 7d (n)	−0.513	**<0.05**
SDMT preop (n)	−0.019	>0.05
SDMT postop 3d (n)	−0.510	**<0.05**
SDMT postop 7d (n)	−0.457	**<0.05**
SCWT-A preop (s)	0.174	>0.05
SCWT-A postop 3d (s)	0.391	**<0.05**
SCWT-A postop 7d (s)	0.524	**<0.05**
SCWT-B preop (s)	0.025	>0.05
SCWT-B postop 3d (s)	0.498	**<0.05**
SCWT-B postop 7d (s)	0.557	**<0.05**
SCWT-C preop (s)	0.001	>0.05
SCWT-C postop 3d (s)	0.387	**<0.05**
SCWT-C postop 7d (s)	0.427	**<0.05**
TICS-M postop 1 m	−0.393	**<0.05**
TICS-M postop 3 m	−0.480	**<0.05**
TICS-M postop 6 m	−0.373	**<0.05**

Correlation coefficients represent non-parametric Spearman's Rho correlation coefficients; Test results are either number of correct answer (n) or time consumption (s); *P* value was followed by Bonferroni correction. *CSF* cerebrospinal fluid, *sTREM2* soluble triggering receptor expressed on myeloid cells 2, *$A\beta_{42}$* β-amyloid 42, *P-tau* phosphorylated tau, *T-tau* total tau; preop, preoperative, *postop 3d* postoperative day 3, *postop 7d* postoperative day 7, *postop 1 m* 1 month after surgery, *postop 3 m* 3 month after surgery, *postop 6 m* 6 month after surgery, *POD* postoperative delirium, *DSFT* Digit Span Forward Test, *DSBT* Digit Span Backward Test, *RAVLT* Rey Auditory Verbal Learning Test, *SDMT* Symbol Digit Modalities Test, *SCWT* Stroop Color Word Test, *TICS-M* Telephone Interviews for Cognitive Status-Modified.

cerebrovascular injury and cognitive impairment [37–41]. A solid relationship between neuroinflammation and POCD has been reported in orthopedic patients, which fully demonstrates the critical role of neuroinflammation in POCD development [42]. Our previous study demonstrated that microglial activation and neuroinflammation involved in the progression of POCD [43]. CSF sTREM2 was increased in AD and considered as a biomarker of microglia activation and neuroinflammation [44, 45]. sTREM2 has been associated with inhibition of the anti-inflammatory function [44]. Similarly, a positive correlation between sTREM2 and the levels of several inflammatory cytokines, suggesting an association between microglial activation and CSF inflammation [46]. Consistent with previous study, this study indicated that POCD development was associated with sTREM2-mediated neuroinflammatory response.

sTREM2 is produced by ectodomain shedding of its receptor, which simultaneously produces peptides that reduce the activity of full-length receptor TREM2 [15]. Our previous study demonstrated that partial hepatectomy downregulated TREM2 expression in APPswe/PS1dE9 mice, coupled with postoperative spatial learning and memory impairment [47]. Thus, the increased level of CSF sTREM2 in the patients with POCD might indirectly reflect that the activity of TREM2 was inhibited following surgery challenge.

Exploring relationship between CSF biomarkers and POCD may provide better understanding of pathogenic mechanism by hinting to simultaneously ongoing processes in the brain [33]. POCD shares similar neuropathological mechanisms with AD. Therefore, multiple studies investigated the association between $A\beta_{42}$, CSF tau or Aβ to tau ratio and POCD [12]. Aβ is generally considered to be associated with POCD [48–50]. A pilot study demonstrated that cognitive decline was related to the reduction of CSF $A\beta_{42}$ in 6 months after cardiac surgery, which is consistent with our study [51]. TREM2 and Aβ precursor protein share common features of ectodomain shedding by ADAMs α-secretase and subsequent γ-secretase cleavage, which suggests the existence of both common biological processes involved in Aβ and sTREM2 [15, 16, 52].

Tau, the main protein component of the neurofibrillary tangles of synapses, has been linked to cognitive dysfunction [9, 53–56]. A study by Freche et al. indicated that sevoflurane exposure increased tau phosphorylation through specific kinases activation and induced spatial memory deficits [57]. Consistent with previous study, the present study demonstrated that surgery and anesthesia-induced accumulation of hyperphosphorylated tau proteins was associated with cognitive impairment. However, a study by Berger et al. failed to reveal the significant change of CSF tau, P-tau-181p, or Aβ levels before and after surgery in non-cardiac surgery [58]. This is contrary to our findings, which may be due to the various time points of assessment, the different definition of POCD, as well as the multiple types of surgery. Xie et at demonstrated that preoperative CSF Aβ/tau ratio was associated with postoperative changes in specific cognitive domains

Table 5 The logistic regression of POCD-associated risk factors

parameters	Univariate		Multivariate	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
CSF sTREM2 postop (pg/ml)	1.04 (1.03–1.06)	< 0.001	1.06 (1.02–1.11)	0.009
CSF $A\beta_{42}$ postop (ng/ml)	0.98 (0.97–1.00)	0.007	0.98 (0.96–1.01)	0.135
CSF P-tau postop (pg/ml)	1.01 (0.99–1.02)	0.27		
CSF T-tau postop (pg/ml)	1.00 (0.99–1.01)	0.92		
CSF $A\beta_{42}$/T-tau ratio postop	0.15 (0.03–0.92)	0.041	2.61 (0.02–6.99)	0.701
Serum sTREM2 postop (pg/ml)	1.15 (1.06–1.26)	< 0.001	1.02 (0.87–1.18)	0.841
Serum $A\beta_{42}$ postop (ng/ml)	1.00 (0.99–1.01)	0.85		
Serum P-tau postop (pg/ml)	1.00 (0.99–1.02)	0.58		
Serum T-tau postop (pg/ml)	0.99 (0.98–1.01)	0.36		
Serum $A\beta_{42}$/T-tau ratio postop	1.61 (0.54–4.79)	0.39		
Age (yr)	1.39 (1.19–1.62)	< 0.001	1.15 (1.03–1.28)	0.014
Education (yr)	0.71 (0.52–0.97)	0.03	0.91 (0.54–1.53)	0.731
POD duration (d)	3.01 (1.88–4.81)	< 0.001	2.47 (1.15–5.29)	0.020

CI confidence interval, *OR* odds ratio, *POCD* postoperative cognitive dysfunction, *CSF* cerebrospinal fluid, *sTREM2* soluble triggering receptor expressed on myeloid cells 2, *$A\beta_{42}$* β-amyloid 42, *P-tau* phosphorylated tau, *T-tau* total tau, *postop* postoperative, *POD* postoperative delirium.

[11]. In line with this, lower postoperative CSF $A\beta_{42}$/tau ratio was observed in patients with POCD in this study. Thus, a combination of CSF sTREM2 and other POCD biomarkers may provide reliable and convenient predictor of POCD.

There are some limitations in this study. Firstly, the sample size is relatively small and more large-scaled multicenter studies are required to determine the predictive value of sTREM2 for POCD. Secondly, the sample of CSF was not obtained conveniently and CSF sTREM2 could not measure routinely in the clinical practice. Thirdly, this study only investigated short-term follow-up outcome. Longer-term follow-up is needed to validate the role of sTREM2 in the progression of POCD. Intubated patients were excluded on postoperative days 3 and 7 in this study. However, CAM-ICU is insensitive for delirium in non-intubated patients. A large fraction of delirium cases might be missed in this study. Finally, the intrathecal catheters were removed on postoperative day 3. However, this experiment could not totally exclude intrathecal catheters-induced neuroinflammation.

In conclusion, the protein level of CSF sTREM2 was significantly increased following surgery and anesthesia. Anesthesia and surgery-induced elevation of CSF sTREM2 is associated with an increased risk of early cognitive dysfunction following surgery. This finding may provide valuable mechanistic insights into the etiology of POCD. Thus, a combination of CSF sTREM2 and other POCD predictors may be reliable to identify high-risk persons of early cognitive dysfunction following surgery.

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Availability of data and material
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Authors' contributions
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Kexin Wang, Xuezhao Cao, Zhe Li, Sidan Liu and Lili Guo. Figures were made by Yongjian Zhou, Pengli Li. The first draft of the manuscript was written by Kexin Wang and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Ethics approval and consent to participate
This study protocol was approved by the Ethics Committee of the First Affiliated Hospital of China Medical University (2020–302-2) and registered in Chinese Clinical Trial Registry Centre (Registration No. ChiCTR2000038634). Informed consent was obtained from all patients. All methods were performed in accordance with the relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors have no relevant financial or non-financial interests to disclose.

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