ORIGINAL RESEARCH

Detection Analysis of Perioperative Plasma and CSF Reveals Risk Biomarkers of Postoperative Delirium of Parkinson's Disease Patients Undergoing Deep Brain Stimulation of the Subthalamic Nuclei

Yongde Zhou[1], Yu Ma[2], Cuiping Yu[1], Yao Chen[1], Jian Ding[1], Jianfeng Yu[1], Rongsong Zhou[2], Xiaoxiao Wang[3], Ting Fan[1], Chengmei Shi [4]

[1]Department of Anesthesiology, Tsinghua University Yuquan Hospital, Beijing, People's Republic of China; [2]Department of Neurosurgery, Tsinghua University Yuquan Hospital, Beijing, People's Republic of China; [3]Research Center of Clinical Epidemiology, Peking University Third Hospital, Beijing, People's Republic of China; [4]Department of Anesthesiology, Peking University Third Hospital, Beijing, People's Republic of China

Correspondence: Chengmei Shi; Ting Fan, Email shichengmei@bjmu.edu.cn; 13681100715@163.com

Objective: This study aimed to explore possible biomarkers of postoperative delirium (POD) of Parkinson's disease (PD) patients received deep brain stimulation (DBS) of the subthalamic nuclei.

Materials and methods: This nested case control study analyzed perioperative plasma and cerebral spinal fluid (CSF) of patients (n = 40) who developed POD undergone DBS surgery (n = 10) and those who did not (n = 30). Blood sample was collected before surgery and on the first day postoperative, CSF sample was collected at the beginning of the operation. POD was assessed by the Confusion Assessment Method (CAM) twice a day between 7:00 am and 7:00 pm after the surgery until discharge. Plasma and CSF sample from the two groups were analyzed to investigate possible biomarkers for POD in PD patients.

Results: There was no difference between POD and Non-POD groups on the concentration of Interleukin 6 and Tumor Necrosis Factor-α in CSF, preoperative plasma and postoperative plasma. There was no difference between POD and Non-POD groups on the concentration of S100 calcium-binding protein β protein (S100β) and Neurofilament light chain (NFL) in preoperative plasma and postoperative plasma. The concentration of C-reactive protein (CRP), NFL and S100β were significant higher in POD group than non-POD group in CSF. The concentration of CRP was significantly higher in POD group than non-POD group in preoperative plasma and postoperative plasma. CSF concentration of S100β might be a potential biomarker for POD via the receiver operating characteristic curve analysis and the area under the curve value of 0.973.

Conclusion: For PD patients received DBS surgery, CSF S100β might be a marker for aiding detection of high-risk patients with delirium. This requires further confirmation in clinical trials.

Keywords: Parkinson's disease, deep brain stimulation, cerebrospinal fluid, postoperative delirium, biomarker

Introduction

Parkinson's disease (PD) is a common neurodegenerative disease,[1] and the advanced PD patients need the Deep brain stimulation of the subthalamic nuclei(STN-DBS) which improves motor and non-motor symptoms,[2–4] and enhance the quality of life.[3–5]

Unfortunately, as one of the most common neuropsychiatric complications following DBS surgery,[6] the incidence of delirium was 22% to 42.6% of patients after DBS surgery.[7,8] Postoperative delirium (POD) is common, serious, costly, under-recognized, and often fatal.[9] For PD patients, POD is an increased risk factor for developing dementia and death.[9]

However, the pathogenesis of POD is unclear.[10] Detecting PD patients at high risk of POD would promote recovery after DBS surgery. Since the pathogenesis of POD is unclear, and clinical symptoms are diverse and fluctuate, the specific biomarkers to predict POD have important implications.[11] The etiology of delirium was multifactorial.[12] Currently, there

is no convincing evidence showed that pharmacologic prevention is effective.[9] Therefore, it is particularly important to screen high-risk patients and intervene in advance. The hypothesized mechanisms of delirium include neurotransmitters,[13] inflammation,[14] physiologic stressors,[15] metabolic derangements,[16] electrolyte disorders,[17] and genetic factors.[18]

This present study was conducted to explore possible biomarkers of POD in PD patients after DBS surgery. The findings might provide valuable scientific clues for the early detection and treatment of POD in PD patients after DBS surgery.

Methods
Study Design
This study was performed in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of Yuquan Hospital of Tsinghua University (20,190,014). All patients enrolled have signed informed consent. The clinical trial registration number was ChiCTR1900027210.

Study Population
The study was conducted between November 2019 and October 2020 in Yuquan Hospital of Tsinghua University (Beijing, China). The PD patients were diagnosed according to the UK Brain Bank criteria[19] and planned to receive bilateral STN-DBS treatment. Bilateral STN-DBS treatment followed the Movement Disorders Society guidelines.[20] The inclusion and contraindications for DBS surgery were according to the Chinese deep brain stimulation therapy for Parkinson's disease Expert Consensus (Second Edition).[21]

The PD patients (1) were unable to read or had severe visual or auditory deficits, or (2) had a history of alcohol abuse and drug dependence or (3) were unwilling to comply with the study protocol or procedures were excluded.[22],128 patients participated in this study, 125 participants (27 POD vs 98 Non-POD) completed the study (Figure 1, flow diagram). It was a nested case control study. Considering the cost of testing, we randomly chose 10 cases from the 27 POD patients using the random number table in order to make sure the two groups are comparable, 10 POD patients and the matched 30 non-POD patients by age (±2 years) and MMSE score (± 2 points) were chosen to analyze.

Neuropsychological Testing
Preoperatively, Clinical Dementia Rating score, Instrumental Activity of Daily Living score, MMSE score, Montreal Cognitive Assessment score, Hamilton Anxiety Rating Scale, and Hamilton depression Rating Scale were performed in order to estimate if these patients were suitable for surgery. The Confusion assessment method (CAM)[9] was used to screen POD twice a day between 7:00 am and 7:00 pm after the surgery until discharge.
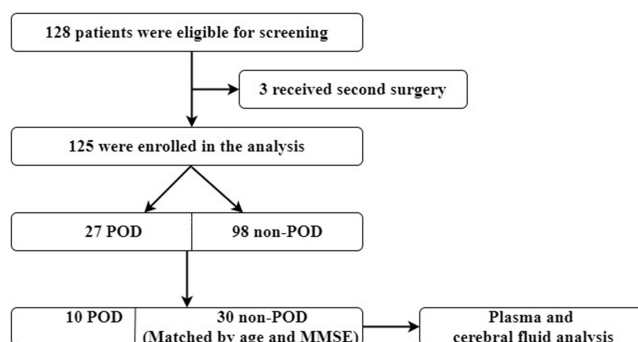

Figure 1 Study flow chart. 128 patients were initially screened for the study, and 40 patientss were finally included in the analysis.
Abbreviations: POD, postoperative delirium; MMSE, Mini-mental state exam.

Anesthesia and Surgery

A specific team is in charge of the general anesthesia and surgery to avoid interfering factors. The electrocardiograph, non-invasive blood pressure, heart rate (HR), saturation of pulse oximetry, and Bispectral Index (BIS) were monitored during anesthesia and were recorded at fixed intervals of 3 min.

The systemic blood pressure was adjusted to be higher than 90 mm Hg. The anesthesia depth was monitored by the BIS (BIS 40–60).[23]

In this study, the surgery was divided into two parts. Firstly, under the local anesthesia with minimal sedation, the stereotactic DBS electrodes were implanted in the STN. And the place of the electrodes was confirmed by imaging examination. Secondly, the DBS batteries and leads were placed in the sub-clavicular region under general anesthesia.

The same analgesic strategy was used to relieve postoperative pain as following: sufentanil 2μg/kg + dexmedetomidine 2.3μg/kg diluted to 100 mL, the background rate was 2 mL/h, the dosage of PCA was 0.5 mL, and the locking time was 15 min.

Sample Collection

2 mL venous blood was collected through the peripheral vein before the anesthesia. During the DBS surgery, bilateral electrode implantation sites were determined under stereo positioning, and then a U-shaped incision about 5cm in diameter was made around the implantation site to peel the scalp and expose the skull. A hole is drilled into the skull centered on the site of implantation and the cerebral dura was cut open. At this point, about 2mL of CSF was taken with a 5mL syringe by the surgeon.

The Visual Analog Scale (VAS) scores following surgery were recorded. The intensity of postoperative pain was evaluated twice daily at 7:00 am and 7:00 pm with the VAS. The VAS pain scale ranged from 0 to 10 with 0 corresponding to "no pain" and 10 to the "worst possible pain", the number patients pointed out to indicate the pain intensity.

On the first postoperative day, 2mL venous blood was taken when routine blood was drawn in the ward for other examinations.

All the samples were centrifuged immediately at 3000 rpm for 10min at 4°C, and the supernatant was gathered and stored at −80°C.

Enzyme-Linked Immunosorbent Assay (ELISA)

Levels of Interleukin 6 (IL-6), Tumor Necrosis Factor-α (TNF-α), Neurofilament light chain (NFL), S100 calcium-binding protein β protein (S100β) and C-reactive protein (CRP) in the supernatant of CSF and plasma were determined using commercial ELISA kits according to the manufacturer's instructions. The CRP and IL-6 kits were from Abcam, ab260058 and ab178013, the TNF-α and NFL kits were from International GmbH, BE58351 and 30,112,458, the S100β kits were from R&D Systems, DY1820-5. The optical density (OD) of each well was determined using an ELISA reader at 450 nm.

Statistical Analysis

The data are described as the mean ± standard deviation (SD), the median, or the number (%). The normality of the variables was test by the Kolmogorov–Smirnov method. Categorical and continuous variables were analyzed using χ^2 test and independent-samples t-test respectively. The non-normal variables were analyzed by Mann–Whitney U-test. Statistical significance was considered at $p < 0.05$. SPSS software (version 21.0; IBM Corp., Armonk, NY, USA) was used for data analysis. In order to evaluate the potential biomarkers for POD, the receiver operating characteristic (ROC) curves and the area under the curve (AUC) were calculated.

Results

Participant Characteristics

In the present study, 10 CSF samples were collected from POD patients, and 30 matched CSF samples were collected from non-POD patients. There were no differences in the basic characteristics between the two groups including age,

Table 1 Subject Characteristics

	Non-POD Group (n=30)	POD Group (n=10)	Statistical Test	*P*-value
Age (years), mean ± SD	63.70±4.28	65.70±4.14	$t = -1.289$	0.205
MMSE score, mean ± SD	28.27±1.51	28.10±0.99	$t = 0.325$	0.747
Male, *n* (%)	14(46.7)	3 (30.0)	$X^2 = 0.853$	0.356
BMI (kg/m², mean ± SD	24.72±5.13	22.66±3.86	$t = 1.163$	0.252
ASA class, *n* (%)				
I	8(26.7)	1 (10.0)		
II	20(66.7)	9 (90.0)	$X^2 = 2.156$	0.340
III	2(6.7)	0 (0)		
Length of anesthesia (min), mean ± SD	97.83±27.03	99.90±27.65	$t = -0.028$	0.836
Length of surgery (min), mean ± SD	69.80±24.78	74.50±25.76	$t = -0.515$	0.610
Postoperative VAS score, mean ± SD	3.7±0.84	3.2±0.63	$t = 1.727$	0.092
Intraoperative infusion volume(mL), mean ± SD	1596.67±396.09	1370.00±505.64	$t = 1.462$	0.152
Estimated blood loss(mL), mean ± SD	78.33±24.51	77.00±28.69	$t = 0.143$	0.887
Intraoperative urinary volume(mL), mean ± SD	471.67±239.86	495.00±256.53	$t = -0.262$	0.795
Length of stay in hospital after surgery, (d)	9.03±1.54	12.5±2.7	$t = -5.543$	0.000

Abbreviations: MMSE, Mini-Mental State Examination; BMI, body mass index; ASA, American Society of Anesthesiologists; VAS, Visual Analogue Scale; kg, kilogram; m, meter; min, minute; mL, milliliter; SD, standard deviation.

MMSE score, gender, body mass index, American Society of Anesthesiologists (ASA) physical class, length of anesthesia and surgery, postoperative VAS scores, intraoperative infusion volume, estimated blood loss and intraoperative urinary volume. The length of stay in the hospital was significantly longer in the POD group than in the non-POD group. There were no deaths in either group (Table 1).

Comparison of CSF Levels of Cytokines Between POD and Non-POD Patients

There was no difference between POD and Non-POD groups on the concentration of IL-6 and TNF-α in CSF at the beginning of surgery (Figure 2A). However, the concentration of S100β, NFL and CRP were significantly higher in POD group than non-POD group at the beginning of surgery (Figure 2B).

Comparison of Preoperative Plasma Levels of Cytokines Between POD and Non-POD Patients

There was no difference between POD and Non-POD groups on the concentration of IL-6, TNF-α, S100β and NFL in preoperative plasma. However, the concentration of CRP was significantly higher in POD group than non-POD group (Figure 3A and B).

Comparison of Postoperative Plasma Levels of Cytokines Between POD and Non-POD Patients

There was no difference between POD and Non-POD groups on the concentration of IL-6, TNF-α, S100β and NFL in postoperative plasma. However, the concentration of CRP was significantly higher in POD group than non-POD group (Figure 4A and B).

Univariate and Multivariate Logistic Regressions

The logistic regressions were performed to identify the potential risk factors of POD. All the variables were screened using the univariate regression and the variables with *P*<0.05 were selected for multivariate logistic regression. Among the variables screened, the S100β concentrations in CSF might be an independent influence factor of POD (Table 2).
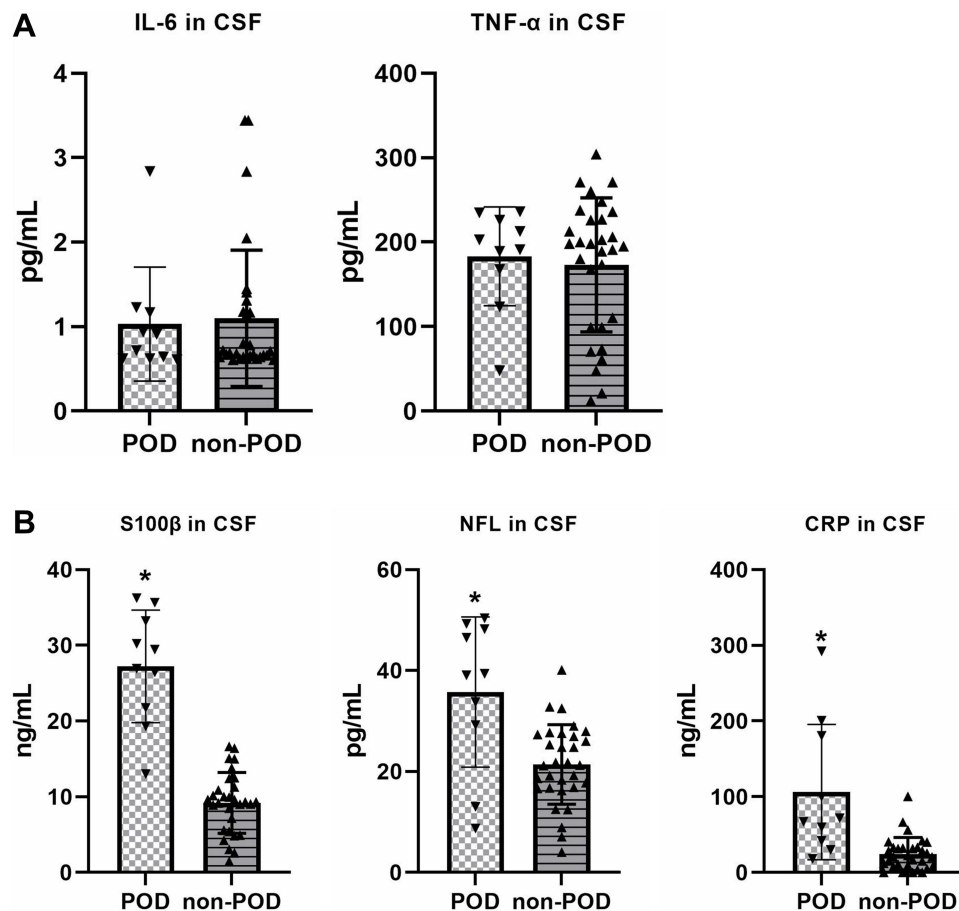
Figure 2 (**A**) There was no difference between POD and Non-POD groups on the concentration of IL-6 and TNF-α in cerebral spinal fluid at the beginning of surgery; (**B**) the concentration of CRP, NFL and S100β were significant higher in POD group than non-POD group at the beginning of surgery. *$p < 0.05$ compared with non-POD group.
Abbreviations: POD, postoperative delirium; CSF, cerebral spinal fluid.

Diagnostic Analysis of Indicators for the Prediction of POD

The total area under the curve AUC, cut-off, sensitivity, specificity, and Youden index of independent influence factors of POD are shown in Table 3.

The receiver operating characteristic (ROC) curve was used to determine the optimal cut-off score for the diagnosis of POD. The optimal score was calculated according to the Youden index (maximum of [sensitivity + specificity-1]).[24]

In the present study, 17.982 as the optimal cut-off score of S100β concentrations in CSF-associated with the POD. The sensitivity and specificity were 90.0% and 96.7%, respectively. The AUC was 0.973 (95% CI: 0.928–1.000, $P < 0.05$) (Table 3, Figure 5).

Discussion

PD is a common neurodegenerative disease in the elders, and the STN-DBS treatment is a standard option for advanced PD patients.[19] However, POD is common after DBS surgery and associated with worsened clinical outcomes, increased costs and mortality.[9]

There was a link between inflammation markers and delirium.[25,26] Elevated inflammatory biomarkers have been indicated as predictors of delirium in the general population[27] including one of the most commonly examined markers of systemic inflammation CRP,[28,29] TNF-α[30] and IL-6.[31,32]

Sarinnapha et al's study showed high preoperative and postoperative day 2 plasma CRP were independently associated with delirium incidence, duration, and feature severity. CRP might be useful to identify individuals who are at risk of developing delirium.[33] Slor, Chantal J also reported that delirium is associated with an increased systemic
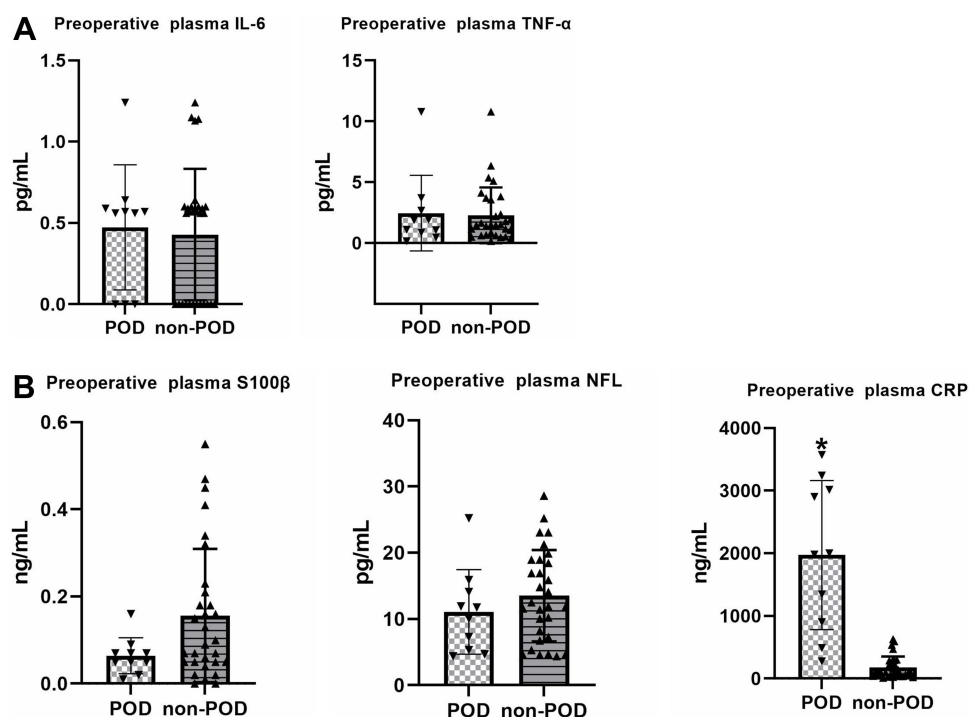
Figure 3 (**A**) There was no difference between POD and Non-POD groups on the concentration of IL-6 and TNF-α in preoperative plasma; (**B**) there was no difference between POD and Non-POD groups on the concentration of S100β and NFL in preoperative plasma. The concentration of CRP was significant higher in POD group than non-POD group in preoperative plasma. *$p < 0.05$ compared with non-POD group.
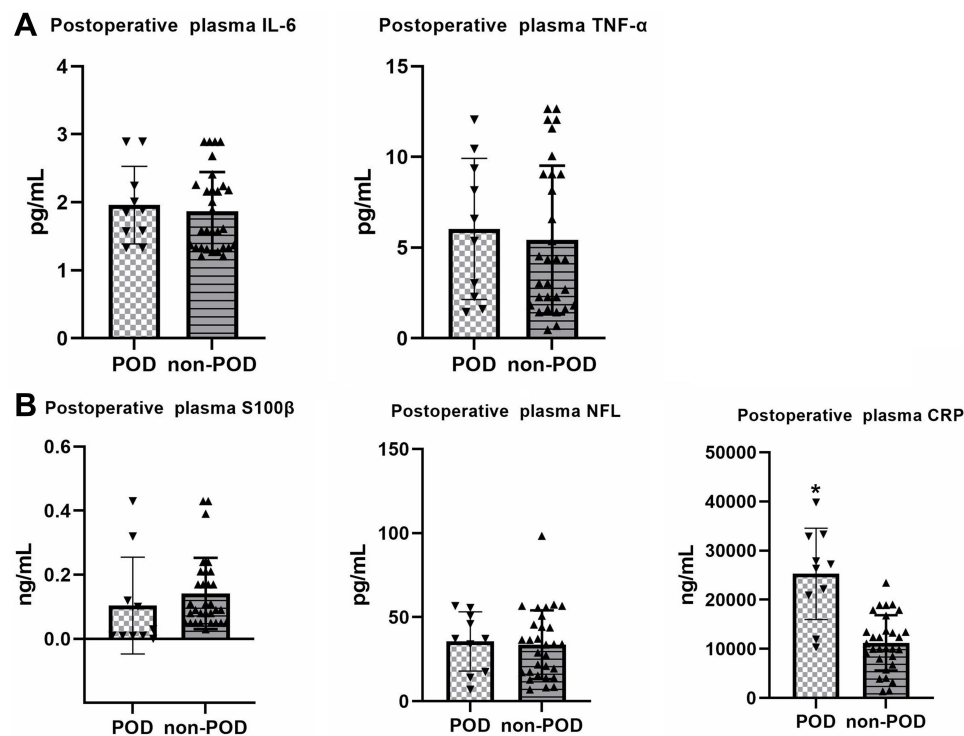**Abbreviations**: POD, postoperative delirium; CSF, cerebral spinal fluid.

Figure 4 (**A**) There was no difference between POD and Non-POD groups on the concentration of IL-6 and TNF-α in postoperative plasma; (**B**) there was no difference between POD and Non-POD groups on the concentration of S100β and NFL in postoperative plasma. The concentration of CRP was significant higher in POD group than non-POD group in postoperative plasma. *$p < 0.05$ compared with non-POD group.
Abbreviations: POD, postoperative delirium; CSF, cerebral spinal fluid.

Table 2 Univariate and Multivariate Logistic Regressions

	Predictor Variable	Univariate Analysis		Multivariate Analysis	
		OR (95% CI)	*P*-value	OR (95% CI)	*P-value*
CSF	CRP, (ng/mL)	1.01(1.00–1.03)	0.035		
	NFL, (pg/mL)	1.23(1.08–1.41)	0.003		
	S100β, (ng/mL)	1.41(1.13–1.77)	0.002	1.55(1.08–2.22)	0.016
Preoperative Plasma	CRP, (ng/mL)	1.01(1.00–1.01)	0.024		
Postoperative plasma	CRP, (ng/mL)	1.00(1.00–1.00)	0.002		

Abbreviations: CSF, cerebral spinal fluid; CRP, C-reactive protein; NFL, neurofilament; S100β, S100 calcium-binding protein β protein.

Table 3 Diagnostic Analysis of Indicators for the Prediction of POD

Variable	AUC	*P*-value	95% CI	
			Low	High
S100β	0.973	0.000	0.928	1.000
Variable	Cut-off	Sensitivity	Specificity	Youden Index
S100β	17.982	90.0%	96.7%	0.867

Abbreviation: AUC, area under the curve.

inflammatory response, and suggest that CRP plays a role in the underlying pathological pathway of POD.[34] Dimitrios Adamis reported that high levels of CRP are associated with delirium in acute orthopaedic and elective abdominal operations.[35] However, Mehmet Alper ÇINAR1and et al reported that there was no difference between POD and non-POD group on the blood level of CRP.[28] Therefore, CRP was also selected as a detection indicator in our study. We also noted that the concentration of CRP was significantly higher in POD group than non-POD group in CSF, preoperative plasma and postoperative plasma.

TNF-α and IL-6 were associated with memory and learning.[36,37] High levels of IL-6 seem a consistent predictor for delirium in surgical samples.[35] Kazmierski et al reported an elevation of TNF-α levels in the postoperative period in coronary artery bypass graft (CABG) patients with delirium.[30] Ganna Androsova1 mentioned IL-6 and TNF-α could be
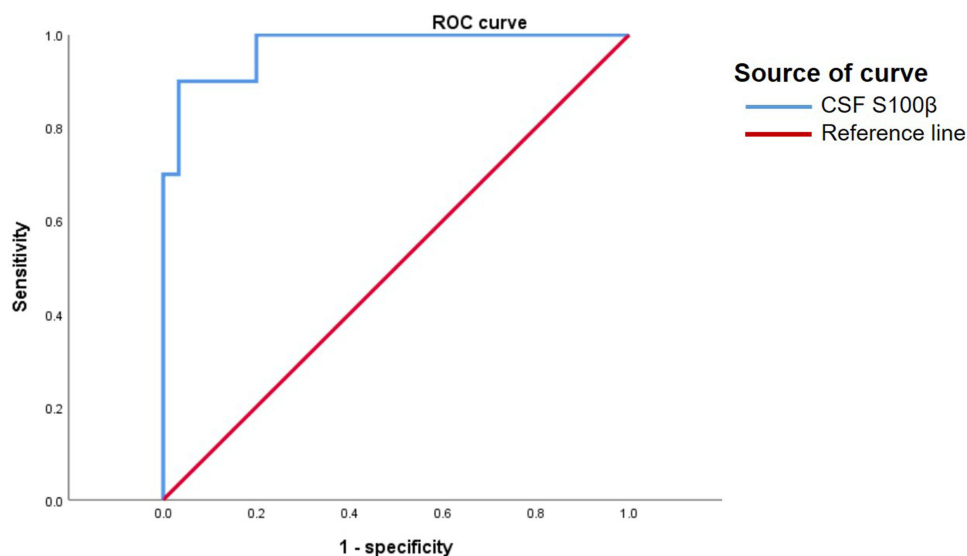
Figure 5 ROC analysis showed the probability of the POD increases with the rise of concentration of S100β in cerebral spinal fluid.

biomarkers in predicting delirium.[32] Plaschke K reported that early POD after cardiac surgery is associated with increased IL-6.[31] However, in the present study, there was no difference between POD and Non-POD groups on the concentration of IL-6 and TNF-α in CSF, preoperative plasma and postoperative plasma.

NFL protein is an intermediate filament in the cytoplasm of neurons, which is mainly expressed in the dendrites and axons of neurons, and plays an important role in the construction of cytoskeleton to maintain the structural stability of neurons.[38,39] At present, the increased level of NFL in CSF and blood has been detected in Alzheimer's disease, amyotrophic lateral sclerosis (ALS) and brain injury, and it is believed that the increased concentration of NFL is correlated with the progression of the disease.[40,41] In the study of Linda P, patients with higher level of CSF neurofilament light were accompanied with worse memory, attentional and executive functioning.[42] Saller mentioned in their study that NFL might be of benefit to identify high risk patients for delirium.[43] In the present study, the concentration of NFL was significantly higher in POD group than non-POD group.

S100β is a member of the calcium-regulated protein S100 family and is characterized by two calcium-binding sites with EF-hand conformations.[44] It is mainly expressed by astrocytes and found both intra- and extra-cellularly in brain tissue.[45] Because of functional impairment of membrane integrity and/or increased blood-brain barrier permeability, it is usually elevated in blood and CSF after nervous system injury.[46] Therefore, it could have a clinical role in the assessment of brain injury and could be a marker of brain damage used in various diseases.[47]

S100β has also attracted attention in the field of biomarkers of delirium.[48–51] Layth Al Tmimi et al reported that serum-levels of S100β measured on the first postoperative day in POD patients were significantly higher than non-POD patients.[52] S100β was proposed by Khan et al as a promising and specific marker for delirium.[53]

In the present study, it was also showed that the S100β level in CSF was indicated to be independent influence factors of POD. There was no difference between POD and Non-POD groups on the concentration of S100β in preoperative plasma and postoperative plasma. However, the concentration of S100β was significant higher in POD group than non-POD group in CSF. And among the variables screened, S100β concentrations in CSF was displayed to be independent risk factors of POD.

One possible mechanism for the higher level of S100β after delirium is active stimulation of astrocytes or increased permeability of the blood-brain barrier.[54–56] The neurobehavioral and cognitive characteristic of delirium associated by the change in synaptic transmission, neural excitability, and cerebral blood flow resulted by high CSF S100β.[57] S100β has been considered as a putative biomarker of CNS damage, and increased CSF and serum levels of S100β are associated with the adverse CNS outcomes, especially delirium.[58–60] Another hypothesis could be activation of the nuclear factor κB signal pathways and lead to up-regulation of proinflammatory mediators.[61] S100β may play a role in BBB disruption and contribute to delirium.[54] Finally, CSF could accurately reflect biochemical changes in the central nervous system.[11] Compared with plasma, CSF S100β level was more significant in predicting the POD.[42]

For PD patients undergoing DBS surgery, it is necessary to cut the dural during the surgery. Collecting CSF at this time is simple to do and without additional damage. So, the CSF S100β might be a marker for aiding early diagnosis of delirium after DBS surgery for PD patients.

We also did a number of measures to reduce the possible risk of POD just as following. Deep anesthesia might associate with delirium.[23] So, in the present study, BIS value was maintained within 40 to 60 in order to avoid episodes of deep anesthesia. POD is also associated with reduction in the intraoperative cerebral blood flow (CBF).[62] Therefore, the systemic blood pressure was kept higher than 90 mm Hg to ensure adequate CBF in the present study. Some studies showed severe pain may induce cognitive decline after surgery,[63] so, all the patients in this study received effective pain control.

Limitations

Although CSF S100β could be regarded as a potential biomarker of delirium in this study, limitations should be noticed. First, we aimed to recruit the maximum number of patients available and have not performed power calculations. Second, it was a monocentric study as only a few hospitals currently perform the DBS surgery. Third, there were only 10 POD patients and 30 non-POD patients in the biomarker analysis. Further analysis needs to be performed in future studies.

Conclusion

In this exploratory study of PD patients received DBS surgery, CSF S100β might be a marker for aiding detect high-risk patients of delirium. This requires further confirmation in clinical trials.

Data Sharing Statement

All the authors intend to share individual deidentified participant data including all the raw data. Immediately after the article is published, all the data could be shared by email to the corresponding author.

Funding

Disclosure

The authors report no conflicts of interest in this work.

References

1. Georgiev D, Mencinger M, Rajnar R, et al. Long-term effect of bilateral STN-DBS on non-motor symptoms in Parkinson's disease: a four-year observational, prospective study. *Parkinsonism Relat Disord*. 2021;89:13–16. doi:10.1016/j.parkreldis.2021.06.017
2. Dafsari HS, Reddy P, Herchenbach C, et al. Beneficial effects of bilateral subthalamic stimulation on non-motor symptoms in parkinson's disease. *Brain Stimul*. 2016;9(1):78–85. doi:10.1016/j.brs.2015.08.005
3. Dafsari HS, Weiß L, Silverdale M, et al. Short-term quality of life after subthalamic stimulation depends on non-motor symptoms in Parkinson's disease. *Brain Stimul*. 2018;11(4):867–874. doi:10.1016/j.brs.2018.02.015
4. Wang XQ, Zhuang HX, Zhang LX, Chen X, Niu CS, Zhao M. Nomogram for predicting postoperative delirium after deep brain stimulation surgery for parkinson's disease. *World Neurosurg*. 2019;130:e551–e557. doi:10.1016/j.wneu.2019.06.151
5. Boussac M, Arbus C, Klinger H, et al. Personality related to quality-of-life improvement after deep brain stimulation in Parkinson's disease (PSYCHO-STIM II). *J Parkinsons Dis*. 2021. doi:10.3233/JPD-212883
6. Li H, Han S, Feng J. Delirium after deep brain stimulation in Parkinson's disease. *Parkinsons Dis*. 2021;2021:8885386. doi:10.1155/2021/8885386
7. Tanaka M, Tani N, Maruo T, et al. Risk factors for postoperative delirium after deep brain stimulation surgery for Parkinson disease. *World Neurosurg*. 2018;114:e518–e523. doi:10.1016/j.wneu.2018.03.021
8. Zhan L, Wang XQ, Zhang LX. Nomogram model for predicting risk of postoperative delirium after deep brain stimulation surgery in patients older than 50 years with Parkinson disease. *World Neurosurg*. 2020;139:e127–e135. doi:10.1016/j.wneu.2020.03.160
9. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383(9920):911–922. doi:10.1016/S0140-6736(13)60688-1
10. Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. *Br J Anaesth*. 2020;125(4):492–504. doi:10.1016/j.bja.2020.06.063
11. Han Y, Chen W, Song Y, et al. Proteomic analysis of preoperative CSF reveals risk biomarkers of postoperative delirium. *Front Psychiatry*. 2020;11:170. doi:10.3389/fpsyt.2020.00170
12. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA*. 1996;275(11):852–857. doi:10.1001/jama.1996.03530350034031
13. Maclullich AM, Ferguson KJ, Miller T, de Rooij SE, Cunningham C. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. *J Psychosom Res*. 2008;65(3):229–238. doi:10.1016/j.jpsychores.2008.05.019
14. Katsumi Y, Racine AM, Torrado-Carvajal A, et al. The Role of Inflammation after Surgery for Elders (RISE) study: examination of [(11)C]PBR28 binding and exploration of its link to post-operative delirium. *Neuroimage Clin*. 2020;27:102346. doi:10.1016/j.nicl.2020.102346
15. Lee SS, Lo Y, Verghese J. Physical activity and risk of postoperative delirium. *J Am Geriatr Soc*. 2019;67(11):2260–2266. doi:10.1111/jgs.16083
16. Kealy J, Murray C, Griffin EW, et al. Acute inflammation alters brain energy metabolism in mice and humans: role in suppressed spontaneous activity, impaired cognition, and delirium. *J Neurosci*. 2020;40(29):5681–5696. doi:10.1523/JNEUROSCI.2876-19.2020
17. Conti E, Andreoni S, Tomaselli D, et al. Serum DBI and biomarkers of neuroinflammation in Alzheimer's disease and delirium. *Neurol Sci*. 2021;42(3):1003–1007. doi:10.1007/s10072-020-04608-x
18. Sepulveda E, Adamis D, Franco JG, Meagher D, Aranda S, Vilella E. The complex interaction of genetics and delirium: a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci*. 2021;271(5):929–939. doi:10.1007/s00406-021-01255-x
19. Fox SH, Katzenschlager R, Lim SY, et al. International Parkinson and movement disorder society evidence-based medicine review: update on treatments for the motor symptoms of Parkinson's disease. *Mov Disord*. 2018;33(8):1248–1266. doi:10.1002/mds.27372
20. Dong Y, Zhang G, Zhang B, et al. The common inhalational anesthetic sevoflurane induces apoptosis and increases beta-amyloid protein levels. *Arch Neurol*. 2009;66(5):620–631. doi:10.1001/archneurol.2009.48
21. Zhang H, Chen, L, Chen, S et al. Chinese deep brain stimulation therapy for Parkinson's disease Expert Consensus (Second Edition). Chin Neurosurg J. 2020;36:325–337. doi:10.376/cma.j.cn112050-20200217-00062.
22. Han Y, Zhang W, Liu J, et al. Metabolomic and lipidomic profiling of preoperative CSF in elderly hip fracture patients with postoperative delirium. *Front Aging Neurosci*. 2020;12:570210. doi:10.3389/fnagi.2020.570210
23. Chan MT, Cheng BC, Lee TM, Gin T. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol*. 2013;25(1):33–42. doi:10.1097/ANA.0b013e3182712fba
24. Bantis LE, Nakas CT, Reiser B. Construction of confidence regions in the ROC space after the estimation of the optimal Youden index-based cut-off point. *Biometrics*. 2014;70(1):212–223. doi:10.1111/biom.12107

25. Beloosesky Y, Grinblat J, Pirotsky A, Weiss A, Hendel D. Different C-reactive protein kinetics in post-operative Hip-fractured geriatric patients with and without complications. *Gerontology*. 2004;50(4):216–222. doi:10.1159/000078350

26. Vasunilashorn SM, Ngo L, Inouye SK, et al. Cytokines and postoperative delirium in older patients undergoing major elective surgery. *J Gerontol a Biol Sci Med Sci*. 2015;70(10):1289–1295. doi:10.1093/gerona/glv083

27. Simone MJ, Tan ZS. The role of inflammation in the pathogenesis of delirium and dementia in older adults: a review. *CNS Neurosci Ther*. 2011;17 (5):506–513. doi:10.1111/j.1755-5949.2010.00173.x

28. Çinar MA, Balikçi A, Sertoğlu E, Mehmet AK, Serdar MA, Özmenler KN. Role of CRP, TNF-a, and IGF-1 in Delirium Pathophysiology. *Noro Psikiyatr Ars*. 2014;51(4):376–382. doi:10.5152/npa.2014.6999

29. Kotfis K, Ślozowska J, Safranow K, Szylińska A, Listewnik M. The practical use of white cell inflammatory biomarkers in prediction of postoperative delirium after cardiac surgery. *Brain Sci*. 2019;9:11. doi:10.3390/brainsci9110308

30. Kazmierski J, Banys A, Latek J, Bourke J, Jaszewski R. Raised IL-2 and TNF-α concentrations are associated with postoperative delirium in patients undergoing coronary-artery bypass graft surgery. *Int Psychogeriatr*. 2014;26(5):845–855. doi:10.1017/S1041610213002378

31. Plaschke K, Fichtenkamm P, Schramm C, et al. Early postoperative delirium after open-heart cardiac surgery is associated with decreased bispectral EEG and increased cortisol and interleukin-6. *Intensive Care Med*. 2010;36(12):2081–2089. doi:10.1007/s00134-010-2004-4

32. Androsova G, Krause R, Winterer G, Schneider R. Biomarkers of postoperative delirium and cognitive dysfunction. *Front Aging Neurosci*. 2015;7:112. doi:10.3389/fnagi.2015.00112

33. Vasunilashorn SM, Dillon ST, Inouye SK, et al. High C-reactive protein predicts delirium incidence, duration, and feature severity after major noncardiac surgery. *J Am Geriatr Soc*. 2017;65(8):e109–e116. doi:10.1111/jgs.14913

34. Slor CJ, Witlox J, Adamis D, et al. The trajectory of C-reactive protein serum levels in older Hip fracture patients with postoperative delirium. *Int J Geriatr Psychiatry*. 2019;34(10):1438–1446. doi:10.1002/gps.5139

35. Adamis D, van Gool WA, Eikelenboom P. Consistent patterns in the inconsistent associations of Insulin-like growth factor 1 (IGF-1), C-Reactive Protein (C-RP) and Interleukin 6 (IL-6) levels with delirium in surgical populations. A systematic review and meta-analysis. *Arch Gerontol Geriatr*. 2021;97:104518. doi:10.1016/j.archger.2021.104518

36. Reichenberg A, Yirmiya R, Schuld A, et al. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry*. 2001;58 (5):445–452. doi:10.1001/archpsyc.58.5.445

37. Sparkman NL, Buchanan JB, Heyen JR, Chen J, Beverly JL, Johnson RW. Interleukin-6 facilitates lipopolysaccharide-induced disruption in working memory and expression of other proinflammatory cytokines in hippocampal neuronal cell layers. *J Neurosci*. 2006;26(42):10709–10716. doi:10.1523/JNEUROSCI.3376-06.2006

38. Laser-Azogui A, Kornreich M, Malka-Gibor E, Beck R. Neurofilament assembly and function during neuronal development. *Curr Opin Cell Biol*. 2015;32:92–101. doi:10.1016/j.ceb.2015.01.003

39. Bridel C, van Wieringen WN, Zetterberg H, et al. Diagnostic value of cerebrospinal fluid neurofilament light protein in neurology: a systematic review and meta-analysis. *JAMA Neurol*. 2019;76(9):1035–1048. doi:10.1001/jamaneurol.2019.1534

40. Martínez MA, Olsson B, Bau L, et al. Glial and neuronal markers in cerebrospinal fluid predict progression in multiple sclerosis. *Mult Scler*. 2015;21(5):550–561. doi:10.1177/1352458514549397

41. Mattsson N, Cullen NC, Andreasson U, Zetterberg H, Blennow K. Association between longitudinal plasma neurofilament light and neurodegeneration in patients with Alzheimer disease. *JAMA Neurol*. 2019;76(7):791–799. doi:10.1001/jamaneurol.2019.0765

42. Oosterveld LP, Kuiper TI, Majbour NK, et al. CSF biomarkers reflecting protein pathology and axonal degeneration are associated with memory, attentional, and executive functioning in early-stage parkinson's disease. *Int J Mol Sci*. 2020;21:22. doi:10.3390/ijms21228519

43. Saller T, Petzold A, Zetterberg H, et al. A case series on the value of tau and neurofilament protein levels to predict and detect delirium in cardiac surgery patients. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub*. 2019;163(3):241–246. doi:10.5507/bp.2019.043

44. Gonçalves CA, Leite MC, Guerra MC. Adipocytes as an important source of serum S100B and possible roles of this protein in adipose tissue. *Cardiovasc Psychiatry Neurol*. 2010;(2010):790431. doi:10.1155/2010/790431

45. Basile AM, Fusi C, Conti AA, et al. S-100 protein and neuron-specific enolase as markers of subclinical cerebral damage after cardiac surgery: preliminary observation of a 6-month follow-up study. *Eur Neurol*. 2001;45(3):151–159. doi:10.1159/000052114

46. Grubb NR, Simpson C, Sherwood RA, Abraha HD, Cobbe SM. O&#x27, et al. Prediction of cognitive dysfunction after resuscitation from out-of-hospital cardiac arrest using serum neuron-specific enolase and protein S-100. *Heart*. 2007;93(10):1268–1273. doi:10.1136/hrt.2006.091314

47. Gonçalves CA, Leite MC, Nardin P. Biological and methodological features of the measurement of S100B, a putative marker of brain injury. *Clin Biochem*. 2008;41(10–11):755–763. doi:10.1016/j.clinbiochem.2008.04.003

48. Beishuizen SJ, Scholtens RM, Vellekoop AE, et al. Timing is critical in determining the association between delirium and S100 calcium-binding protein B. *J Am Geriatr Soc*. 2015;63(10):2212–2214. doi:10.1111/jgs.13696

49. Beishuizen SJ, Scholtens RM, van Munster BC, de Rooij SE. Unraveling the relationship between delirium, brain damage, and subsequent cognitive decline in a cohort of individuals undergoing surgery for hip fracture. *J Am Geriatr Soc*. 2017;65(1):130–136. doi:10.1111/jgs.14470

50. Hov KR, Bolstad N, Idland AV, et al. Cerebrospinal fluid S100B and Alzheimer's disease biomarkers in hip fracture patients with delirium. *Dement Geriatr Cogn Dis Extra*. 2017;7(3):374–385. doi:10.1159/000481853

51. Jorge-Ripper C, Alemán MR, Ros R, et al. Prognostic value of acute delirium recovery in older adults. *Geriatr Gerontol Int*. 2017;17(8):1161–1167. doi:10.1111/ggi.12842

52. Al Tmimi L, Van de Velde M, Meyns B, et al. Serum protein S100 as marker of postoperative delirium after off-pump coronary artery bypass surgery: secondary analysis of two prospective randomized controlled trials. *Clin Chem Lab Med*. 2016;54(10):1671–1680. doi:10.1515/cclm-2015-1012

53. Khan BA, Zawahiri M, Campbell NL, Boustani MA. Biomarkers for delirium--a review. *J Am Geriatr Soc*. 2011;59 Suppl 2(0 2):S256–S261. doi:10.1111/j.1532-5415.2011.03702.x

54. Kanner AA, Marchi N, Fazio V, et al. Serum S100beta: a noninvasive marker of blood-brain barrier function and brain lesions. *Cancer*. 2003;97 (11):2806–2813. doi:10.1002/cncr.11409

55. Kochanek PM, Berger RP, Bayir H, Wagner AK, Jenkins LW, Clark RS. Biomarkers of primary and evolving damage in traumatic and ischemic brain injury: diagnosis, prognosis, probing mechanisms, and therapeutic decision making. *Curr Opin Crit Care*. 2008;14(2):135–141. doi:10.1097/MCC.0b013e3282f57564

56. Blyth BJ, Farhavar A, Gee C, et al. Validation of serum markers for blood-brain barrier disruption in traumatic brain injury. *J Neurotrauma*. 2009;26(9):1497–1507. doi:10.1089/neu.2008.0738

57. Cerejeira J, Firmino H, Vaz-Serra A, Mukaetova-Ladinska EB. The neuroinflammatory hypothesis of delirium. *Acta Neuropathol*. 2010;119 (6):737–754. doi:10.1007/s00401-010-0674-1

58. Bokesch PM, Izykenova GA, Justice JB, Easley KA, Dambinova SA. NMDA receptor antibodies predict adverse neurological outcome after cardiac surgery in high-risk patients. *Stroke*. 2006;37(6):1432–1436. doi:10.1161/01.STR.0000221295.14547.c8

59. van Munster BC, Korevaar JC, Korse CM, Bonfrer JM, Zwinderman AH, de Rooij SE. Serum S100B in elderly patients with and without delirium. *Int J Geriatr Psychiatry*. 2010;25(3):234–239. doi:10.1002/gps.2326

60. Hall RJ, Ferguson KJ, Andrews M, et al. Delirium and cerebrospinal fluid S100B in Hip fracture patients: a preliminary study. *Am J Geriatr Psychiatry*. 2013;21(12):1239–1243. doi:10.1016/j.jagp.2012.12.024

61. Li RL, Zhang ZZ, Peng M, et al. Postoperative impairment of cognitive function in old mice: a possible role for neuroinflammation mediated by HMGB1, S100B, and RAGE. *J Surg Res*. 2013;185(2):815–824. doi:10.1016/j.jss.2013.06.043

62. Jones SC, Radinsky CR, Furlan AJ, et al. Variability in the magnitude of the cerebral blood flow response and the shape of the cerebral blood flow-pressure autoregulation curve during hypotension in normal rats [corrected]. *Anesthesiology*. 2002;97(2):488–496. doi:10.1097/00000542-200208000-00028

63. Vaurio LE, Sands LP, Wang Y, Mullen EA, Leung JM. Postoperative delirium: the importance of pain and pain management. *Anesth Analg*. 2006;102(4):1267–1273. doi:10.1213/01.ane.0000199156.59226.af