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# Higher serum PGE2 is a predicative biomarker for postoperative delirium following elective orthopedic surgery in elderly patients

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## Abstract

**Background:** Postoperative delirium (POD), one of the most common complications following major surgery, imposes a heavy burden on patients and society. The objective of this exploratory study was to conduct a secondary analysis to identify whether there exist novel and reliable serum biomarkers for the prediction of POD.

**Methods:** A total of 131 adult patients ( $\geq 65$  years) undergoing lower extremity orthopedic surgery with were enrolled in this study. Cognitive function was assessed preoperatively with Mini-Mental State Examination (MMSE). Delirium was diagnosed according to the Confusion Assessment Method (CAM) criteria on preoperative day and postoperative days 1–3. The preoperative serum levels of a panel of 16 biochemical parameters were measured by ELISA.

**Results:** Thirty-five patients developed POD, with an incidence of 26.7%. Patients in POD group were older ( $P=0.001$ ) and had lower preoperative MMSE scores ( $P=0.001$ ). Preoperative serum levels of prostaglandin E2 (PGE2,  $P<0.001$ ), S100 $\beta$  ( $P<0.001$ ), glial fibrillary acidic protein ( $P<0.001$ ) and neurofilament light ( $P=0.002$ ) in POD group were significantly increased. Logistic regression analysis showed that advanced age (OR = 1.144, 95%CI: 1.008 ~ 1.298,  $P=0.037$ ), higher serum neurofilament light (OR = 1.003, 95%CI: 1.000 ~ 1.005,  $P=0.036$ ) and PGE2 (OR = 1.031, 95%CI: 1.018 ~ 1.044,  $P<0.001$ ) levels were associated with the development of POD. In addition, serum level of PGE2 yielded an area under the ROC curve (AUC) of 0.897 to predict POD ( $P<0.001$ ), with a sensitivity of 80% and a specificity of 83.3%.

**Conclusions:** Our study showed that higher preoperative serum PGE2 level might be a biomarker to predict the occurrence of POD in elderly patients undergoing elective orthopedic surgery.

**Trial registration:** NCT03792373 [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

**Keywords:** Postoperative delirium, Biomarker, PGE2, Orthopedic surgery

## Introduction

Postoperative delirium (POD), characterized by an acute and fluctuating disturbance in awareness, cognition and attention, is one of the most common complications following major surgery [1, 2]. Although the incidence of POD in the general surgical population is 2.5–3%, it can

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afflict 12% to 51% of patients undergoing orthopedic surgery [3]. In high-risk patient groups, the incidence of POD is reported to be 50–70% [4]. Notably, the incidence of POD is significantly associated with increased morbidity and mortality, activities of daily living impairment, and global cognitive decline [5, 6].

The risk factors for POD are multiple and its pathophysiology remains poorly understood. Previous studies have demonstrated that advanced age, high-risk surgical procedures, cardiopulmonary comorbidities, poor functional status, preoperative fragility and cognitive impairment, pain and metabolic derangement might contribute to the occurrence of POD [7–9]. In animal studies, it has been proposed that neuroinflammation, neurohormone alterations, apoptosis, and oxidative stress may be the underlying molecular mechanism of POD [10–12]. As effective strategies exist to prevent the occurrence and development of POD [3, 4], especially in the high-risk population, there is a growing necessity to identify those patients who are vulnerable to POD.

Biomarkers not only indicate a certain pathological state, but also provide information about disease activity and progression. Although several biomarkers are reported to predict POD [10, 13], biomarkers with high sensitivity and specificity are still lacking. Therefore, we conducted this study aiming at identifying novel and reliable biomarkers for the prediction of POD. In the present study, a panel of 16 biochemical parameters in serum samples from elderly patients undergoing elective orthopedic surgery were assessed, including brain derived neurotrophic factor (BDNF), fibroblast growth factor-23 (FGF-23), irisin, C3a, C3, C5a, interleukin-17A (IL-17A), interleukin-33 (IL-33), prostaglandin E2 (PGE2), S100 $\beta$ , glial fibrillary acidic protein (GFAP), neurofilament light (NfL), vascular cell adhesion molecule 1 (VCAM1), E-selectin and matrix metalloprotein 9 (MMP9). Among them, BDNF, FGF-23 and irisin were selected because they are associated with neurocognitive regulation [14–16]. S100 $\beta$ , NfL and GFAP were implicated in neuronal injury [17, 18]. In addition, biochemical parameters associated with complement cascade (C3a, C3, C5a) and inflammatory response (IL-17A, IL-33, E-selectin, MMP9) were involved as well. These pathophysiological changes have been reported to play an essential part in the occurrence and development of POD [3, 4].

## Methods

### Study overview

This prospective observational study was approved by the local institutional research ethics board of Zhongda Hospital affiliated to Southeast University (2018ZDSYLL144-P01) and registered on ClinicalTrials.gov as NCT03792373. The primary aim of this study was

to determine which factors significantly influence postoperative outcome. As POD is a serious postoperative adverse complication, we included it as one of the indicators in this study. We performed this study according to the ethical principles for medical research involving human subjects detailed in the Declaration of Helsinki. Subjects were enrolled from February 1 to June 1, 2019. Written informed consent was obtained from patients prior to participation. In this secondary analysis, the inclusion criteria were age  $\geq 65$  years, American Society of Anesthesiologists (ASA) status I-III and undergoing elective lower extremity orthopedic surgery. Exclusion criteria were baseline delirium, refusal to follow the experimental procedures, inability to communicate with reach staff (Fig. 1).

### Delirium and cognition assessment

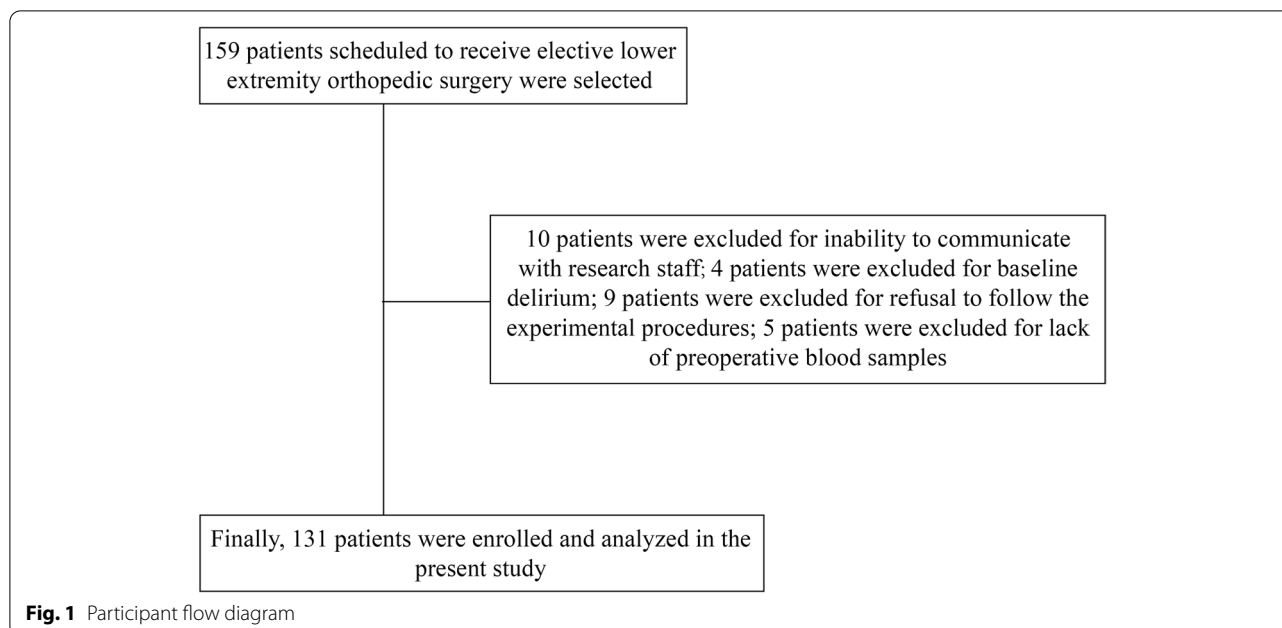
Mini-mental state examination (MMSE) was used to assess the preoperative cognitive function of participants on the day before surgery. The Confusion Assessment Method (CAM) was utilized for the evaluation of delirium, which comprises four clinical features: (a) acute onset of cognitive changes with a fluctuating course, (b) inattention, (c) disorganized thinking, and (d) altered level of consciousness. The diagnosis of delirium was based on the presence of (a) and (b) plus either (c) or (d). For baseline delirium assessment, participants enrolled were evaluated by a well-trained anesthesiologist on the day before surgery. For POD diagnosis, participants enrolled were evaluated by the same anesthesiologist twice daily on postoperative days 1–3.

### Biochemical measurements

Patients had blood draws in the morning on the day before surgery. The collected serum samples were stored at  $-80^{\circ}\text{C}$  for the later detection. The serum levels of 16 biochemical parameters were measured by enzyme linked immunosorbent assay (ELISA, CUSABIO, Wuhan, China), including BDNF, FGF-23, irisin, C3a, C3, C5a, IL-17A, IL-33, PGE2, S100 $\beta$ , GFAP, NfL, VCAM1, E-selectin and MMP9.

### Statistical analysis

This was a secondary analysis of data from a prospective observational study. Statistical analysis was performed using the SPSS version 25.0 software (SPSS, Chicago, IL). Normally distributed quantitative data were presented as mean and SD and were analyzed with independent-sample t-test, while non-normally distributed quantitative data were presented as median and interquartile range (IQR) and were analyzed with Mann–Whitney U test. Categorical data were analyzed with  $\chi^2$  test or Fisher exact test. The effect size of all significant group



differences was calculated with the formula Cohen's  $d = (M_A - M_B) / \sigma$  or  $r = Z / \sqrt{N}$  depending on the distribution of the data [19]. The risk factors for POD were evaluated by multivariate logistic regression analysis, in which variables with  $P$  values less than 0.05 were included. The prediction of serum biomarkers for POD was analyzed by using receiver operating characteristic (ROC) curve.  $P < 0.05$  was regarded as statistically significant.

## Results

### Patient characteristics at baseline

A total of 131 patients were finally included in this study, and 35 of them were diagnosed with POD (35/131, 26.7%). The baseline characteristics in POD and non-POD groups were presented in Table 1. No significant difference was observed between the two groups in terms of sex, BMI, ASA status, medical comorbidities (hypertension, diabetes mellitus, coronary artery disease, history of stroke, chronic pulmonary disease), duration of surgery, blood loss (all  $P > 0.05$ ). Patients in POD group were older ( $P = 0.001$ ) and had lower preoperative MMSE scores ( $P = 0.001$ ) compared with those in non-POD group.

### Differences in the levels of preoperative biochemical parameters between patients with and without POD

As shown in Table 2, serum levels of PGE2 ( $P < 0.001$ ), S100 $\beta$  ( $P < 0.001$ ), GFAP ( $P < 0.001$ ), and NfL ( $P = 0.002$ ) were significantly increased in POD group. However, no significant difference was observed in BDNF, FGF-23, irisin, C3a, C3, C5a, IL-17A, IL-33, VCAM1, E-selectin and MMP9. ( $P > 0.05$ ).

### Preoperative biomarker associations with POD

Then, a total of six clinical and biochemical variables with significant difference were assessed as potential predictors of POD by using multivariate logistic regression. As illustrated in Table 3, regression analysis showed that advanced age (OR = 1.144, 95%CI: 1.008 ~ 1.298,  $P = 0.037$ ), higher serum NfL (OR = 1.003, 95%CI: 1.000 ~ 1.005,  $P = 0.036$ ) and PGE2 (OR = 1.031, 95% CI: 1.018 ~ 1.044,  $P < 0.001$ ) levels were predicative factors for POD.

### The predicative performance of age, NfL and PGE2 for POD

The predicative performance of age, serum NfL and PGE2 levels for POD was identified by plotting ROC curve. As shown in Fig. 2, preoperative serum level of PGE2 had a good performance in predicting POD with the area under the ROC curve (AUC) value of 0.897 and 95% CI of 0.842–0.952 ( $P < 0.001$ ). The cut-off point of PGE2 level to predict POD was  $\geq 124.1$  ng/L, while the sensitivity and specificity for PGE2 were 80% and 83.3%, respectively. In addition, advanced age (AUC = 0.698, 95%CI: 0.590 ~ 0.806,  $P = 0.001$ ), and higher NfL level (AUC = 0.690, 95%CI: 0.581 ~ 0.798,  $P = 0.001$ ) could also discriminated patients with POD.

## Discussion

Our study showed that preoperative serum level of PGE2 was closely associated with the development of POD in elderly patients undergoing elective orthopedic surgery. Thus, preoperative PGE2 could serve as a new serum biomarker to identify patients at risk for developing POD.

**Table 1** Preoperative characteristics of patients with or without POD

Characteristics	POD group (n = 35)	Non-POD group (n = 96)	<sup>a</sup> P value	effect size
Sex (n, male/female)	15/20	39/57	0.818	/
Age (year)	77(70~82)	72(67~76)	0.001	0.30
ASA status (I/II/III)	2/22/11	8/73/15	0.169	/
BMI (kg/m <sup>2</sup> )	21.88(19.58~25.40)	23.50(22.04~26.38)	0.058	/
Preoperative MMSE	22(18~27)	26(23~29)	0.001	0.30
Medical comorbidities (n)				
Hypertension	29(82.86%)	78(81.25%)	0.833	/
Diabetes mellitus	13(37.14%)	30(31.25%)	0.525	/
Coronary artery disease	11(31.43%)	27(28.13%)	0.712	/
History of stroke	10(28.57%)	19(19.79%)	0.284	/
Chronic pulmonary disease	6(17.14%)	16(16.67%)	0.949	/
Duration of surgery (min)	85(75~95)	80(70~90)	0.454	/
Blood loss(ml)	250(200~300)	250(200~350)	0.815	/

POD Postoperative delirium, ASA American Society of Anesthesiologists, BMI Body Mass Index, MMSE Mini-Mental State Examination

<sup>a</sup> Continuous normally distributed variables (data presented as mean and SD) were analyzed with independent-sample t-test. Continuous non-normally distributed variables (data presented as median and IQR) were analyzed with Mann–Whitney U test. Categorical data were analyzed with  $\chi^2$  test or Fisher exact test (n = 131)

**Table 2** Intergroup comparisons of the preoperative serum biochemical parameters

Parameters	POD group (n = 35)	Non-POD group (n = 96)	<sup>a</sup> P value	effect size
BDNF (ng/ml)	0.43(0.38~0.54)	0.48(0.41~0.63)	0.109	/
FGF-23 (pg/ml)	504.07(456.31~577.63)	513.83(466.68~588.38)	0.894	/
Irisin (ng/ml)	47.64(18.94~74.45)	63.01(26.67~115.62)	0.070	/
IL-17A (pg/ml)	6.00(5.71~6.61)	6.02(5.58~6.69)	0.320	/
IL-33 (pg/ml)	11.50(5.35~33.07)	16.21(5.13~185.00)	0.353	/
C3a (ng/ml)	504.07(456.31~577.63)	513.83(466.68~588.38)	0.894	/
C3 ( $\mu$ g/ml)	264.87(136.56~297.21)	207.81(103.38~271.51)	0.065	/
C5a (ng/ml)	102.57(52.33~165.90)	85.77(52.71~141.67)	0.297	/
iNOS (IU/ml)	8.81(6.21~13.6)	8.54(6.07~12.16)	0.274	/
PGE2 (pg/ml)	181.23(126.08~235.65)	61.63(39.96~105.65)	<0.001	0.61
S100 $\beta$ (pg/ml)	199.22(183.52~283.19)	181.36(170.91~207.67)	<0.001	0.33
GFAP (ng/ml)	11.76(7.77~14.61)	7.38(5.84~10.29)	<0.001	0.36
NfL (ng/ml)	1.47 $\pm$ 0.2960	1.29 $\pm$ 0.2961	0.002	0.60
VCAM1 (ng/ml)	691.11 $\pm$ 263.50	652.18 $\pm$ 196.83	0.364	/
E-selectin (ng/ml)	2.95(2.14~3.99)	2.79(1.98~4.26)	0.718	/
MMP9 (ng/ml)	4.00(1.37~5.32)	3.36(1.71~9.68)	0.649	/

POD Postoperative delirium, BDNF Brain derived neurotrophic factor, FGF-23 Fibroblast growth factor 23, IL Interleukin, iNOS Inducible nitric oxide synthase, PGE2 Prostaglandin E2, GFAP Glial fibrillary acidic protein, NfL Neurofilament light, VCAM Vascular cell adhesion molecule, MMP Matrix metalloprotein

<sup>a</sup> Continuous normally distributed variables (data presented as mean and SD) were analyzed with independent-sample t-test. Continuous non-normally distributed variables (data presented as median and IQR) were analyzed with Mann–Whitney U test (n = 131)

To the best of our knowledge, this is the first study to link preoperative PGE2 level with POD following elective orthopedic surgery.

The incidence of POD was 26.7% in our study, which was similar to 27% in orthopedic surgery reported by a systematic review [20], and was also comparable with 20.4% in the aged patients undergoing similar type of

surgery in a recent study [21]. It is widely accepted that the occurrence of POD was resulted from the complicated interactions of multiple predisposing factors. Among the known risk factors for POD, advanced age and pre-existing dementia or cognitive impairment have been considered as the major risk factors [3]. Consistently, our study showed advanced age was

**Table 3** Logistics regression analysis of POD risk factors

Variables	OR	95% CI	P value
Age	1.144	1.008 ~ 1.298	0.037
Preoperative MMSE	0.922	0.810 ~ 1.049	0.217
PGE2	1.031	1.018 ~ 1.044	<0.001
S100β	1.002	0.997 ~ 1.008	0.456
NfL	1.003	1.000 ~ 1.005	0.036
GFAP	1.021	0.967 ~ 1.078	0.452

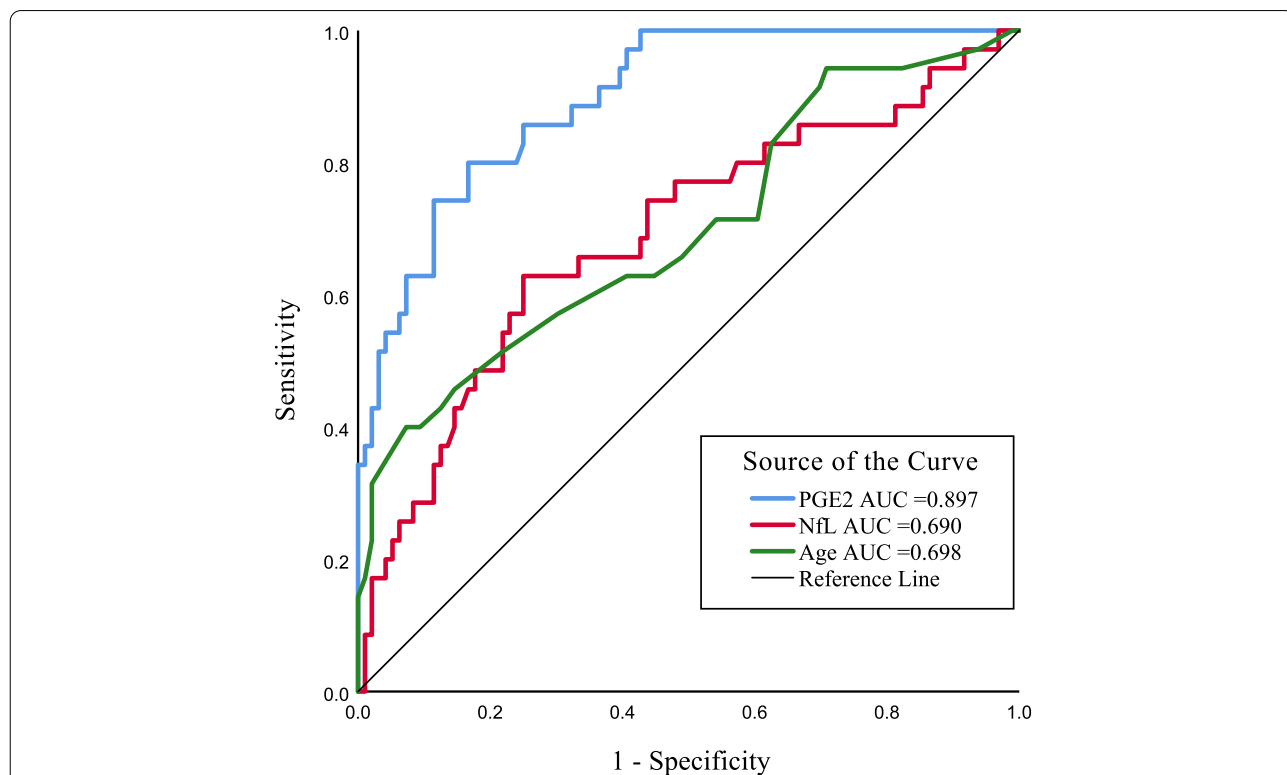
POD Postoperative delirium, OR Odds ratio, CI Credibility interval, MMSE Mini-Mental State Examination, PGE2 Prostaglandin E2, NfL Neurofilament light, VCAM Vascular cell adhesion molecule, GFAP Glial fibrillary acidic protein; (n = 131)

an independent risk factor of POD, and patients with POD were prone to have poor preoperative cognition as reflected by MMSE. Although delirium is significantly associated with adverse outcomes, fortunately, it is preventable and treatable [3]. Currently, non-pharmacological multicomponent intervention is thought to be the most effective prevention strategy, which mainly includes the Hospital Elder Life Program and proactive old age medicine consultation [22–24]. In addition, the fundamental aim of all preoperative screening instruments, whether scale- or biomarker-based, is to identify those

vulnerable patients, who then can benefit from optimized perioperative evaluation, monitoring and management. Thus, identifying high-risk patients is an important step in successfully reducing the risk for POD.

Despite various mechanisms have been implicated in the development of POD [12, 25], neuroinflammation and altered neurotransmitters are thought to be the two leading hypotheses [26]. For neuroinflammation, both preoperative and postoperative elevation of peripheral C-reactive protein and IL-6 were reported to be associated with higher risks of POD [27]. The underlying mechanism may be that peripheral inflammation causes the breakdown of the blood–brain barrier, leading to neuroinflammation, which in turn results in synaptic loss, neuronal death, and neurogenesis damage [28]. On the other hand, studies have showed alteration of neurotransmitters in the process of POD, including acetylcholine, glutamate, gamma-aminobutyric acid, dopamine, and serotonin systems, of which deficient choline or excessive dopamine, or both, are the most frequently linked to delirium [3, 4, 26].

In the present study, we assessed a panel of 16 parameters implicated in inflammatory response, neurotransmitter disturbance, complement cascade, and neuronal injury in serum samples from elderly patients undergoing



**Fig. 2** ROC curve analysis of age, preoperative serum NfL and PEC2 levels for distinguishing POD. (n = 131). ROC: receiver operating characteristic; NfL: neurofilament light; PGE2: prostaglandin E2; POD: postoperative delirium



elective orthopedic surgery. Importantly, we showed that serum level of preoperative PGE2 was significantly increased and appeared to be a potential biomarker of POD after elective orthopedic surgery. Indeed, PGE2 is reported to be an important modulator of inflammation, which is of particular interest due to its relatively high concentrations in the brain compared with other prostaglandins [29]. PGE2 works through four distinct G protein-coupled E-prostanoid receptors, EP1 to EP4, and a growing number of studies suggest that PGE2 exerts neurotoxic effects by binding to EP1, EP2 or EP3 receptors in models of chronic neurodegenerative disease like Alzheimer's disease (AD) and Parkinson's disease [29, 30]. In aged mice, blockade of peripheral PGE2 signaling is sufficient to reverse cognitive decline associated with aging [31]. Moreover, the cerebrospinal fluid concentration of PGE2 is elevated in both probable AD patients and in AD patients with memory decline [32, 33]. Strikingly, subsequent analysis of several studies indicated that chronic non-steroid anti-inflammatory drug use was associated with lower risk of AD in normal aging people [29, 34]. However, there are a number of studies suggesting that PGE2 had a role in synaptic plasticity and neuroprotection by binding EP4 receptors [35, 36]. Therefore, the role of PGE2 is complex and whether PGE2 inhibitor can be used as a prevention or treatment target for POD in elderly patients needs further research.

Our study also showed that NfL was also an independent risk factor for POD. As one of the neuroaxonal injury markers, NfL has been reported to be elevated in multiple conditions including stroke, traumatic brain injury, multiple sclerosis, AD and frontotemporal dementia [37]. Recently, a clinical study by Tamara and colleagues showed that patients with the highest preoperative NfL levels were more likely to develop POD, which is consistent with our finding [38]. Additionally, the increased serum levels of S100 $\beta$  and GFAP were observed in POD group. S100 $\beta$ , a calcium binding protein, has different effects during different stages of human development. In the first three months of life, S100 $\beta$  exerts neurotrophic effects on the central nervous system (CNS) [39]. However, elevated S100 $\beta$  levels at other points in life mostly correlate with blood–brain barrier injury, which has been observed in cerebrovascular and neurodegenerative diseases [40, 41]. S100 $\beta$  has been reported as a potential biomarker for delirium, but its particular relationship with POD remains controversial [42, 43]. GFAP, an intermediate filament protein, is mainly expressed in astrocytes and its plasma level has been proposed as a biomarker for nervous system injury in traumatic brain injury and stroke [44, 45]. Overall, these increased preoperative serum levels of S100 $\beta$  and GFAP reflect pre-existing brain function impairment in patients with POD, which

makes them more susceptible to brain injury in response to surgical trauma.

A few limitations should be noted in our study. Firstly, despite suitable for identifying biomarker, this clinical study involved a single-center, single-surgery procedure and was conducted in a relatively small sample, which may produce biases unintentionally, thus further studies in larger sample size are required. Moreover, detecting PGE2 levels postoperatively would be more informative to determine the relationship between PGE2 and POD, which merits further investigation. Finally, the information about the perioperative use of non-steroid anti-inflammatory drug was not collected, which might have an effect on our study results and should be considered in future study.

## Conclusions

Our study showed that preoperative serum PGE2 levels might be a biomarker to predict the occurrence of POD in elderly patients undergoing elective orthopedic surgery. Meanwhile, this finding may provide a target for possible interventions to prevent POD. However, further studies in different surgical populations are required to confirm our results.

## Abbreviations

AD: Alzheimer's disease; ASA: American Society of Anesthesiologists; AUC: Area under the ROC curve; BDNF: Brain derived neurotrophic factor; BMI: Body mass index; CAM: The Confusion Assessment Method; CI: Confidence interval; CSF: Cerebrospinal fluid; ELISA: Enzyme linked immunosorbent assay; FGF-23: Fibroblast growth factor; GFAP: Glial fibrillary acidic protein; IL: Interleukin; IQR: Interquartile range; MMP9: Matrix metalloprotein 9; MMSE: Mini-Mental State Examination; NfL: Neurofilament light; OR: Odds ratio; PGE2: Prostaglandin E2; POD: Postoperative delirium; ROC: Receiver operating characteristic; VCAM1: Vascular cell adhesion molecule 1.

## Acknowledgements

Not applicable.

## Authors' contributions

Qiang Sun, Mu-huo Ji and Meng Mao conceived and designed the study. Meng Mao, Lan-yue Zhu, Fei Wang and Jian-hua Tong carried out the experiments. Meng Mao, Lei-yuan Wang analyzed the research data and wrote the manuscript. Qiang Sun, Mu-huo Ji, Jian-hua Tong, Ying Ding and Jie Sun reviewed and edited the manuscript. All authors read and approved the final manuscript.

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## Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

This study was approved by the local institutional research ethics board of Zhongda Hospital affiliated to Southeast University (2018ZDSYLL144-P01)

and registered on ClinicalTrials.gov as NCT03130231. We performed this study according to the ethical principles for medical research involving human subjects detailed in the Declaration of Helsinki. The patients provided their written informed consent to participate in this study.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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