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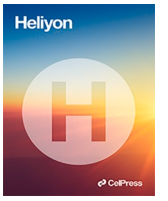

Research article

COVID-19 vaccination may prevent postoperative delirium in elderly patients undergoing elective non-cardiac surgery: The PNDRFAP and PNDABLE studies☆

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ABSTRACT

Background: Postoperative delirium (POD) often occurs in elderly patients after surgery. We conducted two clinical studies to determine whether COVID-19 vaccination has a protective effect on POD and to explore the role of CSF biomarkers in this process.

Methods: We conducted two clinical studies, Perioperative Neurocognitive Disorder Risk Factor and Prognosis (PNDRFAP) and Perioperative Neurocognitive Disorder and Biomarker Lifestyle (PNDABLE), in which patients more than or equal to 65 years old who have had elective non-cardiac surgery were enrolled. The preoperative cognitive status of patients were evaluated by Mini-Mental State Examination (MMSE) one day preoperatively. Confusion Assessment Method (CAM) was used to diagnose POD. We used the mediation model to analyze the relationship between CSF biomarkers, COVID-19 vaccination and POD, as well as Dynamic Nomogram to calculate the incidence of Non-Postoperative Delirium (NPOD). The main outcome of these studies was the incidence of POD during seven days postoperatively or before discharge, which was assessed by CAM.

Results: In the final, 705 participants were enrolled in the PNDRFAP study, and 638 patients in the PNDABLE. In both studies, we found that the occurrence of POD was lower in patients who had injected COVID-19 vaccination before surgery compared with those without vaccination (PNDRFAP: 10.20 % [21/205] vs 25.80 % [129/500], $P < 0.001$; PNDABLE: 2.40 % [4/164] vs 34.60 % [164/474], $P < 0.001$). Mediation analysis showed that the protective effect of preoperative COVID-19 vaccine on POD was significantly mediated by CSF Aβ42 (proportion = 17.56

Abbreviations: POD, Postoperative delirium; PNDRFAP, Perioperative Neurocognitive Disorder Risk Factor and Prognosis; PNDABLE, Perioperative Neurocognitive Disorder and Biomarker Lifestyle; MMSE, Mini-Mental State Examination; CAM, Confusion Assessment Method; NPOD, Non-Postoperative Delirium; PNDs, Perioperative neurocognitive disorders; Aβ42, β-amyloid42; T-tau, total tau; P-tau, phosphorylated tau; CSF, cerebrospinal fluid; CNS, central nervous system; AHN, enhancing hippocampal neurogenesis; ASA, American Society of Anesthesiologists; ELISA, Enzyme-linked immunosorbent assay; PACU, Postanaesthesia care unit; MDAS, Memorial Delirium Assessment Scale; SD, Standard deviation; IQR, Inter-quartile range; CRP, C-reactive protein; OR, Odds ratio.

☆ **Trial registration:** Chinese Clinical Trial Registry Identifier: PNDRFAP: ChiCTR2000033639, PNDABLE: ChiCTR2000033439.

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%), T-tau (proportion = 19.64 %), Aβ42/T-tau (proportion = 29.67 %), and Aβ42/P-tau (proportion = 12.26 %).
Conclusions: COVID-19 vaccine is a protective factor for POD in old patients, which is associated with CSF biomarkers.

1. Introduction

Perioperative neurocognitive disorders (PNDs) refers to cognitive impairments or changes happening before or after surfery, of which postoperative delirium (POD) is an important component [1]. POD is a common complication after the surgery [1–5], and aging is a recognized risk factor [6]. It has a high incidence in old patients according to our previous research [7]. POD ultimately causes lots of adverse outcomes, such as prolonged hospitalization [8], decreased organ function [9], long-time cognitive decline [2], and increased mortality [10,11]. Each of these outcomes imposes an enormous burden on society, patients and their families. However, POD is often ignored due to its variety of symptoms, especially among the elderly [2,12]. In addition, the more risk factors, the higher the incidence of POD [13]. Therefore, it is crucial to increase the protective factors and reduce potential risk factors before surgery for preventing the POD.

Although the pathophysiology of POD is not fully understood until now, there is increasing evidence which indicated that the blood-brain barrier damage, CSF biomarkers, neuroinflammation and so on play a key part in POD occurrence [14–17]. Among these mechanisms, the relationships between POD and CSF biomarkers, such as β-amyloid42 (Aβ42), total tau (T-tau), and phosphorylated tau (P-tau), have been extensively studied [18,19]. As an independent predictor, Aβ42 couldforecast the incidence of POD. Meanwhile, the hyperphosphorylation of tau protein is closely related to POD. It should be noted that the changes of Aβ42 are not as same as that of tau protein content in cerebrospinal fluid (CSF) of patients with POD. The amount of Aβ42 in CSF of patients with POD decreased, while the level of tau protein changed in reverse.

As a global epidemic disease, COVID-19 was caused by SARS-CoV-2 and broke out in late 2019 [20]. Although it was considered as a respiratory disease at the beginning of COVID-19, symptoms of the central nervous system (CNS) have subsequently been observed in patients with COVID-19 [21,22]. Elderly patients usually have higher mortality rates and more serious adverse consequences after suffering COVID-19. There is evidence to suggest that SARS-CoV-2 will cause cognitive impairment through mechanism similar to PNDs [23]. Therefore, COVID-19 is considered as a new risk factor for PNDs. In response to containing COVID-19 epidemic, vaccines are considered to be the critical and highly effective measure [24]. The effective rate of vaccination against COVID-19 exceeds 90 % [25]. Recently, evidence has emerged that COVID-19 vaccination has potential neurotrophic effects and can prevent age-related cognitive decline by enhancing hippocampal neurogenesis (AHN) in adults [26]. Based on these studies, we propose a hypothesis that COVID-19 vaccination may prevent POD in geriatric patients as a protective factor.

Therefore, we conducted the PNDABLE clinical study to determine whether COVID-19 vaccination is a beneficial factor for POD in elderly and to explore the mediating role of CSF biomarkers in this process, and the PNDRFAP study was performed to validate the conclusions of the PNDABLE study.

1.1. Methods design, ethical approval, and participants

For achieving the purpose of this study, we conducted two clinical studies according to different anesthesia methods: Perioperative Neurocognitive Disorder Risk Factor and Prognosis (PNDRFAP) and Perioperative Neurocognitive Disorder and Biomarker Lifestyle (PNDABLE). PNDABLE study was designed to determine whether vaccinating COVID-19 was an influential factor for POD in elderly. In addition to the above purposes, PNDABLE study was also designed to verify the relationship between COVID-19 vaccination, POD and CSF biomarkers.

The PNDABLE study was used to verify whether the conclusions of the PNDRFAP study regarding the relationship between COVID-19 vaccines and POD were accidental.

All these studies were conducted with the approval of the Ethics Committee of Qingdao Municipal Hospitaland registered in the Chinese Clinical Trial Registry (Clinical registration number of PNDRFAP: ChiCTR2000033639, PNDABLE ChiCTR2000033439). Patients were admitted to the clinical study only after getting the written informed consent signed by patients themselves or their legal representatives.

Patients eligible for inclusion in this study must meet the following conditions:(1) Aging more than or equal to 65 years old; (2) American Society of Anesthesiologists (ASA) Grade I or II; (3) Mini-Mental State Examination (MMSE) score $\geq$24 before surgery; (4) Communicating normally; (5) Accepting elective non-cardiac surgery; (6) Within six months of receiving COVID-19 vaccine. In addition, the participants enrolled in the PNDRFAP study all received general anesthesia, while the participants in the PNDABLE study received combined spinal-epidural anesthesia.

Patients with preoperative MMSE score $<$24 or with severe psychological or hearing impairment were excluded in the study of PNDRFAP, while those with following criteria were excluded in the study of PNDABLE: (1) Preoperative MMSE score $<$24; (2) Drug abuse; (3) Severe visual or auditory impairment or psychological disorder; (4) Preoperative coagulation dysfunction; (5) Major mental disorders other than Alzheimer's disease (AD); (6) Disease that may affect CSF biomarkers, such as malignant tumors; (7) Family history of inherited disease.

1.2. Data collection

The data included patients' characteristics and the contents of CSF biomarkers. The basic characteristics of patients were composed of gender, age, COVID-19 vaccination, years of education, MMSE score and other data. Vaccination information was collected through Qingdao Municipal Hospital Operation Anesthesia System Software.

In PNDABLE, the collected CSF was centrifuged for 10 min at the speed of 2,000 g and then stored at −80 °C. The content of CSF biomarkers was determined by enzyme-linked immunosorbent assay (ELISA) using the microplate readers (Thermo Scientific Multiskan MK3). The numerical value of CSF Aβ42, Aβ40, T-tau, P-tau were measured and then the levels of Aβ42/T-tau, Aβ42/P-tau were calculated.

1.3. Anesthesia and postoperative analgesia management

Standard preoperative preparations, including fasting and water deprivation, were received by the participants. And ECG, respiration, oxygen saturation and blood pressure were routinely monitored during their operation.

Participants in the group of PNDABLE received different types of anesthesia than those in the group of PNDRFAP. They had combined spinal-epidural anesthesia, and the puncture site of anesthesia was the lumbar space between the lumbar spine 3–4 spinous processes in the lateral decubitus position. After the puncture needle successfully entered the subarachnoid space, we extracted 2 ml of CSF at first and then injected 0.66 % ropivacaine into the space. The level of injection was determined by the anesthesiologist based on the type of operation. During the operation, patients used masks to continuously inhale oxygen at a rate of 5 L min^{-1}. Vasoactive drugs were used when necessary to maintain blood pressure and heart rate in the stable level.

Participants of the PNDRFAP received general anesthesia, which was induced by sufentanil, and etomidate and maintained by remifentanil, *cis*-atracurium and sevoflurane.

After operation, the patients involved in the study of PNDRFAP were sent to postanaesthesia care unit (PACU) after removing their tracheal catheter, whereas the patients in the study of PNDABLE were sent directly to PACU. And all patients were monitored in PACU for 30 min s and then sent back to the ward.

1.4. Outcome measurements

Thebaseline cognitive function of patients was evaluated by neurologist using MMSE one day before operation. Only patients with MMSE score $\geq$24 were enrolled in these studies. Postoperative cognitive function was assessed by a trained anesthesiologist between 1 and 7 days after surgery or until discharge of hospital. Anesthesiologists evaluated the patients for POD according to the criteria of Confusion Assessment Method (CAM) [27]. If the patients had POD, then we used Memorial Delirium Assessment Scale (MDAS) to assess the severity and the type of delirium.

The main outcome of these study was the occurrence of POD during 7 days after surgery or until leaving hosptial. All the data was assigned to POD group (POD) and non POD (NPOD) according to whether delirium occurred after operation.

1.5. Sample size calculation

Based on the preliminary research, the PNDABLE study is expected to include 10 covariates, and the PNDRFAP study is expected to include 8 covariates into logistic regression. Based on our previous study, the incidence of POD was set at 14 % [28]. We assumed that 20 % of patients lost follow-up after surgery. So the sample size required by PNDABLE study is 893 cases [$10 \times 10 \div 14\ \% \div (1–20\ \%) = 893$], and PNDRFAP study is 714 cases [$8 \times 10 \div 14\ \% \div (1–20\ \%) = 714$].

1.6. Statistical analysis

These peoplewere divided into two groups based on whether they had been vaccinated against COVID-19. For data with skewed distribution, the measurement data were presented with median (inter-quartile range [IQR]) and compared by Mann-Whitney *U* test. Number (percentage) was used for counting data, and χ^2 test or Fisher's exact test was used to compare the differences.

To explore the relationship between the factors in our research and POD, logistic regression equation was performed. After that, we put all potential confounding variables into one multivariable model in logistic regression and applied a backward selection with $p = 0.157$ to come up with a minimal sufficient confounder set. And based on confounding factors of different variables, we designed several models and used sensitivity analysis to reduce the influence of confounding factors on the results.

In addition, we excluded C-reactive protein (CRP) > 10 and conducted subgroup analysis of PNDABLE study after adjusting age, gender, years of education, smoking history, drinking history, hypertension history and diabetes history. This step can exclude the impact of preoperative inflammation on our results.We used Dynamic Nomogram to calculate the NPOD incidence of the first dose of COVID-19 vaccine combined with other influencing factors to verify the protective effect of COVID-19 vaccination.

Finally, the total effect of COVID-19 vaccination on POD was verified by mediating effect analysis to clear out whether it is a comprehensive result of the effect of COVID-19 vaccination on CSF biomarkers, the effect of CSF biomarkers on POD and the direct effect of COVID-19 vaccination on POD. When the following criteria were met, we considered the mediation effect model was meaningful: (1) COVID-19 vaccination significantly affected the changes of CSF biomarkers; (2) The changes of CSF biomarkers had a marked impact on the incidence of POD; (3) COVID-19 vaccination significantly affected the occurrence of POD; (4) The proportion of

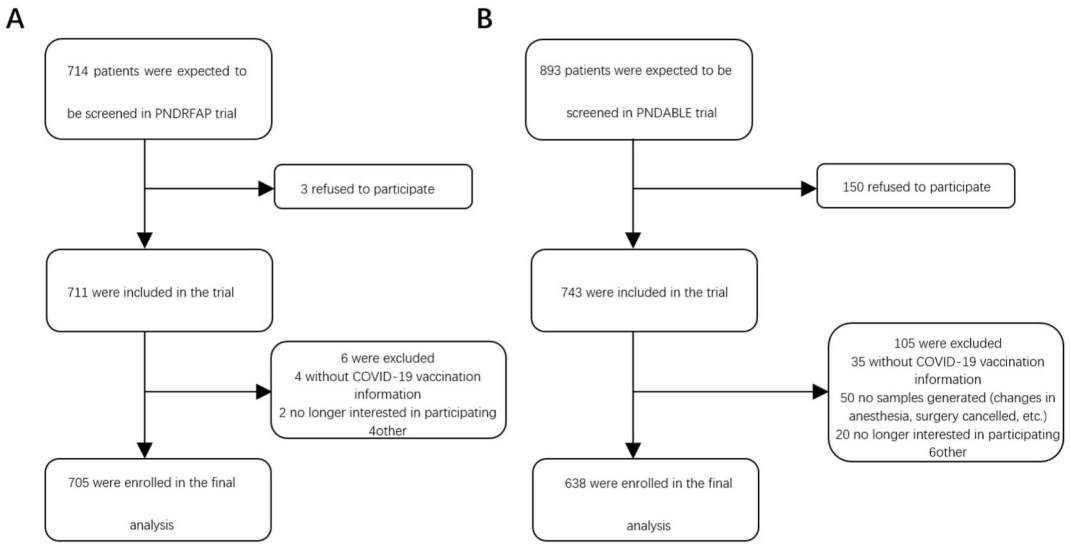


Fig. 1. Diagram of study design.
A The Perioperative Neurocognitive Disorder Risk Factor and Prognosis (PNDRFAP) study. **B** The Perioperative Neurocognitive Discorder and Biomarker Lifestyle (PNDABLE) study.

Table 1
Characteristics of participants in PNDRFAP.

Characteristic	PNDRFAP		
	FD (n = 205)	NFD (n = 500)	*P*
Age(year), median(IQR)	69 (7)	71 (11)	0.004[a]
Male, n (%)	117 (57.10 %)	311 (62.20 %)	0.206
Education(year), median(IQR)	9 (4)	9 (5)	0.072
MMSE (score), median(IQR)	26 (2)	26 (2)	<0.001[a]
Smoking, n (%)	41 (20.00 %)	179 (35.80 %)	<0.001[a]
Drinking, n (%)	26 (12.70 %)	158 (31.60 %)	<0.001[a]
Hypertension, n (%)	121 (59.00 %)	296 (59.20 %)	0.966
Diabetes, n (%)	70 (34.10 %)	148 (29.60 %)	0.236
Coronary Heart Disease, n (%)	47 (22.90 %)	163 (32.60 %)	0.011[a]
POD, n (%)	21 (10.20 %)	129 (25.80 %)	<0.001[a]
MDAS (score), median(IQR)	3 (4)	3 (8)	0.008

PNDRFAP, the Perioperative Neurocognitive Disorder Risk Factor and Prognosis study; FD, the first dose; NFD, the non-first dose; MMSE, Mini-Mental State Examination; POD, postoperative delirium; MDAS, the Memorial Delirium Assessment Scale.
[a] $P < 0.05$.

mediation effect >10 %.

The data analysis process was carried out using SPSS 25.0 (IBM SPSS Inc, Chicago, IL), R software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria) and Stata MP16.0 (Solvusoft Corporation, Inc., Chicago, Illinois, USA). The criterion of significance was two-sided $P < 0.05$.

2. Results

2.1. Characteristics of participants

In PNDRFAP study and PNDABLE study, we allocated patients to two groups according to whether they received the first dose of COVID-19 vaccine: the first dose (FD) group and the non-first dose (NFD) group. All patients in this study were not infected with COVID-19.

After exclusion, a total of 705 patients in the PNDRFAP study were included in the final analysis (Fig. 1A). By comparing the FD group and the NFD group, we found that there were no significant differences between the two groups in gender, years of education, hypertension history and diabetes history. However, patients receiving the first dose had a lower median age (69 [7] vs 71 [11], $P = 0.004$), lower proportion of smoking history (20.00 % vs 35.80 %, $P < 0.001$), drinking history (12.70 % vs 31.60 %, $P < 0.001$)and MDAS score (3 [4] vs 3 [8], $P = 0.008$) (Table 1).

The PNDABLE study ultimately enrolled 638 participants (Fig. 1B). In the study, there were no significant differences in age,

Table 2
Characteristics of participants in PNDABLE.

Characteristic	PNDABLE		
	FD(n = 164)	NFD(n = 474)	P
Age(year), median(IQR)	68 (8)	69 (7)	0.546
Male, n (%)	94 (57.30 %)	293 (61.80 %)	0.310
Education(year), median(IQR)	9 (7)	9 (4.25)	<0.001[a]
MMSE (score), median(IQR)	27 (4)	28 (2)	<0.001[a]
Smoking, n (%)	46 (28.20 %)	138 (29.10 %)	0.828
Drinking, n (%)	45 (27.40 %)	160 (33.80 %)	0.135
Hypertension, n (%)	74 (45.10 %)	219 (46.20 %)	0.811
Diabetes, n (%)	27 (16.50 %)	121 (25.50 %)	0.018[a]
Coronary Heart Disease, n (%)	22 (13.40 %)	91 (19.20 %)	0.094
POD, n (%)	4 (2.40 %)	164 (34.60 %)	<0.001[a]
MDAS (score), median(IQR)	2 (3)	7 (14.25)	<0.001[a]
Aβ42(pg/ml), median(IQR)	505.10 (264.48)	348.04 (275.12)	<0.001[a]
T-tau(pg/ml), median(IQR)	186.85 (107.60)	230.88 (128.02)	<0.001[a]
P-tau(pg/ml), median(IQR)	45.47 (20.80)	41.88 (29.66)	0.041[a]
Aβ42/T-tau, median(IQR)	2.62 (1.77)	1.53 (1.63)	<0.001[a]
Aβ42/P-tau, median(IQR)	11.41 (8.12)	8.24 (8.04)	<0.001[a]

PNDABLE, the Perioperative Neurocognitive Disorder and Biomarker Lifestyle study; FD, the first dose; NFD, the non-first dose; MMSE, Mini-Mental State Examination; POD, postoperative delirium; MDAS, the Memorial Delirium Assessment Scale; Aβ42, β-amyloid42; T-tau, total tau; P-tau, phosphorylated tau.
[a] $P < 0.05$.

Table 3
The relationship between COVID-19 vaccination and POD in PNDRFAP.

	OR (95 % CI)	*P*
Model 1[a]	0.328 [0.200,0.538]	<0.001[e]
Model 2[b]	0.397 [0.238,0.662]	<0.001[e]
Model 3[c]	0.448 [0.259,0.777]	0.004[e]
Model 4[d]	0.423 [0.242,0.737]	0.002[e]

[a] Model 1:Unadjusted.
[b] Model 2:Adjusted for age、gender.
[c] Model 3:Adjusted for age、gender、years of education、MMSE scores.
[d] Model 4: Adjusted for age、gender、years of education、MMSE scores and diabetes.
[e] $P < 0.05$.

Table 4
The relationship between COVID-19 vaccination and POD in PNDABLE.

	OR (95 % CI)	*P*
Model 1[a]	0.047 [0.017,0.130]	<0.001[e]
Model 2[b]	0.014 [0.004,0.047]	<0.001[e]
Model 3[c]	0.016 [0.005,0.053]	<0.001[e]
Model 4[d]	0.015 [0.004,0.050]	<0.001[e]

[a] Model 1:Unadjusted.
[b] Model 2:Adjusted for age.
[c] Model 3:Adjusted for age、MMSE scores.
[d] Model 4: Adjusted for age、MMSE scores and drinking history.
[e] $P < 0.05$.

gender, smoking history, drinking history, hypertension history and coronary heart disease history between the FD group and the NFD group. Years of education (9 [7] vs 9 [4.25], $P < 0.001$), MMSE scores (27 [4] vs 28 [2], $P < 0.001$) and MDAS score (2 [3] vs 7[14.25], $P < 0.001$) were lower in the FD group. And in the FD group, it had a lower incidence of diabetes (16.50 % vs 25.50 %, $P = 0.018$). The analysis of CSF biomarkers showed that the level of CSF Aβ42 (505.10 [264.48] vs 348.04[275.12], $P < 0.001$), P-tau (45.47[20.80] vs 41.88 [29.66], $P = 0.041$), Aβ42/T-tau (2.62 [1.77] vs 1.53 [1.63], $P < 0.001$) and Aβ42/P-tau (11.40 [8.12] vs 8.24 [8.04], $P < 0.001$) in the FD group were higher than that of the NFD group, while the level of T-tau (186.85 [107.60] vs 230.88 [128.02], $P < 0.001$) in CSF was lower (Table 2).

Table 5
The relationship between CSF biomarkers and POD in PNDABLE.

A		
	OR (95 % CI)	*P*
Model 1[a]	0.997 [0.996,0.998]	<0.001[h]
Model 2[b]	0.997 [0.996,0.998]	<0.001[h]
Model 3[c]	0.997 [0.996,0.998]	<0.001[h]
Model 4[d]	0.997 [0.996,0.998]	<0.001[h]
B		
	OR (95 % CI)	*P*
Model 1[a]	1.006 [1.004,1.007]	<0.001[h]
Model 2[b]	1.005 [1.004,1.006]	<0.001[h]
Model 3[c]	1.005 [1.004,1.007]	<0.001[h]
Model 5[e]	1.005 [1.004,1.007]	<0.001[h]
C		
	OR (95 % CI)	*P*
Model 1[a]	1.054 [1.043,1.065]	<0.001[h]
Model 2[b]	1.047 [1.036,1.059]	<0.001[h]
Model 3[c]	1.048 [1.036,1.060]	<0.001[h]
Model 6[f]	1.050 [1.038,1.062]	<0.001[h]
D		
	OR (95 % CI)	*P*
Model 1[a]	0.404 [0.327,0.499]	<0.001[h]
Model 2[b]	0.427 [0.339,0.537]	<0.001[h]
Model 3[c]	0.418 [0.331,0.529]	<0.001[h]
Model 4[d]	0.415 [0.327,0.525]	<0.001[h]
E		
	OR (95 % CI)	*P*
Model 1[a]	0.825 [0.788,0.863]	<0.001[h]
Model 2[b]	0.845 [0.806,0.885]	<0.001[h]
Model 3[c]	0.845 [0.806,0.885]	<0.001[h]
Model 7[g]	0.841 [0.801,0.882]	<0.001[h]

A The relationship between CSF Aβ42 and POD in PNDABLE. B The relationship between CSF T-tau and POD in PNDABLE. C The relationship between CSF P-tau and POD in PNDABLE. D The relationship between CSF Aβ42/T-tau and POD in PNDABLE. E The relationship between CSF Aβ42/P-tau and POD in PNDABLE.

[a] Model 1: Unadjusted.
[b] Model 2: Adjusted for age.
[c] Model 3: Adjusted for age、MMSE scores.
[d] Model 4: Adjusted for age、MMSE scores、drinking history and diabetes.
[e] Model 5: Adjusted for age、MMSE scores、hypertension and diabetes.
[f] Model 6: Adjusted for age、MMSE scores、smoking history、hypertension and diabetes.
[g] Model 7: Adjusted for age、MMSE scores、drinking history、hypertension and diabetes.
[h] $P < 0.05$.

2.2. The relationship between COVID-19 vaccination, CSF biomarkers and POD

In the PNDRFAP, comparing with patients who did not inoculate the first dose of COVID-19 vaccine, the incidence of POD in vaccinated patients was lower (10.20 vs 25.80 %, $P < 0.001$) (Table 1). Similarly, the incidence of POD decreased in the FD group (2.40 % vs 34.60 %, $P < 0.001$) (Table 2).

We adopted logistic regression to explore the relationship between POD, COVID-19 vaccination, and CSF biomarkers. Moreover, we also verified the stability of the model through sensitivity analysis.

In PNDRFAP, the first dose of COVID-19 vaccination was significantly related to the reduction of POD without adjusting the relevant factors (Model 1) (odds ratio [OR], 0.328[95 % CI, 0.200–0.538]; $P < 0.001$). After adjusting age, gender (Model 2), we obtained the similar results (OR, 0.397 [95 % CI 0.238–0.662]; $P < 0.001$). After adjusting age, gender, years of education, MMSE score (Model 3), the results were similar (OR, 0.448 [95 % CI 0.259–0.777]; $P = 0.004$). In the Model 4, we adjusted age、gender、years of education、MMSE scores and diabetes, the results remained robust (OR, 0.423 [95 % CI 0.242–0.737]; $P = 0.002$) (Table 3).

In PNDABLE study, the first dose of COVID-19 vaccination can reduce the occurrence of POD (OR, 0.047 [95 % CI, 0.017–0.130]; $P < 0.001$) (Table 4). In addition, we found that the occurrence of POD was significantly related to the increase of CSF P-tau and CSF T-tau level, while the relationship between CSF Aβ42, Aβ42/T-tau, Aβ42/P-tau level and POD was opposite. The above results were still

Table 6
Subgroup analysis of PNDABLE study after exclusion of patients with CRP >10 mg/L and adjusting confounder.

	OR (95 % CI)	P
FD	0.004 [0.000,0.048]	<0.001[a]

Subgroup analysis of PNDABLE study after exclusion of patients with CRP >10 mg/L and adjusting age, gender, years of education, smoking history, drinking history, hypertension history and diabetes history.
[a] $P < 0.05$.

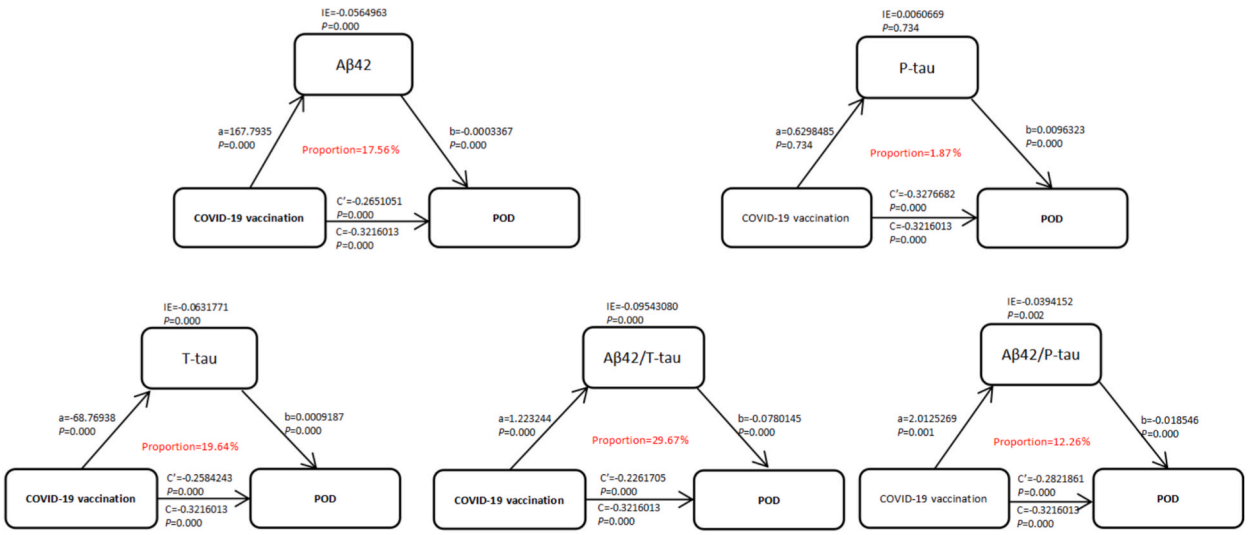


Fig. 2. Mediation analysis.
The relationship between COVID-19 vaccination and POD was mediated by Aβ42 (proportion = 17.56 %), T-tau (proportion = 19.64 %), Aβ42/T-tau (proportion = 29.67 %) and Aβ42/P-tau(proportion = 12.26 %).

maintain robust after the correction of confounding factors (Table 5). The results of this study further verified the conclusion of PNDRFAP logistic regression.

In addition, we also excluded patients with C-reactive protein>10 from repeating subgroup analysis, which can exclude the impact of preoperative inflammation on our results. After excluding patients with CRP>10 (n = 231) and repeating subgroup analysis in PNDABLE study, the above conclusion still holds (Table 6).

2.3. Mediation analysis

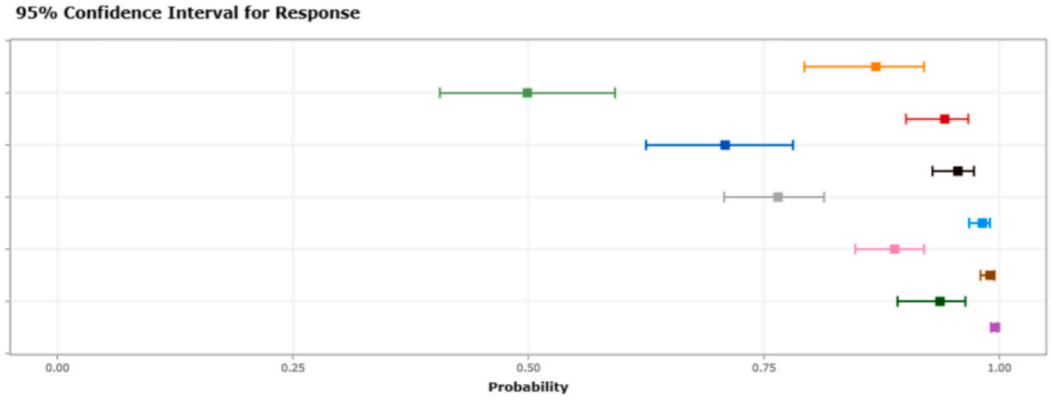
From the above results, it can be concluded that COVID-19 vaccination is a beneficial factor of POD in elderly,the difference in CSF biomarker levels between the vaccination and non vaccination group was statistically significant. Therefore, we used mediation analysis to determine whether CSF biomarkers were mediators reducing POD occurrence after COVID-19 vaccination. The analysis results showed that the effect of COVID-19 vaccination on preventing POD was mediated by Aβ42 (proportion = 17.56 %), T-tau (proportion = 19.64 %), Aβ42/T-tau (proportion = 29.67 %) and Aβ42/P-tau (proportion = 12.26 %) (Fig. 2).

2.4. Dynamic Nomogram

To verify the protective effect of COVID-19 vaccination, we used Dynamic Nomogram to calculate the NPOD incidence of the first dose of vaccine combined with other factors. The results showed that regardless of whether the type of anesthesia changed, the incidence of NPOD in patients receiving preoperative COVID-19 vaccine injection was higher than that in patients who did not receive preoperative injection (Fig. 3).

3. Discussion

In thesestudy, we discussed and explored the relationship between COVID-19 vaccination and POD in geriatric patients. The results suggested that the incidence of POD in elderly patients receiving COVID-19 vaccine was lower than that without COVID-19 vaccine. Besides, we also found that CSF Aβ42, T-tau, Aβ42/T-tau and Aβ42/P-tau were mediating effect factor of the COVID-19 vaccine on



	Thefirstdose	Age	MMSE	Education	Type	Prediction	Lower.bound	Upper.bound
1	non-Thefirstdose	74	27	9	1	0.753	0.708	0.794
2	Thefirstdose	74	27	9	1	0.953	0.926	0.971
3	non-Thefirstdose	74	27	9	2	0.555	0.502	0.607
4	Thefirstdose	74	27	9	2	0.893	0.842	0.929
5	non-Thefirstdose	58	29	0	1	0.973	0.949	0.986
6	Thefirstdose	58	29	0	1	0.996	0.991	0.998
7	non-Thefirstdose	58	29	0	2	0.937	0.892	0.964
8	Thefirstdose	58	29	0	2	0.990	0.980	0.995
9	non-Thefirstdose	68	28	5	1	0.889	0.847	0.920
10	Thefirstdose	68	28	5	1	0.982	0.968	0.990
11	non-Thefirstdose	68	28	5	2	0.765	0.708	0.814
12	Thefirstdose	68	28	5	2	0.956	0.929	0.973
13	non-Thefirstdose	76	27	16	1	0.709	0.625	0.781
14	Thefirstdose	76	27	16	1	0.942	0.901	0.967
15	non-Thefirstdose	76	27	16	2	0.499	0.406	0.592
16	Thefirstdose	76	27	16	2	0.869	0.793	0.920

Fig. 3. Incidence of NPOD.
Incidence of NPOD. Dynamic Nomogram calculated the incidence of NPOD combined with other influencing factors. Type, type of anesthesia (1, general, anesthesia; 2, combined spinal-epidural anesthesia).

POD. This is the first time to conclude that COVID-19 vaccination is a protective factor of POD.

POD can be induced by multiple factors, but aging is one of the key factors [29]. The incidence of postoperative delirium increases with age [30]. At present, the role of CSF biomarkers in the development of POD has attracted much attention. Previous studies have suggested that tau protein forms and aggregates in neurodegenerative disease, and hyperphosphorylation of protein is an important factor for its aggregation [31,32]. At the same time, the view that Aβ deposition is the trigger of POD has become the leading pathogenic theory [33].Furthermore, according to our previous study, low levels of CSF Aβ42 before surgery also increase the risk of POD [7]. On the basis of these studies, we analyzed CSF biomarkers and found that T-tau and P-tau were risk factors for POD, while Aβ42 had the opposite effect.

More and more evidence shows that COVID-19 can cause cognitive dysfunction in patients [20,34,35]. But for COVID-19 vaccination, our results showed it was a protective risk for POD. And the result of Dynamic Nomogram also suggested there was a high incidence of NPOD in patients who inoculate the COVID-19 vaccine. As mentioned above, there is no research have been made on the relationship between COVID-19 vaccination and POD, so the specific relationship between them and the mechanism of action are still unclear. But we try to explain the potential mechanism according to existing research. There is evidence that COVID-19 vaccination may enhance adult hippocampal neurogenesis (AHN), which is the basis for influencing us to establish the concept of learning and memory mechanisms [26,36]. With this enhancement, COVID-19 vaccination can prevent neural degeneration and reduce the

occurrence of POD. In addition, studies proposed that the level of CSF Tau protein, which is a marker of neuronal damage, elevated in patients with COVID-19 [37,38]. The vaccine can increase the level of neurotrophic molecules to reduce the damage of neurons, which may decrease the level of CSF tau protein [26,38]. This is consistent with the negative regulation of tau protein by COVID-19 vaccination in mediation analysis. This suggests that COVID-19 vaccination may improve postoperative cognitive impairment by inhibiting neuronal damage. Mediation analysis also showed that COVID-19 vaccine injection was positively correlated with CSF Aβ42 level. This shows that COVID-19 vaccination can improve the level of CSF Aβ42, which is a protective factor of POD. Therefore, COVID-19 vaccination may prevent POD by increasing the level of Aβ42. In conclusion, COVID-19 vaccination may reduce the incidence of POD through the above three ways. However, these assumptions have not yet been verified, so further study is urgently needed to prove the pathophysiological changes in the process of action.

This study is innovative to some extent. As far as we know, it is the first time to that COVID-19 vaccination has been associated with POD in the olds and that COVID-19 vaccination has been found to be a protective factor for POD. Secondly, the relationship between COVID-19 vaccination, POD and CSF biomarkers was analyzed by mediation effect model.

But it is undeniable that this study has several limitations. First of all, we only studied the occurrence of POD within 7 days after surgery. And in further studies, the time of postoperative cognitive screening can be prolonged. Second, only the role of CSF biomarkers has been studied. Third, the number of patients included in this study is insufficient, so the clinical representativeness needs further verification.

In conclued, we found that COVID-19 vaccination is a protective factor for POD in elderly patien for the first time, and this protective effect is associated with CSF biomarkers. Therefore, preoperative COVID-19 vaccination for elderly patients is recommended, but the results still need to be verified by a large-scale study.

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Data availability

The research related data has not been deposited into a publicly available repository yet. The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request. And the data will be made available on request.

CRediT authorship contribution statement

Haoran Zhang: Writing – original draft, Project administration. **Aihua Zhang:** Project administration. **Yanan Lin:** Data curation. **Chuan Li:** Data curation. **Yunchao Yang:** Project administration. **Rui Dong:** Writing – review & editing. **Xu Lin:** Writing – review & editing. **Bin Wang:** Writing – review & editing. **Yanlin Bi:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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