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BRIEF REPORT **Open Access**

Efficacy and safety of gastrodin in preventing postoperative delirium following cardiac surgery: a randomized placebo controlled clinical trial

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Abstract

Background Delirium and postoperative cognitive dysfunction (POCD) are common complications post-cardiac surgery, yet no specific medical intervention is currently recommended for prevention. This study aimed to evaluate the efficacy of gastrodin infusion in preventing delirium and POCD in critically ill patients following cardiac surgery.

Material and Methods A double-blind, randomized, placebo-controlled trial was conducted on patients aged 18–75, scheduled for coronary artery bypass grafting (CABG) surgery, with or without valve replacement. Participants were randomized in a 1:1 ratio to receive gastrodin infusion 600 mg twice daily or placebo from the day of surgery until the postoperative day (POD) 6. The co-primary outcomes were the incidences of delirium and POCD, assessed from ICU admission until POD 7 and at 1 and 3 months postoperatively. This study was registered with the Chinese Clinical Trials Registry (ChiCTR1800020414).

Results Of 160 randomized participants, 155 were analyzed (77 gastrodin, 78 placebo) according to a modified intention to treat principle. The incidence of postoperative delirium was 19.5% in the gastrodin group and 35.9% in the placebo group, with a significant relative risk of 0.54 (95% CI 0.32–0.93, $p=0.022$). The incidence of in-hospital POCD was 2.9% and 4.0% in the placebo and gastrodin groups, respectively. The odds of hospital discharge were significantly greater in the gastrodin group (subhazard ratio, 1.20; 95% CI 1.00–1.84; $p=0.049$). Adverse events occurred in 9.1% (7/77) of patients administered gastrodin and 14.1% (11/78) of patients administered the placebo, with none being drug-related.

Conclusion Gastrodin infusion significantly reduced postoperative delirium and improved discharge outcomes in patients undergoing CABG, but larger studies are needed to confirm its efficacy in preventing delirium.

Keywords Delirium, Gastrodin, Cardiac surgery

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Introduction

Delirium is among the most common complications following cardiac surgery, with an incidence varying from 20 to 52% [1, 2], and is associated with prolonged hospital stay [3], dementia [4], and mortality [5]. While robust literature has demonstrated its preventability [6, 7], no specific treatment has been recommended for preventing delirium.

Gastrodin (PubChem CID: 115,027), the primary active ingredient of *Gastrodia elata* with the chemical structure of 4-hydroxybenzyl alcohol-4-O-β-D-glucopyranoside, [8] has been approved in China for the clinical treatment of anxiety, depression, and insomnia [9–11] and exhibits analgesic, anticonvulsant, and sedative effects [12]. Gastrodin could mitigate neuroinflammation and oxidative stress [9, 11], which are cornerstones in the pathophysiology of delirium [13]. However, clinical trials regarding its use in preventing delirium following cardiac surgery lacks.

This study aimed to evaluate the efficacy and safety of gastrodin in preventing delirium and postoperative cognitive dysfunction (POCD) in critically ill patients after cardiac surgery.

Methods

Study design

This prospective, randomized, double-blind, placebo-controlled study was conducted from December 2018 to March 2021 in Union Hospital, Wuhan, China. The Institutional Ethics Committee approved this study (2018(S026)) and was registered (ChiCTR1800020414). Written informed consent was obtained from all participants.

Patients

Patients aged 18–75 years, scheduled for elective coronary artery bypass grafting (CABG) with or without valve replacement, and expected to stay in the intensive care unit (ICU) for at least one night after surgery, were included. Exclusion criteria included neurological disorders, severe liver or kidney dysfunction, and current sedative use (complete exclusion criteria in Additional file 1).

Randomization and blinding

Before surgery, eligible participants were randomized into either group in a ratio of 1:1 in blocks of four, according to a computer-generated random number sequence. The infusion solutions were prepared by an independent nurse uninvolved in the research, ensuring blinding of investigators and clinicians.

Intervention

600mg of gastrodin was diluted in 50ml NaCl and administered twice daily as a one-hour infusion (total daily dose 1200mg). Treatment or placebo commenced on the day of surgery and continued to POD6, a total of 7 days. The gastrodin dose was determined according to the prescribing information [14–16], while the timing of administration was based on findings from prior clinical practice. All patients received the same anesthetic protocol. During the trial, cognitive-affecting medications were avoided (full list in Additional file 1).

Study outcomes

The co-primary outcomes were the incidence of delirium and the incidence of POCD.

Delirium assessments were performed twice daily from POD 1 to POD7 (6:00–8:00 AM and from 6:30 to 8:30 PM) using the confusion assessment method for the ICU (CAM-ICU). POCD assessments were conducted at screening, and at 7 days, 1, and 3 months postoperatively using the mini-mental status examination (MMSE).

Secondary outcomes included changes in the total MMSE score and its dimension scores, as well as changes in the 7-item generalized anxiety disorder scale (GAD-7), activities of daily living (ADL) scale, and the patient health questionnaire-9 (PHQ-9) between baseline and postoperative day 7, month 1, and month 3. Additional secondary outcomes included protocol compliance rate, cardiopulmonary bypass (CPB) time, cross-clamp time, intubation time, length of ICU stay and postoperative hospital stay, and 30-day and 90-day all-cause mortality.

Safety evaluation

All adverse events (AE) possibly or probably related to the intervention were assessed at each follow-up visit, with detailed recording of timing, severity, frequency, and duration of AE alleviation.

Statistical analysis

The sample size was estimated based on a previous study at the Beth Israel Deaconess Medical Center, where 42% of cardiac surgery patients experienced postoperative delirium [17]. Assuming gastrodin reduces this rate by 50%, with a one-sided α of 0.05, β of 0.2, and 10% loss to follow-up, the required sample size was 160.

Outcome analyses were primarily performed in the full analysis set (FAS), which follows a modified intention-to-treat (mITT) principle. For the primary endpoint and adverse events, we also conducted per protocol analyses. Data were presented as frequencies and proportions, means and standard deviations, or medians and interquartile ranges, as appropriate. Continuous variables were compared using t-tests or Wilcoxon rank-sum tests, and categorical variables were analyzed using χ^2 or Fisher's exact tests. Primary endpoints were analyzed using binary logistic regression, while secondary endpoints were analyzed using log-linked binomial or generalized linear models. In post-hoc analyses, the cumulative incidence of delirium was calculated using the Kaplan–Meier method and Cox proportional hazards model. Competing risk models (Fine-Gray method) were applied on an exploratory basis to two outcomes: delirium and hospital discharge, with death as the competing event.

Statistical analyses were performed using R version 4.2.2 (R Foundation, Vienna, Austria). Statistical significance was set at $p \leq 0.05$. Study protocol and statistical analysis plan are provided in Additional file 1.

Results

Of 160 randomized participants, 155 (77 in the gastrodin group, 78 in the placebo group) who received at least one treatment and completed assessments were analyzed (Fig. 1). Baseline characteristics were well balanced between the two groups (Table 1).

The incidence of delirium was 19.5% in the gastrodin group and 35.9% in the placebo group, demonstrating a significant relative risk of 0.54 (95% CI 0.32–0.93, $p = 0.02$) (Fig. 2). Similar results were observed in the PP population, with a RR of 0.54 (95% CI 0.30–0.95, $p = 0.028$; Additional File 2 Supplemental Table 1). The cumulative incidence of postoperative delirium was also reduced in the gastrodin group (hazard ratio 0.50, 95% CI 0.27–0.94, $p = 0.02$). Similarly, competing risk analyses also demonstrated reduced the risk of delirium with gastrodin infusion (subhazard ratio [sHR], 0.53; 95% CI 0.30–0.94; $p = 0.03$).

No significant differences were found in the incidence of POCD between the two groups at 7 days, 1 month, and 3 months postoperatively in either the FAS or PP populations (Table 2, Additional File 2 Supplemental Table 1). In the post-hoc analysis, patients with delirium showed significantly greater declines in MMSE scores at 7 days, 1 month, and 3 months postoperatively compared to those without delirium (−1.38 vs. −0.44, 0.14 vs. −0.59, −0.82 vs. −0.02, respectively; all $p < 0.05$).

Gastrodin infusion did not significantly alter the median lengths of stay in either the ICU (median, 50.67 vs. 67.12 h; $p = 0.71$) or the hospital (median, 15.0 vs. 15.0 days; $p = 0.51$), nor did it significantly impact CPB time, cross-clamp time, or intubation time. Competing risk analyses revealed that the odds of hospital discharge were significantly greater in the gastrodin group (sHR, 1.20; 95% CI, 1.00–1.84; $p = 0.049$). No significant differences were observed in MMSE, ADL, GAD-7, and PHQ-9 at 7 days, 1 month, and 3 months between the gastrodin and placebo groups, except for the GAD-7 scores at 3 months (0 (0, 2) vs. 0 (0, 2); $p = 0.01$) (Table 2). In the post-hoc analysis, patients with postoperative delirium had longer ICU stay than those without delirium (median, 73.1 vs. 56.5 h; $p = 0.04$). However, no significant difference in length of hospital stay was observed between patients with and without delirium (median, 15.0 vs. 15.0 h; $p = 0.83$). No significant differences in 30-day and 90-day mortality were found during follow-up (Table 2).

No significant differences in adverse events were observed between the two groups (Table 2), with none being drug-related. Adverse events in the PP population were consistent with those in the FAS population (Additional File 2 Supplemental Table 2).

Discussion

In this randomized trial involving critically ill patients after CABG, twice-daily gastrodin infusion from the day of surgery to POD 6, compared to placebo, reduced the incidence of delirium and increased the likelihood of hospital discharge, with no drug-related adverse events.

Gastrodin exhibits antioxidant and anti-inflammatory effects, making it promising for preventing delirium after cardiac surgery. Cardiac surgery and CPB trigger the release of psychoactive inflammatory mediators, which may lead to delirium through dopamine, GABA, and/or cholinergic pathways [13]. Inflammation can also impair microcirculation through leukocyte adhesion, endothelial dysfunction, perivascular edema, and reduced capillary function, potentially compromising the blood–brain barrier and causing neurological dysfunction [18]. Wang et al. observed that gastrodin reduced neuroinflammation and lowered the risk of POCD [19].

Our trial utilized the MMSE, the most widely validated tool for cognitive assessment, to evaluate POCD as per guidelines. The observed POCD incidence in the present study was 4.0% in the gastrodin group and 2.9% in the placebo group, lower than previously reported [20]. A prospective study involving 225 cardiac surgical patients reported that MMSE scores declined initially postoperatively, reaching a nadir around day 2, then rapidly increased from day 3 to 5, and slowly improved thereafter, potentially returning to ≥ 24 by day 5 [21]. In our study, the MMSE assessments were conducted on POD 7 rather than daily, which may have missed patients who developed POCD earlier and had partially recovered by then, resulting in a lower observed incidence. In the post-hoc analysis, patients with postoperative delirium had greater MMSE declines, consistent with previous findings. A recent meta-analysis has reported that delirium is often accompanied by long-term cognitive decline [22]. However, our study

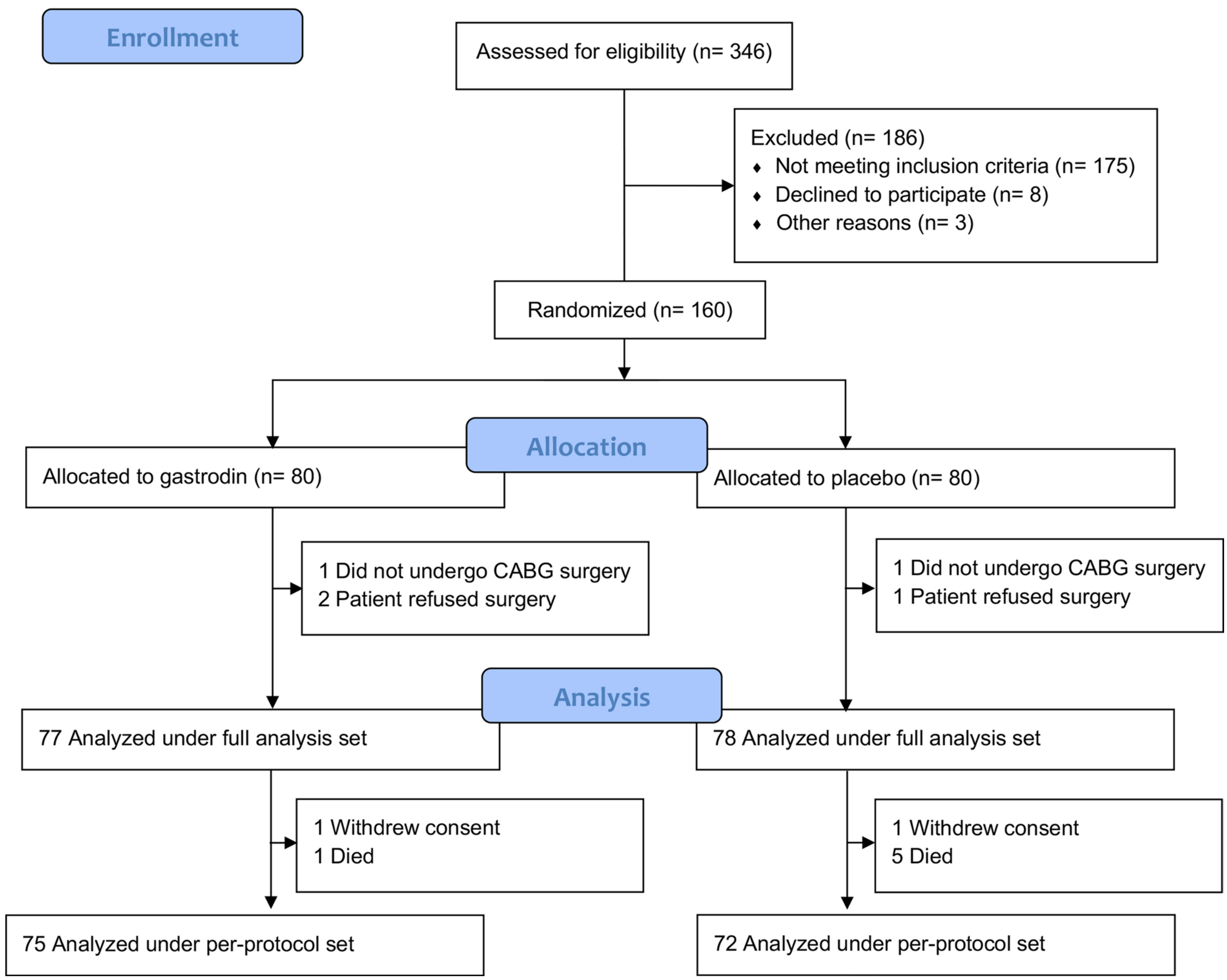

Fig. 1 Participant flow in the trial

demonstrated a significant reduction in delirium but no significant difference in POCD. Likewise, a recent multicenter randomized controlled trial in cardiac surgical populations found significant differences in delirium but not in POCD between cognitive training and routine care groups [23]. Discrepant findings may be due to differences in patient populations, cognitive assessment timing and sensitivity, and definitions of delirium or POCD across studies.

The competing risk analysis indicated that gastrodin was associated with a higher likelihood of hospital discharge, yet the median LOS did not differ significantly between groups. This discrepancy may arise because the competing risk model simultaneously accounts for death

Table 1 Baseline characteristics of the participants in the full analysis set

Characteristics	Missing	Gastrodin (n = 77)	Missing	Placebo (n = 78)	*P* value
Age (years), mean (SD)	–	58.0 (8.5)	–	58.3 (9.0)	0.666
Sex, n (%)	–		–		0.858
Male		65 (84.4)		64 (82.1)	
Female		12 (15.6)		14 (17.9)	
Body mass index, mean (SD)	11	24.7 (3.4)	8	25.0 (4.1)	0.719
Current smoker, n (%)	9	11 (16.2)	7	21 (29.6)	0.094
Current drinker, n (%)	9	9 (13.2)	7	15 (21.1)	0.314
Ethnicity, n (%)	–		–		0.988
Han		74 (96.1)		76 (97.4)	
Others		3 (3.9)		2 (2.6)	
Duration of education (years), n (%)	–		–		0.645
< = 9		35 (45.5)		30 (38.5)	
9–12		24 (31.2)		29 (37.2)	
> 12		18 (23.3)		19 (24.3)	
Marital status, n (%)	4		4		0.620
Unmarried		2 (2.6)		1 (1.3)	
Married		71 (92.2)		73 (93.6)	
Medical history, n (%)	–		–		0.613
Hypertension		27 (35.1)		38 (48.7)	
Diabetes		15 (19.5)		17 (21.8)	
Dyslipidaemia		1 (1.3)		2 (2.6)	
Chronic obstructive pulmonary disease		2 (2.6)		1 (1.3)	
ADL score at randomization, mean (SD)	1	20.1 (0.6)	2	20.1 (0.4)	0.504
MMSE score at randomization, mean (SD)	–	29.0 (1.2)	–	29.2 (1.1)	0.203
ASA class 3, n (%)		68 (88.3)		72 (92.3)	0.569
Charlson comorbidity index		1.68 (0.9)		1.74 (1.0)	0.610
Procedure, n (%)	–		–		> 0.999
CABG		63 (81.8)		63 (80.8)	
CABG + Valve repair		14 (18.2)		15 (19.2)	
Cardiopulmonary bypass, n (%)	–		–		0.694
No		34 (44.2)		31 (39.7)	
Yes		43 (55.8)		47 (60.3)	

Data are presented as n (%) or mean (SD), as appropriate

SD, standard deviation; CABG, coronary artery bypass graft; ADL, activities of daily living; MMSE, mini-mental state examination

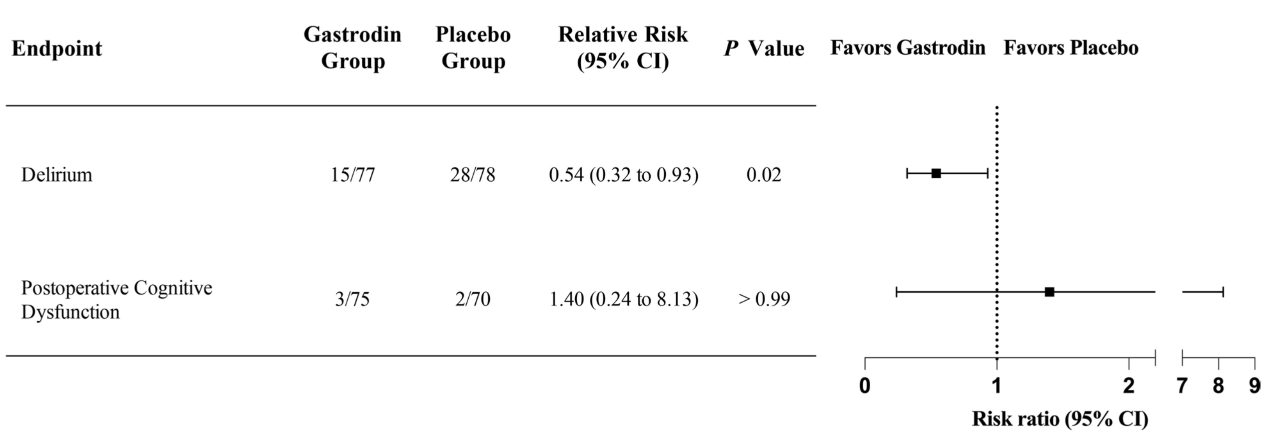

Fig. 2 Forest plot of primary endpoints

Table 2 Primary/secondary outcomes and adverse events

Outcomes	Gastrodin (n = 77)	Placebo (n = 78)	*P* value
Delirium			
Delirium at 7 days, n (%) (primary outcome)	15/77 (19.5)	28/78 (35.9)	0.022
Days with delirium, median (IQR)	0 (0, 0)	0 (0, 2)	0.021
Postoperative cognitive dysfunction			
Cognitive dysfunction at 7 days, n (%) (primary outcome)	3/75 (4.0)	2/70 (2.9)	> 0.999
Cognitive dysfunction at 1 month, n (%) (primary outcome)	1 (1.3%)	0 (0%)	> 0.999
Cognitive dysfunction at 3 months, n (%) (primary outcome)	0 (0%)	1 (1.4%)	0.493
MMSE Change from baseline †, median (IQR)	0 (− 2, 1)	0 (− 2, 0)	0.913
Time-related outcomes			
CPB time (hours), median (IQR)	1.73 (1.43, 2.40)	1.87 (1.50, 2.62)	0.220
Cross-clamp time (hours), median (IQR)	1.08 (0.87, 1.45)	1.27 (0.91, 1.73)	0.464
Length of postoperative hospital stay (days), median (IQR)	15 (11, 20)	15 (12, 20)	0.508
ICU length of stay (hours), median (IQR)	50.67 (44.00, 114.58)	67.12 (44.00, 95.58)	0.714
Intubation time (hours), median (IQR)	20.50 (15.75, 26.42)	20.59 (17.90, 26.20)	0.646
Follow-up outcomes ‡			
30-day all-cause mortality	1 (1.30)	5 (6.41)	> 0.999
90-day all-cause mortality	1 (1.30)	5 (6.41)	> 0.999
Adverse events			
Total number, n (%) §	14 (18.18)	21 (26.92)	0.267
Constipation, n (%)	0 (0)	1 (1.28)	> 0.999
Insomnia, n (%)	0 (0)	1 (1.28)	> 0.999
Poor wound healing, n (%)	2 (2.60)	1 (1.28)	0.620
Pneumonia, n (%)	1 (1.30)	0 (0)	0.497
Pleural effusion, n (%)	0 (0)	1 (1.28)	> 0.999
Respiratory failure, n (%)	2 (2.60)	0 (0)	0.245
Acute kidney injury, n (%)	4 (5.19)	7 (8.97)	0.534
Liver dysfunction, n (%)	0 (0)	2 (2.56)	0.497
Ileus, n (%)	0 (0)	1 (1.28)	> 0.999
Stroke, n (%)	0 (0)	0 (0)	> 0.999
Atrial Fibrillation, n (%)	4 (5.19)	2 (2.56)	0.442
Death, n (%)	1 (1.30)	5 (6.41)	0.210 †

Data are presented as n (%) or median (IQR), as appropriate. Primary outcomes are specifically annotated

† The MMSE is scored on a scale from 0 (worst) to 30 (best)

‡ The effect on 30-day and 90-day all-cause mortality was assessed with Cox proportional hazards model. One patient in the gastrodin group and one patient in the placebo group lost to follow-up

§ The total number of adverse events is reported based on the number of occurrences. Adverse events occurred in 7 patients in the gastrodin group and 11 patients in the placebo group

* From Fisher exact test

IQR, interquartile range; MMSE, mini-mental status examination; CPB, cardiopulmonary bypass; ICU, intensive care unit

and its timing, thus providing a different perspective on patient outcomes compared to a direct LOS comparison, which can be skewed by data bias, censoring, and small sample sizes.

This trial had several limitations. The observed incidence of POCD was lower than previously reported [20], likely due to MMSE scores recovering by POD 7 and subsequent assessments [21]. We conducted a post-hoc analysis showing that patients with delirium had significantly greater declines in MMSE scores, aligning with previous findings and validating our POCD assessment. Second, this was a single-center study, limiting the generalizability of our findings. Third, the sample size was calculated based on an anticipated 50% reduction in delirium, an estimate derived from prior small-scale clinical observations with gastrodin, which may seem ambitious. However, the observed delirium incidence (19.5% in gastrodin vs. 35.9% in placebo) aligned closely with our initial assumptions. Fourth, assessment timepoints for co-primary outcomes were not detailed in the registration. Fifth, blood samples were collected during the study primarily to monitor liver and kidney functions. Consequently, neuroinflammatory mediators were not analyzed. Finally, our application of competing risk models was exploratory, intended to generate preliminary insights and guide future research and clinical practice.

Conclusions

In conclusion, perioperative gastrodin infusion appears to be an effective and safe pharmacological option for delirium prevention in critically ill patients after CABG. Large sample-sized randomized clinical trials are warranted.

Abbreviations

POCD	Postoperative cognitive dysfunction
CABG	Coronary artery bypass grafting
POD	Postoperative day
ICU	Intensive care unit
CAM-ICU	Confusion assessment method for the ICU
MMSE	Mini-mental status examination
GAD-7	7-item generalized anxiety disorder scale
ADL	Activities of daily living
PHQ-9	Patient health questionnaire-9
CPB	Cardiopulmonary bypass

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05331-9.

Additional file1 (DOCX 45 KB)

Additional file2 (DOCX 21 KB)

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Author contributions

Yun-Xiao Bai: conceptualization, methodology, formal analysis, writing—original draft. Hui-Liang Wu: software, formal analysis, visualization. Wan-Li Xie: validation, resources, data curation. Xia Li: methodology, formal analysis, writing—review and editing. Jing-Jing Han: software, data curation, visualization. Jie Liu: methodology, validation, supervision. Shi-Qiang Chen: Data curation, validation, supervision. Ping Yin: methodology, data curation. Nian-Guo Dong: resources, supervision, writing—review and editing. Qing-Ping Wu: conceptualization, funding acquisition, resources, supervision, writing—review and editing.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. The Institutional Ethics Committee approved this study (2018(S026)). Written informed consent was obtained from all participants before enrolment.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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