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Postoperative delirium mediates the association between preoperative psychological symptoms and delayed neurocognitive recovery in older adults undergoing off-pump coronary artery bypass grafting: a prospective cohort study

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Abstract

Background

Preoperative anxiety and depression are common in older surgical patients and may increase vulnerability to adverse postoperative neurocognitive outcomes. However, their associations with postoperative delirium and delayed neurocognitive recovery, as well as the potential mediating role of postoperative delirium, remain unclear in older adults undergoing off-pump coronary artery bypass grafting.

Methods

In this single-center prospective cohort study, we consecutively enrolled patients aged 60 years or older who underwent elective off-pump coronary artery bypass grafting between January 2024 and December 2024. Preoperative anxiety and depression were assessed one day before surgery using the Hospital Anxiety and Depression Scale. Cognitive function was assessed using the Montreal Cognitive Assessment-Basic before surgery and on postoperative day 28. Postoperative delirium was assessed twice daily on postoperative days 1–7 using the Confusion Assessment Method for the Intensive Care Unit in the intensive care unit and the 3-Minute Diagnostic Interview for CAM-defined Delirium in the general ward. Delayed neurocognitive recovery was defined as a decline of at least 4 points in the postoperative day-28 Montreal Cognitive Assessment-Basic score from baseline. Multivariable logistic regression and bootstrap mediation analyses were performed.

Results

A total of 168 patients were included in the final analysis. Delayed neurocognitive recovery occurred in 71 patients (42.26%), and postoperative delirium occurred in 61 patients (36.31%). The prevalences of preoperative anxiety and depression were 34.52% and 26.79%, respectively. After adjustment for potential confounders, preoperative anxiety was associated with higher odds of delayed neurocognitive recovery (odds ratio 2.41, 95% confidence interval 1.06–5.48; P = 0.037) and postoperative delirium, and preoperative depression was also associated with higher odds of delayed neurocognitive recovery (odds ratio 2.53, 95% confidence interval 1.05–6.08; P = 0.038) and postoperative delirium. Mediation analysis showed that postoperative delirium partially mediated the associations of preoperative anxiety and depression with delayed neurocognitive recovery, accounting for 27.88% and 27.45% of the total effects, respectively.

Conclusions

In older adults undergoing off-pump coronary artery bypass grafting, preoperative anxiety and depression were associated with increased risks of postoperative delirium and delayed neurocognitive recovery. Postoperative delirium partially mediated these associations, suggesting that preoperative psychological symptoms and delirium prevention may both be important targets in perioperative brain health management.

Trial registration

Chinese Clinical Trial Registry, ChiCTR2300079246. Registered on 28 December 2023.

Background

Coronary artery bypass grafting (CABG) is a crucial revascularization strategy for patients with complex coronary artery disease, particularly multivessel or left main coronary artery disease [1]. Due to an aging population and advances in perioperative care, the number of older adults undergoing CABG is rising. Despite this, perioperative neurological complications have emerged as a major concern, adversely affecting recovery and long-term prognosis. As prominent complications, POD and DNR can prolong hospitalization, increase healthcare costs, and result in lasting deficits in quality of life, functional status, and cognitive function [2–4].

In 2018, an international multidisciplinary working group recommended the term perioperative neurocognitive disorders (PND) as an overarching nomenclature for cognitive changes identified before and after surgery [5]. Within this framework, postoperative delirium (POD) and delayed neurocognitive recovery (DNR) are two clinically important postoperative neurocognitive outcomes in older adults. Both conditions have been associated with prolonged hospitalization, increased healthcare burden, and poorer postoperative recovery [2–6].

Preoperative psychological symptoms, especially anxiety and depression, are common in older surgical patients and are increasingly recognized as potentially important determinants of perioperative outcomes [7–9]. These symptoms may influence postoperative neurocognitive trajectories through several biological and behavioral pathways, including dysregulation of the stress response, sleep disturbance, increased pain sensitivity, reduced cognitive reserve, and enhanced inflammatory vulnerability [10–12]. Previous studies have suggested that preoperative anxiety and depression may be associated with POD or postoperative cognitive decline, but the findings have been inconsistent [13–20]. These discrepancies may be related to differences in psychological assessment tools, outcome definitions, study populations, and surgical types [13, 21].

In cardiac surgery, cardiopulmonary bypass may introduce additional inflammatory activation, microembolization, and cerebral perfusion fluctuation, thereby complicating the interpretation of associations between preoperative psychological symptoms and postoperative neurocognitive outcomes [6, 21]. Off-pump coronary artery bypass grafting (OPCABG), by avoiding cardiopulmonary

bypass, may provide a relatively more homogeneous clinical setting for investigating these relationships. In addition, POD and DNR may represent related manifestations within the spectrum of PND rather than entirely separate postoperative events [5, 6]. Recent evidence has further suggested that POD is not only an important short-term postoperative complication but may also be linked to subsequent cognitive decline and other adverse postoperative outcomes [4, 6]. It is therefore clinically plausible that preoperative psychological symptoms may influence delayed postoperative cognitive recovery partly through increasing the risk of POD. However, evidence specifically examining the mediating role of POD in the association between preoperative psychological symptoms and DNR remains limited.

Accordingly, in this prospective cohort study, we investigated the associations of preoperative anxiety and depression with POD and DNR in older adults undergoing elective OPCABG. We further examined whether POD mediated the relationship between preoperative psychological symptoms and DNR. We hypothesized that preoperative anxiety and depression would be associated with increased risks of both POD and DNR, and that POD would partially mediate the association between preoperative psychological symptoms and delayed postoperative cognitive recovery.

Methods

Study design and participants

This was a single-centre prospective observational cohort study. Consecutive patients scheduled to undergo elective off-pump coronary artery bypass grafting at the Second Hospital of Hebei Medical University between January 2024 and December 2024 were screened for eligibility. The study protocol was approved by the Institutional Ethics Committee of the Second Hospital of Hebei Medical University (approval No. 2023-R628) and registered with the Chinese Clinical Trial Registry (ChiCTR2300079246; registered on 28 December 2023). The study was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all participants before enrolment.

Patients were eligible if they met all of the following criteria: (1) age 60 years or older; (2) scheduled for elective OPCABG; and (3) willingness to participate and provide written informed consent. Patients were excluded if they had (1) previously diagnosed dementia or cognitive impairment that precluded cooperation with cognitive assessment; (2) severe psychiatric illness requiring specialist treatment; or (3) severe visual or hearing impairment that prevented completion of study-related assessments. Patients were further excluded after enrollment if (1) surgery was cancelled for any reason; (2) they withdrew consent or refused further participation after surgery; (3) reoperation was required; (4) off-pump surgery was converted to on-pump surgery intraoperatively; or (5) they died during follow-up.

Data collection

Study data were collected through the electronic medical record system, anaesthesia records, surgical records, bedside assessments, and follow-up visits. Baseline data were collected one day before surgery

and included demographic characteristics, body mass index, years of education, occupational and marital information, comorbidities, surgical history, American Society of Anesthesiologists physical status, medication use, sleep quality, preoperative psychological symptoms, and baseline cognitive function.

Intraoperative variables were extracted from anaesthesia and surgical records and included the number of grafts, duration of surgery, duration of anaesthesia, intraoperative blood pressure and its fluctuation range, episodes and duration of hypotension, core temperature, doses of sedative and analgesic agents, intraoperative blood loss, and autologous and allogeneic transfusion volumes.

Postoperative variables were obtained from bedside assessment, electronic medical records, and follow-up and included postoperative complications, duration of intensive care unit stay, postoperative hospital stay, total hospital stay, postoperative transfusion, inflammatory markers, pain scores, delirium severity and duration, and repeated cognitive assessments. Venous blood samples were collected on postoperative days 1, 3, and 5 to assess routine laboratory indicators, inflammatory markers, and myocardial enzymes. Pain at rest and during activity was assessed on postoperative days 1–5 using a visual analogue scale (VAS), and the mean postoperative pain score was calculated for subsequent analyses.

Assessments

All study assessments, including preoperative psychological and sleep assessments as well as postoperative delirium and cognitive assessments, were performed face to face by trained research personnel according to a prespecified study protocol. Before study initiation, all assessors received standardised training to ensure consistency in administration, interviewing, scoring, and outcome ascertainment. Assessments were conducted at predefined time points and, whenever feasible, in a quiet environment to enhance reliability. To minimise assessment bias, preoperative psychological assessments and postoperative outcome assessments were performed by different trained assessors. Assessors responsible for postoperative delirium and postoperative cognitive outcome assessments were blinded to the results of the preoperative anxiety and depression assessments, whereas personnel conducting the preoperative psychological assessments were not involved in postoperative outcome evaluation.

Assessment of preoperative anxiety and depression

Preoperative anxiety and depression were assessed one day before surgery using the Hospital Anxiety and Depression Scale (HADS) [25]. A HADS-A score of ≥ 8 indicated anxiety, and a HADS-D score of ≥ 8 indicated depression [25].

Assessment of sleep quality

Preoperative sleep quality during the 28 days before surgery was assessed using the Pittsburgh Sleep Quality Index (PSQI) [26]. Higher total scores indicate poorer sleep quality [26].

Assessment of postoperative delirium

Patients were screened for postoperative delirium twice daily from postoperative day 1 to day 7, between 08:00–10:00 and 18:00–20:00. During intensive care unit stay, delirium was assessed using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [27], and after transfer to the general ward, it was assessed using the 3-Minute Diagnostic Interview for CAM-defined Delirium (3D-CAM) [28]. POD was diagnosed if criteria were met at any postoperative assessment during the observation period. Delirium severity was assessed using the CAM-S Short Form [29], and delirium duration was recorded as the number of days from onset to resolution [29].

Cognitive assessment and definition of DNR

Cognitive function was assessed using the Montreal Cognitive Assessment-Basic (MoCA-B) [22] one day before surgery and on postoperative day 28. In accordance with the 2018 recommendations on perioperative neurocognitive nomenclature, delayed neurocognitive recovery refers to delayed recovery of cognitive function within 30 days after surgery [5]. In the present study, DNR was defined as a decline of at least 4 points in the postoperative day-28 MoCA-B score relative to baseline [5, 23, 24]. For sensitivity analyses, a decline of 4–5 points was classified as milder DNR and a decline of ≥ 6 points as more severe DNR [23, 24].

Outcomes

The primary outcome was delayed neurocognitive recovery (DNR) on postoperative day 28. The secondary outcome was postoperative delirium (POD) occurring during postoperative days 1–7. A prespecified mediation analysis was additionally conducted to examine whether POD mediated the association between preoperative psychological symptoms and DNR.

Covariates

Covariates were selected a priori based on clinical relevance and previously reported risk factors for perioperative neurocognitive disorders. For the analysis of DNR, the adjusted covariates included sex, age, body mass index, years of education, drinking history, preoperative cognitive function, preoperative PSQI score, postoperative red blood cell transfusion, and POD. For the analysis of POD, the adjusted covariates included sex, age, body mass index, preoperative cognitive function, duration of surgery, time to extubation, and mean postoperative pain score.

Statistical analysis

All statistical analyses were performed using R software (version 4.3.3). A two-sided P value < 0.05 was considered statistically significant. Continuous variables with normal distribution were expressed as mean ± standard deviation and compared using the independent-samples t test. Non-normally distributed continuous variables were expressed as median (interquartile range) and compared using the Wilcoxon rank-sum test. Categorical variables were expressed as number (percentage) and compared using the chi-square test or Fisher's exact test, as appropriate.

Binary logistic regression models were used to evaluate the associations of preoperative psychological symptoms with POD and DNR. Results were reported as odds ratios (ORs) with 95% confidence intervals (CIs). In addition to the main analyses of preoperative anxiety and preoperative depression, stratified exposure analyses were performed using symptom categories, including anxiety only, depression only, and anxiety and/or depression, with patients without psychological symptoms as the reference group.

Mediation analysis

A prespecified mediation analysis was performed to evaluate whether POD mediated the association between preoperative psychological symptoms and DNR. A two-stage modeling strategy was used. In the first stage, logistic regression models were constructed with preoperative psychological symptoms as the exposure and POD as the mediator. In the second stage, logistic regression models were constructed with preoperative psychological symptoms and POD simultaneously entered as predictors of DNR.

Mediation effects were estimated using the mediation package in R. Nonparametric bootstrap resampling with 5000 repetitions was applied to estimate the indirect effect, direct effect, total effect, and their 95% confidence intervals. The mediation proportion was calculated as the indirect effect divided by the total effect. All mediation analyses were adjusted for the same covariates as those used in the primary DNR models. Additional models were further constructed for anxiety only, depression only, and anxiety and/or depression, using patients without psychological symptoms as the reference group, to assess the robustness of the mediation findings across different symptom categories.

Sensitivity analysis

To test the robustness of the findings, sensitivity analyses were conducted using a stricter threshold for postoperative cognitive decline. A decrease of 6 or more points in the MoCA-B score on postoperative day 28 relative to baseline was defined as significant cognitive decline, and binary logistic regression models were reconstructed accordingly. The same covariates as in the primary analyses were retained in the sensitivity analyses.

Sample size calculation

Sample size estimation was based on the primary objective of examining the association between preoperative psychological symptoms and DNR on postoperative day 28. Because both the primary exposure and primary outcome were binary variables, the sample size was estimated using the logistic regression method proposed by Hsieh et al. [30]. This method is suitable for regression analyses with

binary predictors and binary outcomes and can be used as the basis for sample size planning in prospective observational cohort studies. Since mediation analyses involving binary exposure, mediator, and outcome variables are more appropriately addressed through simulation-based approaches [31], mediation analysis was considered a secondary analysis in the present study and was powered on the basis of the primary association analyses.

Using the association between preoperative anxiety and DNR as an example, the pilot data suggested a preoperative anxiety prevalence of approximately 34.52%, a DNR incidence of approximately 30.0% among patients without anxiety, and an expected OR of 3.64. With a two-sided alpha of 0.05 and 80% power, the minimum required sample size was estimated to be 87 patients. Using the association between preoperative depression and DNR as another example, the prevalence of preoperative depression was approximately 26.79%, the DNR incidence among patients without depression was approximately 34.1%, and the expected OR was 3.56, yielding a minimum required sample size of 102 patients. After inflating the estimate by 30% to account for possible dropout, conversion to on-pump surgery, withdrawal, or missing key assessments, the final required sample size was at least 146 patients.

Results

Participant flow and baseline characteristics

A total of 213 older adults scheduled to undergo elective off-pump coronary artery bypass grafting were initially screened for eligibility. Thirteen patients who were converted to on-pump surgery intraoperatively and eight patients who died during follow-up were excluded. In addition, 24 patients were excluded because of missing postoperative delirium or postoperative cognitive assessment data. Ultimately, 168 patients were included in the final analysis. The participant selection process is shown in Fig. 1. Of these, 71 patients developed delayed neurocognitive recovery (DNR), corresponding to an incidence of 42.26%, whereas 97 did not.

In the overall cohort, 125 patients (74.40%) were male, and the median age was 67 (IQR, 63–70) years. Preoperative psychological symptoms were common. Fifty-eight patients (34.52%) met the criterion for preoperative anxiety, and 45 patients (26.79%) met the criterion for preoperative depression. In addition, 27 patients (16.07%) had anxiety only, 14 patients (8.33%) had depression only, and 72 patients (42.86%) had anxiety and/or depression.

Compared with patients without DNR, those who developed DNR were older [68 (65, 70) vs. 66 (62, 69) years, P = 0.002], were less likely to be male (64.79% vs. 81.44%, P = 0.015), had fewer years of education [7 (4, 9) vs. 8 (6, 9) years, P = 0.033], and were less likely to report a drinking history (7.04% vs. 18.56%, P = 0.032). They also had poorer preoperative sleep quality, reflected by higher PSQI scores [5 (3, 7) vs. 3 (1, 5), P = 0.006], and a higher prevalence of preoperative cognitive impairment (56.34% vs. 25.77%, P < 0.001).

Marked differences were also observed in preoperative psychological symptoms between the two groups. Patients who developed DNR had higher prevalences of anxiety (53.52% vs. 20.62%, $P < 0.001$), depression (40.85% vs. 16.49%, $P < 0.001$), anxiety only (26.76% vs. 8.25%, $P = 0.001$), depression only (14.08% vs. 4.12%, $P = 0.021$), and anxiety and/or depression (67.61% vs. 24.74%, $P < 0.001$) than those without DNR. No statistically significant differences were found between the two groups in other baseline variables, including preoperative hospital stay, body mass index, working status, smoking history, surgical history, anesthesia type, hypertension, diabetes, prior PCI, heart failure, atrial fibrillation, cerebral infarction, COPD, duration of coronary artery disease, or recent myocardial infarction (all $P > 0.05$).Demographic and baseline variables are shown in Table 1.

Table 1
Demographic and baseline variables

Variable	Total (n = 168)	No DNR (n = 97)	DNR (n = 71)	P value
Age, years, median (IQR)	67 (63, 70)	66 (62, 69)	68 (65, 70)	0.002
Male, n (%)	125 (74.40)	79 (81.44)	46 (64.79)	0.015
BMI, kg/m², mean ± SD	25.84 ± 3.05	25.65 ± 2.91	26.10 ± 3.24	0.349
Years of education, median (IQR)	8 (5, 9)	8 (6, 9)	7 (4, 9)	0.033
Smoking history, n (%)	68 (40.48)	41 (42.27)	27 (38.03)	0.580
Drinking history, n (%)	23 (13.69)	18 (18.56)	5 (7.04)	0.032
Currently working within the past 3 months, n (%)	47 (27.98)	28 (28.87)	19 (26.76)	0.764
Surgical history, n (%)	61 (36.31)	34 (35.05)	27 (38.03)	0.692
Neuraxial anesthesia, n (%)	17 (10.12)	12 (12.37)	5 (7.04)	0.258
General anesthesia, n (%)	29 (17.26)	16 (16.49)	13 (18.31)	0.758
Preoperative comorbidities				
Hypertension, n (%)	114 (67.86)	63 (64.95)	51 (71.83)	0.345
Diabetes mellitus, n (%)	58 (34.52)	31 (31.96)	27 (38.03)	0.414
History of PCI, n (%)	8 (4.76)	7 (7.22)	1 (1.41)	0.168
Heart failure, n (%)	6 (3.57)	2 (2.06)	4 (5.63)	0.417
Arrhythmia / atrial fibrillation, n (%)	3 (1.79)	2 (2.06)	1 (1.41)	1.000
Cerebral infarction, n (%)	35 (20.83)	18 (18.56)	17 (23.94)	0.396
COPD, n (%)	1 (0.60)	1 (1.03)	0 (0.00)	1.000
Recent myocardial infarction, n (%)	29 (17.26)	17 (17.53)	12 (16.90)	0.916
Duration of coronary artery disease				**0.414**
< 1 month, n (%)	53 (31.55)	27 (27.84)	26 (36.62)	
1 month to 1 year, n (%)	65 (38.69)	41 (42.27)	24 (33.80)	
> 1 year, n (%)	50 (29.76)	29 (29.90)	21 (29.58)	

Note: DNR, delayed neurocognitive recovery; BMI, body mass index; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease; PSQI, Pittsburgh Sleep Quality Index; HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale.

Variable	Total (n = 168)	No DNR (n = 97)	DNR (n = 71)	P value
Preoperative hospital stay, days, median (IQR)	12 (8, 16)	12 (8, 17)	12 (8, 16)	0.460
PSQI score, median (IQR)	4 (2, 7)	3 (1, 5)	5 (3, 7)	0.006
Preoperative cognitive impairment, n (%)	65 (38.69)	25 (25.77)	40 (56.34)	< 0.001
Anxiety (HADS-A ≥ 8), n (%)	58 (34.52)	20 (20.62)	38 (53.52)	< 0.001
Depression (HADS-D ≥ 8), n (%)	45 (26.79)	16 (16.49)	29 (40.85)	< 0.001
Anxiety only, n (%)	27 (16.07)	8 (8.25)	19 (26.76)	0.001
Depression only, n (%)	14 (8.33)	4 (4.12)	10 (14.08)	0.021
Anxiety and/or depression, n (%)	72 (42.86)	24 (24.74)	48 (67.61)	< 0.001

Note: DNR, delayed neurocognitive recovery; BMI, body mass index; PCI, percutaneous coronary intervention; COPD, chronic obstructive pulmonary disease; PSQI, Pittsburgh Sleep Quality Index; HADS-A, Hospital Anxiety and Depression Scale-Anxiety subscale; HADS-D, Hospital Anxiety and Depression Scale-Depression subscale.

Intraoperative characteristic

Comparison of intraoperative characteristics between the DNR and non-DNR groups showed no statistically significant differences in duration of anesthesia, duration of surgery, number of grafts, intraoperative hypotension, hypothermia, sufentanil dose, midazolam dose, blood loss, intraoperative plasma transfusion, intraoperative red blood cell transfusion, or intraoperative autologous blood transfusion (all P > 0.05).Intraoperative characteristics are shown in Table 2.

Table 2
Intraoperative characteristics

Variable	Total (n = 168)	No DNR (n = 97)	DNR (n = 71)	P value
Duration of anesthesia, min, median (IQR)	320 (300, 355)	320 (300, 355)	320 (300, 350)	0.923
Duration of surgery, min, median (IQR)	255 (230, 285)	255 (230, 285)	255 (230, 282)	0.606
Number of grafts, median (IQR)	3 (3, 4)	3 (3, 4)	3 (3, 4)	0.494
Hypotension, n (%)	60 (35.7)	36 (37.1)	24 (33.8)	0.780
Hypothermia, n (%)	27 (16.1)	12 (12.4)	15 (21.1)	0.189
Sufentanil dose, μg, median (IQR)	300 (238, 355)	295 (240, 350)	300 (227, 360)	0.469
Midazolam dose, mg, median (IQR)	1 (1, 2)	1 (1, 2)	1 (1, 2)	0.620
Blood loss, mL, median (IQR)	400 (300, 500)	400 (300, 500)	350 (300, 425)	0.374
Intraoperative plasma transfusion, mL, median (IQR)	400 (350, 600)	400 (350, 550)	400 (350, 600)	0.463
Intraoperative red blood cell transfusion, U, median (IQR)	0 (0, 0)	0 (0, 0)	0 (0, 0)	0.970
Intraoperative autologous blood transfusion, mL, median (IQR)	375 (250, 500)	375 (250, 625)	375 (250, 500)	0.361

Note: DNR, delayed neurocognitive recovery.

Postoperative characteristics

Comparison of postoperative characteristics between the DNR and non-DNR groups showed that the incidence of postoperative delirium was significantly higher in the DNR group than in the non-DNR group (56.34% vs. 21.65%, P < 0.001), and the duration of POD was also longer [1 (0, 3) vs. 0 (0, 0) days, P < 0.001]. Postoperative characteristics are shown in Table 3.In addition, postoperative red blood cell transfusion was greater in the DNR group than in the non-DNR group [3 (2, 4) U vs. 2 (2, 4) U, P = 0.010]. No statistically significant differences were observed between the two groups in time to extubation, ICU length of stay, postoperative plasma transfusion, mean postoperative pain score, number of postoperative complications, postoperative hospital stay, or total hospital stay (all P > 0.05).

Table 3
Postoperative characteristics

Variable	Total (n = 168)	No DNR (n = 97)	DNR (n = 71)	P value
Time to extubation, h, median (IQR)	18 (16, 20)	18 (16, 20)	18 (17, 19)	0.951
ICU length of stay, h, median (IQR)	66 (43, 68)	62 (42, 67)	66 (43, 70)	0.244
Postoperative red blood cell transfusion, U, median (IQR)	2 (2, 4)	2 (2, 4)	3 (2, 4)	0.010
Postoperative plasma transfusion, mL, median (IQR)	800 (587, 1200)	800 (450, 1150)	800 (600, 1200)	0.146
Mean postoperative pain score, median (IQR)	3 (2, 4)	3 (2, 4)	3 (2, 4)	0.782
Duration of POD, days, median (IQR)	0 (0, 2)	0 (0, 0)	1 (0, 3)	< 0.001
Number of postoperative complications, median (IQR)	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.416
POD, n (%)	61 (36.3)	21 (21.6)	40 (56.3)	< 0.001
Postoperative hospital stay, days, median (IQR)	8 (7, 10)	8 (7, 9)	8 (7, 10)	0.139
Total hospital stay, days, median (IQR)	20 (15, 25)	21 (15, 25)	19 (16, 25)	0.504

Note: DNR, delayed neurocognitive recovery; ICU, intensive care unit; POD, postoperative delirium.

Association between preoperative psychological symptoms and postoperative delirium

Postoperative delirium occurred in 61 of 168 patients (36.31%). In multivariable logistic regression analyses adjusted for sex, age, body mass index, baseline cognitive function, duration of surgery, time to extubation, and mean postoperative pain score, preoperative anxiety was significantly associated with an increased risk of POD (OR 3.87, 95% CI 1.97–7.58; P < 0.001). Preoperative depression was also independently associated with POD (OR 2.94, 95% CI 1.35–6.37; P = 0.006).The multivariable logistic regression results for the associations between preoperative psychological symptoms and postoperative delirium are presented in Table 4.

Table 4
Multivariable logistic regression analysis of preoperative psychological symptoms and postoperative delirium

Group	β	S.E.	Z	P value	OR (95% CI)
Main analysis					
Preoperative anxiety	1.35	0.34	3.93	< 0.001	3.87 (1.97–7.58)
Preoperative depression	1.08	0.40	2.73	0.006	2.94 (1.35–6.37)
Stratified analysis					
No preoperative anxiety or depression	Reference				
Anxiety only	1.55	0.53	2.94	0.003	4.71 (1.68–13.22)
Depression only	1.53	0.66	2.32	0.020	4.62 (1.27–16.82)
Anxiety and/or depression	1.81	0.40	4.55	< 0.001	6.08 (2.80-13.23)

Note: Adjusted for sex, preoperative cognitive function, age, BMI, duration of surgery, time to extubation, and mean postoperative pain score. POD, postoperative delirium; CI, confidence interval.

In stratified exposure analyses using patients without anxiety or depression as the reference group, anxiety only was associated with higher odds of POD (OR 4.71, 95% CI 1.68–13.22; P = 0.003), as was depression only (OR 4.62, 95% CI 1.27–16.82; P = 0.020). The strongest association was observed for anxiety and/or depression, with an adjusted OR of 6.08 (95% CI 2.80–13.23; P < 0.001). These findings indicate that preoperative psychological symptoms were independently associated with POD after OPCABG, with a particularly pronounced association in patients presenting with anxiety and/or depression.

Association between preoperative psychological symptoms and delayed neurocognitive recovery

DNR was identified in 71 of 168 patients (42.26%). In multivariable logistic regression analyses adjusted for sex, age, body mass index, years of education, drinking history, preoperative cognitive function, postoperative delirium, preoperative PSQI score, and postoperative red blood cell transfusion, preoperative anxiety was independently associated with DNR (OR 2.41, 95% CI 1.06–5.48; P = 0.037). Preoperative depression was likewise independently associated with DNR (OR 2.53, 95% CI 1.05–6.08; P = 0.038).The multivariable logistic regression results for the associations between preoperative psychological symptoms and delayed neurocognitive recovery are presented in Table 5.

Table 5
Multivariable logistic regression analysis of preoperative psychological symptoms and delayed neurocognitive recovery

Group	β	S.E.	Z	P value	OR (95% CI)
Main analysis					
Preoperative anxiety	0.88	0.42	2.09	0.037	2.41 (1.06–5.48)
Preoperative depression	0.93	0.45	2.08	0.038	2.53 (1.05–6.08)
Stratified analysis					
No preoperative anxiety or depression	Reference				
Anxiety only	1.17	0.56	2.09	0.037	3.23 (1.08–9.68)
Depression only	1.77	0.76	2.31	0.021	5.85 (1.31–26.08)
Anxiety and/or depression	1.56	0.44	3.56	< 0.001	4.75 (2.01–11.19)

Note: Adjusted for sex, drinking history, preoperative cognitive function, postoperative delirium, age, years of education, BMI, preoperative PSQI score, and postoperative red blood cell transfusion. DNR, delayed neurocognitive recovery; CI, confidence interval

When symptom categories were analyzed using patients without psychological symptoms as the reference group, anxiety only was associated with increased odds of DNR (OR 3.23, 95% CI 1.08–9.68; P = 0.037), depression only with even higher odds (OR 5.85, 95% CI 1.31–26.08; P = 0.021), and anxiety and/or depression with markedly increased odds overall (OR 4.75, 95% CI 2.01–11.19; P < 0.001). Overall, these results suggest that different forms of preoperative psychological symptoms were all associated with poorer cognitive recovery after surgery, with larger effect sizes observed for depression only and for the combined anxiety/depression exposure category.

Mediation analysis

Mediation analysis was performed to examine whether postoperative delirium mediated the association between preoperative psychological symptoms and delayed neurocognitive recovery. In the model for preoperative anxiety, the indirect effect mediated through postoperative delirium was 0.05 (95% CI, 0.02–0.10), the direct effect was 0.14 (95% CI, 0.02–0.26), and the total effect was 0.19 (95% CI, 0.03–0.32). The proportion mediated was 27.88% (95% CI, 4.85%–33.33%), indicating that postoperative delirium partially mediated the association between preoperative anxiety and delayed neurocognitive recovery.

Similarly, in the model for preoperative depression, the indirect effect mediated through postoperative delirium was 0.06 (95% CI, 0.02–0.11), the direct effect was 0.14 (95% CI, 0.02–0.27), and the total effect

was 0.20 (95% CI, 0.04–0.33). The proportion mediated was 27.45% (95% CI, 9.09%–40.00%), suggesting that postoperative delirium also partially mediated the association between preoperative depression and delayed neurocognitive recovery.

Further stratified mediation analyses were performed using patients without preoperative anxiety or depression as the reference group. For patients with anxiety only, the indirect effect was 0.06 (95% CI, 0.01–0.12), the direct effect was 0.18 (95% CI, 0.01–0.33), the total effect was 0.24 (95% CI, 0.03–0.39), and the proportion mediated was 25.00% (95% CI, 8.33%–45.45%). For patients with depression only, the indirect effect was 0.07 (95% CI, 0.02–0.15), the direct effect was 0.26 (95% CI, 0.05–0.43), the total effect was 0.33 (95% CI, 0.07–0.50), and the proportion mediated was 20.00% (95% CI, 7.14%–50.00%). For patients with anxiety and/or depression, the indirect effect was 0.06 (95% CI, 0.01–0.13), the direct effect was 0.25 (95% CI, 0.14–0.38), the total effect was 0.31 (95% CI, 0.22–0.49), and the proportion mediated was 17.07% (95% CI, 3.23%–31.48%).

Overall, these findings consistently indicate that postoperative delirium partially mediated the associations between preoperative psychological symptoms and delayed neurocognitive recovery.The mediation analysis results are presented in Table 6.

Table 6
Mediation analysis of postoperative delirium in the association between preoperative psychological symptoms and delayed neurocognitive recovery

Group	Indirect effect (95% CI)	Direct effect (95% CI)	Total effect (95% CI)	Mediation proportion
Main analysis				
Anxiety	0.05 (0.02–0.10)	0.14 (0.02–0.26)	0.19 (0.03–0.32)	27.88%
Depression	0.06 (0.02–0.11)	0.14 (0.02–0.27)	0.20 (0.04–0.33)	27.45%
Stratified analysis				
No preoperative anxiety or depression	Reference			
Anxiety only	0.06 (0.01–0.12)	0.18 (0.01–0.33)	0.24 (0.03–0.39)	25.00%
Depression only	0.07 (0.02–0.15)	0.26 (0.05–0.43)	0.33 (0.07–0.50)	20.00%
Anxiety and/or depression	0.06 (0.01–0.13)	0.25 (0.14–0.38)	0.31 (0.22–0.49)	17.00%

Note: Bootstrap mediation analysis with 5000 resamples. Indirect, direct, and total effects are presented in standardized decimal format. Mediation proportion is shown as a percentage. HADS cutoffs were standardized to HADS-A ≥ 8 and HADS-D ≥ 8 for consistency with the Methods section.

Sensitivity analysis

Sensitivity analyses were performed by classifying DNR into milder and more severe cognitive decline. In the main analyses, preoperative anxiety was associated with both mild DNR (OR 2.41, 95% CI 1.01–5.78; P = 0.050) and severe DNR (OR 5.38, 95% CI 1.24–23.28; P = 0.024). Preoperative depression was also associated with mild DNR (OR 2.59, 95% CI 1.01–6.62; P = 0.047) and severe DNR (OR 4.52, 95% CI 1.12–18.22; P = 0.034).

In stratified exposure analyses, anxiety only was associated with mild DNR (OR 3.17, 95% CI 1.02–9.83; P = 0.046), but not severe DNR (OR 3.00, 95% CI 0.52–17.18; P = 0.217). Depression only was associated with mild DNR (OR 5.80, 95% CI 1.24–27.13; P = 0.025), whereas its association with severe DNR did not reach statistical significance (OR 9.29, 95% CI 0.72–120.16; P = 0.088). Anxiety and/or depression was associated with both mild DNR (OR 4.83, 95% CI 1.94–12.03; P < 0.001) and severe DNR (OR 9.15, 95% CI 1.99–42.09; P = 0.004). These findings generally support the robustness of the primary results and suggest that the associations between preoperative psychological symptoms and postoperative cognitive decline may be stronger for more severe DNR.The sensitivity analysis results are presented in Table 7.

Table 7
Sensitivity analysis of the association between preoperative psychological symptoms and different degrees of delayed neurocognitive recovery

Group	Mild DNR OR (95% CI)	P value	Severe DNR OR (95% CI)	P value
Main analysis				
Anxiety	2.41 (1.01–5.78)	0.050	5.38 (1.24–23.28)	0.024
Depression	2.59 (1.01–6.62)	0.047	4.52 (1.12–18.22)	0.034
Stratified analysis				
No symptoms	Reference			
Anxiety only	3.17 (1.02–9.83)	0.046	3.00 (0.52–17.18)	0.217
Depression only	5.80 (1.24–27.13)	0.025	9.29 (0.72-120.16)	0.088
Anxiety and/or depression	4.83 (1.94–12.03)	< 0.001	9.15 (1.99–42.09)	0.004

Note: Mild DNR was defined as a 4-5-point decline in the postoperative day-28 MoCA-B score from baseline; severe DNR was defined as a decline of ≥ 6 points. Models were adjusted for sex, age, BMI, years of education, drinking history, postoperative delirium, preoperative PSQI score, and postoperative red blood cell transfusion.

Discussion

In this prospective cohort study of older adults undergoing elective off-pump coronary artery bypass grafting, we found that preoperative psychological symptoms were common and were significantly associated with both postoperative delirium and delayed neurocognitive recovery. After adjustment for relevant covariates, both preoperative anxiety and preoperative depression were independently associated with increased odds of POD and DNR, and similar patterns were observed in the stratified analyses of anxiety only, depression only, and anxiety and/or depression. Importantly, mediation analysis further showed that POD partially mediated the associations between preoperative anxiety and DNR and between preoperative depression and DNR, accounting for 27.88% and 27.45% of the total effects, respectively. These findings extend previous evidence linking preoperative anxiety or depression with postoperative delirium in older surgical and cardiac surgical populations [13–19], and are also broadly consistent with literature suggesting that psychological vulnerability before surgery may contribute to adverse postoperative cognitive outcomes [9–12]. By focusing specifically on older patients undergoing OPCABG, our study adds evidence that even in a surgical setting that avoids cardiopulmonary bypass, preoperative psychological symptoms remain clinically relevant correlates of perioperative neurocognitive vulnerability [5, 13, 21].

Several mechanisms may explain why preoperative psychological symptoms were associated with increased risks of POD and DNR in the present study. First, anxiety and depression are closely linked to dysregulation of the stress response system, including activation of the hypothalamic–pituitary–adrenal axis and sympathetic nervous system, which may increase perioperative vulnerability to acute brain dysfunction [9, 10]. Second, preoperative psychological symptoms are often accompanied by sleep disturbance, increased pain sensitivity, reduced cognitive reserve, and other geriatric vulnerabilities, all of which may compromise the ability of older patients to tolerate the physiological stress of major surgery [10, 12]. Third, accumulating evidence suggests that neuroinflammation plays a central role in perioperative neurocognitive disorders. Surgical trauma, anesthetic exposure, blood–brain barrier disruption, microglial activation, and systemic inflammatory responses may together trigger central nervous system inflammation, thereby contributing to delirium and subsequent cognitive decline [11, 12, 21]. Within this framework, preoperative anxiety and depression may function as predisposing factors that amplify the brain's susceptibility to perioperative inflammatory and stress-related insults.

Our mediation findings further support the possibility of a staged pathway linking preoperative psychological symptoms to later postoperative cognitive impairment. POD is an acute and fluctuating form of postoperative brain dysfunction and has been consistently associated with worse short- and long-term cognitive outcomes [5, 21]. In the present study, POD accounted for approximately 27% of the total association between preoperative anxiety or depression and DNR, suggesting that delirium may be an important intermediate clinical process linking preoperative psychological symptoms and delayed cognitive recovery. At the same time, because a substantial direct effect remained after accounting for POD, the pathway from preoperative psychological symptoms to DNR is likely multifactorial. In other words, POD may be one important mediator, but not the only one. Other mechanisms, such as persistent sleep disruption, postoperative pain burden, inflammatory activation, and reduced postoperative rehabilitation engagement, may also contribute to delayed cognitive recovery [10–12, 21].

The present findings have several clinical implications. First, preoperative anxiety and depression are common, measurable, and potentially modifiable, making them clinically relevant targets for perioperative risk stratification in older adults undergoing OPCABG. Brief preoperative screening using tools such as the HADS may help identify patients at increased risk of POD and DNR before surgery [13–19]. Second, our results suggest that perioperative brain health management should not focus solely on intraoperative and postoperative factors, but should also incorporate preoperative psychological assessment into multidisciplinary care pathways. For patients with evident psychological symptoms, closer delirium surveillance, optimization of sleep, pain control, communication, early mobilization, and individualized perioperative support may be particularly important [5, 13, 21]. Third, the partial mediating role of POD suggests that prevention, early recognition, and timely management of delirium may help reduce subsequent cognitive deterioration, even if they do not completely eliminate the adverse cognitive effects associated with preoperative psychological symptoms. From a practical perspective, this supports a dual-target approach: addressing preoperative psychological vulnerability while simultaneously strengthening POD prevention strategies during the early postoperative period. Taken together, our findings indicate that preoperative psychological symptoms should be viewed not merely as background emotional states, but as clinically meaningful markers of perioperative neurocognitive vulnerability in older cardiac surgical patients [9–13, 21].

This study has several strengths. First, we focused specifically on older adults undergoing elective off-pump coronary artery bypass grafting, which reduced heterogeneity related to different surgical procedures and avoided the additional cerebral burden associated with cardiopulmonary bypass exposure. This relatively homogeneous clinical setting may have allowed a clearer assessment of the associations between preoperative psychological symptoms and perioperative neurocognitive outcomes [5]. Second, the prospective cohort design ensured a relatively clear temporal sequence among exposure, mediator, and outcome, thereby strengthening the clinical interpretability of the observed associations. Third, key variables were assessed in a standardized manner: preoperative anxiety, depression, sleep quality, and baseline cognitive function were evaluated before surgery, POD was screened repeatedly during the early postoperative period, and DNR was assessed on postoperative day 28, which improved the consistency of outcome ascertainment [5, 13, 21]. Finally, beyond examining the independent associations of preoperative anxiety and depression with POD and DNR, we further performed mediation and stratified analyses, which provided a more nuanced understanding of the potential pathway linking preoperative psychological symptoms with postoperative cognitive recovery. Taken together, these features add to the clinical relevance of our findings in the context of perioperative brain health in older cardiac surgical patients [13–21].

Several limitations should be acknowledged. First, this was a single-center prospective observational study with a relatively modest sample size. In particular, the numbers of patients in the anxiety-only and depression-only subgroups were limited, resulting in relatively wide confidence intervals for some stratified estimates. Therefore, these subgroup findings should be interpreted with caution and require confirmation in larger multicenter cohorts. Second, anxiety, depression, and cognitive function were primarily assessed using screening instruments rather than comprehensive psychiatric evaluation or

formal neuropsychological test batteries. Although these tools are practical and clinically feasible, the identification of DNR in this study should be interpreted as research-oriented detection of postoperative cognitive decline rather than a definitive clinical diagnosis of postoperative neurocognitive disorder [5]. Third, although we adjusted for multiple clinically relevant confounders, residual confounding cannot be excluded. Unmeasured factors such as social support, pre-existing psychiatric history, perioperative sedative exposure, depth of sedation, inflammatory biomarkers, and postoperative rehabilitation engagement may also have influenced the observed associations [10–12, 21]. Fourth, the mediation analysis was conducted within an observational framework. Although the temporal order of preoperative psychological symptoms, POD, and DNR was clinically plausible, the mediation results should be interpreted as supporting a potential intermediary pathway rather than establishing definitive causality.

Conclusions

In older adults undergoing elective off-pump coronary artery bypass grafting, both preoperative anxiety and preoperative depression were independently associated with increased risks of postoperative delirium and delayed neurocognitive recovery. Postoperative delirium partially mediated the associations between preoperative psychological symptoms and delayed neurocognitive recovery, and the stratified analyses further supported this overall pattern. These findings suggest that preoperative psychological symptoms are clinically meaningful correlates of perioperative neurocognitive vulnerability in older cardiac surgical patients. Incorporating preoperative psychological screening into perioperative risk stratification, together with targeted delirium prevention and postoperative cognitive follow-up, may help inform perioperative brain health management [5, 13–21, 38, 39].

Abbreviations

CABG
Coronary artery bypass grafting
CI
Confidence interval
DNR
Delayed neurocognitive recovery
HADS
Hospital Anxiety and Depression Scale
ICU
Intensive care unit
MoCA-B
Montreal Cognitive Assessment-Basic
OPCABG
Off-pump coronary artery bypass grafting
OR
Odds ratio

PND
Perioperative neurocognitive disorders
POD
Postoperative delirium
PSQI
Pittsburgh Sleep Quality Index
VAS
Visual analogue scale

Declarations

Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the Second Hospital of Hebei Medical University (approval number: 2023-R628). The study was prospectively registered with the Chinese Clinical Trial Registry (ChiCTR2300079246; registered on 28 December 2023). Written informed consent was obtained from all participants before enrollment. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

YL and SC contributed equally to this work. YL, SC and LH conceived and designed the study. YL, SC, RL and JL collected the data. YL performed the statistical analysis and drafted the manuscript. LH critically revised the manuscript. All authors read and approved the final manuscript.

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Authors' information

Not applicable.

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Figures

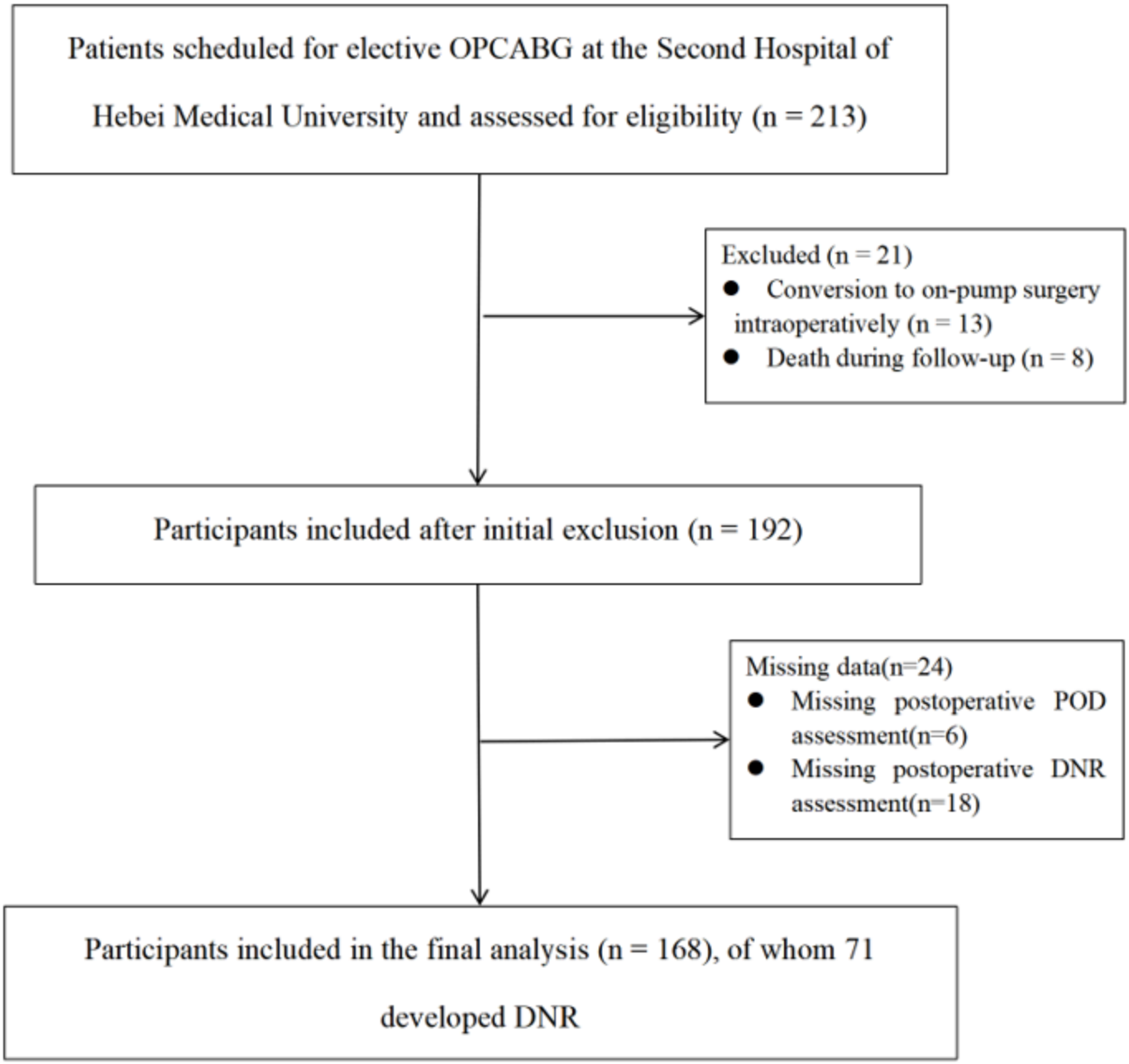


Figure 1

Flow diagram of patient screening, exclusion, and final inclusion in the analysis.