


Association Between Preoperative Psychological Symptoms and Chronic Postsurgical Pain in Older Patients Undergoing off-Pump Coronary Artery Bypass Grafting: Mediation Analysis of Acute Pain

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Purpose: This study aimed to investigate the association between preoperative psychological symptoms and chronic postsurgical pain (CPSP) in older patients undergoing off-pump coronary artery bypass grafting, and explore the mediating effect of acute postsurgical pain.

Patients and Methods: A total of 172 patients aged ≥ 60 years, undergoing off-pump CABG were enrolled. Preoperative anxiety and depression were assessed using the Hospital Anxiety and Depression Scale. Acute pain intensity was recorded daily (postoperative days 1–5), with time-weighted average (TWA) scores calculated. CPSP was defined as persistent pain at 3 months after surgery. Logistic regression evaluated associations between preoperative psychological symptoms (individually and by stratification) and CPSP. Mediation analysis explored the role of acute pain between preoperative psychological factors and CPSP.

Results: Prevalence of CPSP was 37.8% (29.1% mild, 8.7% moderate-to-severe). CPSP patients exhibited higher female proportion (36.9%, $P=0.012$), precordial pain (56.9%, $P=0.044$), anxiety (46.2%, $P<0.001$), depression (35.4%, $P<0.001$), and TWA scores (4.0 vs 3.0, $P<0.001$). Preoperative anxiety (OR = 3.64, $P = 0.002$) and depression (OR = 3.26, $P = 0.004$) independently predicted CPSP, with comorbid symptoms conferring higher risk (OR = 7.83, $P = 0.002$). Acute pain partially mediated anxiety-CPSP association (indirect effect: 7.7%; $P = 0.002$).

Conclusion: Preoperative anxiety and depression elevate CPSP risk in older off-pump CABG patients. Acute postsurgical pain partially mediates the anxiety-CPSP relationship. Integrated perioperative strategies targeting psychological health and pain management are critical to mitigate long-term pain outcomes.

Keywords: chronic postsurgical pain, preoperative psychological symptoms, mediation analysis, acute pain, aging

Introduction

Chronic postsurgical pain (CPSP), defined as persistent pain that develops or intensifies after surgical procedures and extends beyond the normal tissue healing period (typically >3 months),¹ represents a significant clinical challenge in postoperative recovery. The prevalence of CPSP varies substantially across different surgical types, and it is noteworthy that cardiac surgery involving a median sternotomy demonstrates a particularly high incidence rate, ranging from 29% to 50%.² In China, approximately 700,000 cardiac surgeries are performed annually, with coronary artery bypass grafting (CABG) being one of the predominant procedures. Notably, the majority of CABG patients are aged 60 years or older.³ Studies indicate that, although lower than in younger patients, the incidence of CPSP in older CABG patients remains at 35%,^{4,5} with symptoms frequently persisting for months to years postoperatively. CPSP not only contributes to delayed

postoperative functional recovery but is also strongly associated with chronic sleep disturbances, impaired immune function, and an elevated risk of suicidal ideation.^{6,7} These multifaceted consequences severely compromise quality of life while imposing substantial socioeconomic burdens on patients, their families, and healthcare systems.

Preoperative anxiety and depression, as common psychological symptoms, have been increasingly linked to adverse postoperative outcomes.^{8,9} However, the predictive role of these psychological factors in the development of CPSP remains controversial, particularly in cardiac surgery patients. For instance, a cohort study of 767 cardiac surgery patients identified depression as an independent risk factor for CPSP,¹⁰ whereas another study demonstrated preoperative anxiety correlates with CPSP without a significant link to depression.¹¹ Paradoxically, an observational study on CABG showed that preoperative psychological factors had no significant correlation with long-term CPSP.¹² Notably, the frequent co-occurrence of anxiety and depression—stemming from patients' preoperative psychophysiological vulnerability—complicates the differentiation of their distinct versus overlapping impacts on CPSP. Further prospective studies incorporating multidimensional psychological assessments and stratified analyses are warranted to elucidate the differential contributions of preoperative psychological factors to CPSP development following cardiac surgery.

Acute pain is a well-known risk factor for CPSP. Prior studies have shown that acute pain is an independent predictor of CPSP in cardiac surgery¹⁰ and is considered one of the most effective targets for clinical prevention. However, despite the implementation of multimodal analgesic strategies (eg, nerve block, combined use of multiple analgesics), 48.7% of patients experienced moderate to severe postsurgical acute pain.¹³ In recent years, a growing number of studies have investigated the relationship between preoperative psychological symptoms and acute pain. One study involving cardiac surgery patients found that each percentile increase in preoperative state anxiety resulted in an additional 0.068 mg of morphine being administered postoperatively.¹⁴ In spinal surgery, moderate to severe preoperative depression has been identified as an independent predictor of poor pain control within 24 hours after surgery.¹⁵ Given the established links between acute pain, preoperative psychological symptoms, and CPSP, we sought to investigate whether acute pain might mediate the association between preoperative psychological symptoms and CPSP.

Therefore, this study targeted elderly patients undergoing off-pump CABG surgery to investigate whether preoperative anxiety, depression and their coexistence are associated with subsequent CPSP risk. Additionally, we examined the mediating role of acute postsurgical pain in these associations, aiming to identify actionable targets for clinical intervention.

Material and Methods

Study Design and Participants

This study is a secondary analysis of a prospective cohort study that investigated the association between preoperative anxiety and perioperative neurocognitive disorders, as well as their influencing factors, in elderly patients undergoing CABG. Patients aged 60 years or older who underwent off-pump CABG at the Second Hospital of Hebei Medical University were enrolled between January and December 2024. Participants were recruited from hospital wards one day before surgery through face-to-face interviews conducted by trained investigators. Data collection included baseline demographics, assessments of psychological status (anxiety, depression, and sleep quality), and evaluations of cognitive function. Blood samples were collected preoperatively and on postoperative day 1 (POD 1). In-hospital follow-up was conducted daily from POD 1 to 7 to evaluate delirium, pain, and sleep quality, with repeat cognitive testing performed prior to discharge. A 30-day follow-up involved an in-person reassessment of cognitive function, while a 3-month follow-up used telephone interviews to assess both cognitive function and chronic pain. The study received approval from the Institutional Ethics Committee of the Second Hospital of Hebei Medical University (2023-R628) and was registered on the Chinese Clinical Trial Registry (ChiCTR2300079246). The study complied with the Declaration of Helsinki and written informed consent was obtained from all participants before enrollment.

A total of 213 patients were included in the main observational study. Among these, 13 patients were converted to on-pump procedures during surgery, and 8 patients died during the follow-up period. In this study, we excluded 9 patients due to missing preoperative Hospital Anxiety and Depression Scale data and 11 patients due to missing pain assessments

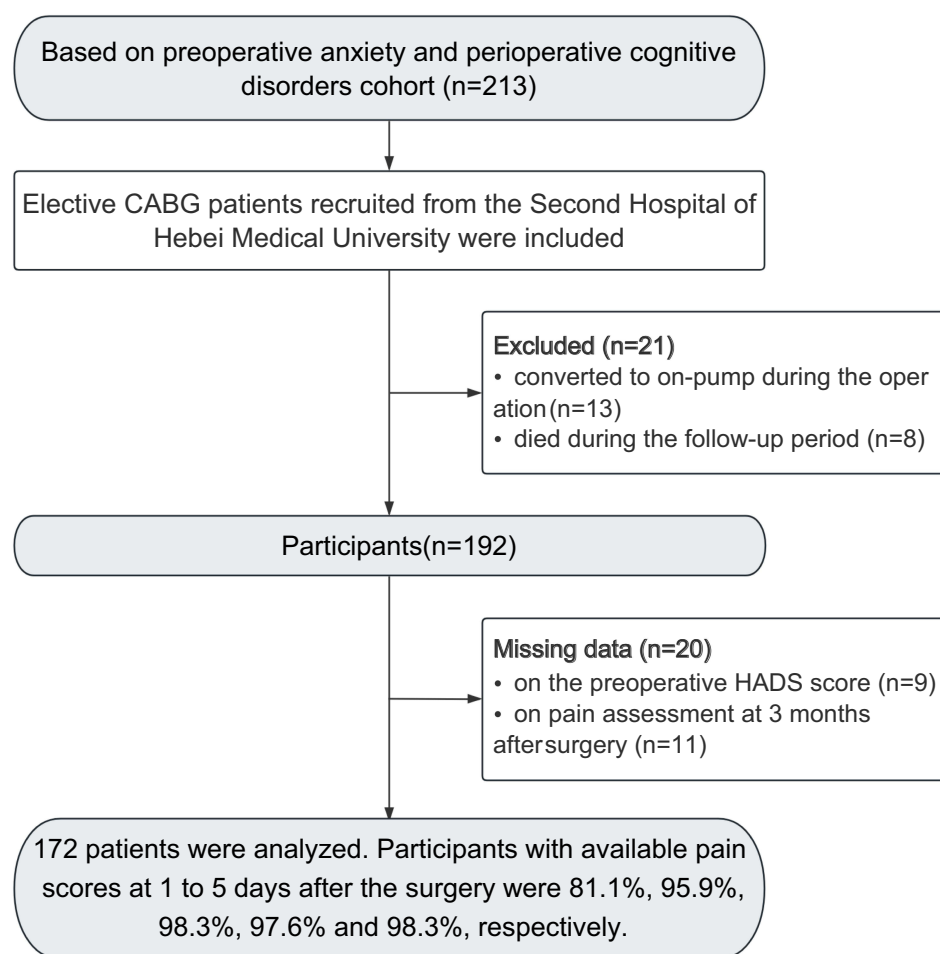


Figure 1 Flow chart of the study.

Abbreviations: CABG, Coronary Artery Bypass Grafting; HADS, the Hospital Anxiety and Depression Scale.

at 3 months after surgery. Finally, data from 172 patients were analyzed (Figure 1). The response rates for pain scores on postoperative days 1, 2, 3, 4, and 5 were 81.1%, 95.9%, 98.3%, 97.6%, and 98.3%, respectively.

Assessment and Outcomes

Patient demographic data were collected the day before surgery, including age, sex, body mass index (BMI), years of education, marital status and employment status, history of smoking and drinking, previous surgeries, and comorbidities (eg, hypertension, diabetes, heart failure, previous myocardial infarction, arrhythmia, and cerebrovascular disease). Additionally, data regarding the duration since CHD diagnosis, history of coronary interventions, precordial pain, and the type of preoperative medication were recorded. The patients' anxiety and depression levels, sleep quality, and cognitive function were also evaluated.

Anxiety and Depression Assessment

Preoperative anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS).¹⁶ The HADS is a widely used self-assessment instrument that consists of seven anxiety items (HADS-A) and seven depression items (HADS-D), with higher scores indicating more severe symptoms. Both HADS-A and HADS-D have demonstrated high sensitivity and specificity at a cutoff score of 7/8, making them suitable for elderly patients.¹⁷ Consequently, clinical anxiety and depression were defined as scores of ≥ 8 on HADS-A and HADS-D, respectively, in this study.

Sleep Quality Assessment

Sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI).¹⁸ The PSQI consists of 19 self-rated items and 5 additional items rated by a peer; however, only the self-rated items contribute to the final score. Among these, 18 items are grouped into 7 components. Each component is scored on a scale from 0 to 3, and the total PSQI score is calculated by summing the scores of all components.

Cognitive Function Assessment

Preoperative cognitive function was evaluated using the Montreal Cognitive Assessment-Basic (MoCA-B).¹⁹ This version, adapted for patients with lower levels of education, assesses the same core cognitive domains as the original MoCA, and it also demonstrates good sensitivity and specificity (>80%).

After the operation, surgical and postoperative variables were extracted via chart review. The surgical variables included the number of vascular grafts, operation time (in minutes), anesthesia time (in minutes), the presence of hypotension and hypothermia, morphine equivalent consumption, blood loss, and blood transfusion, while the postoperative variables encompassed cumulative morphine equivalent consumption over the first 5 postoperative days, postoperative complications, additional blood transfusions, extubation time (in hours), and duration of ICU stay (in hours).

Acute Postsurgical Pain Assessment

Acute postsurgical pain was measured using the NRS (0 to 10 rating scale) on each of the first five postoperative days. The initial pain assessment was conducted after tracheal extubation. On the subsequent days, assessments were performed at 10 a.m., with patients rating the intensity of their worst postsurgical pain since the previous assessment. The time-weighted average (TWA) pain score²⁰ was calculated by multiplying the time interval between two consecutive pain score measurements by the average of the corresponding pain scores, summing these products, and dividing by the total duration. The TWA was analyzed as the main mediator in the mediation analysis.

Chronic Postsurgical Pain Assessment

The primary outcome measure was the presence of chronic pain at 3 months after surgery. According to the International Association for the Study of Pain,¹ chronic postsurgical pain was defined as: 1) chronic pain that developed or intensified after surgery and persisted beyond tissue healing (more than 3 months), with a numeric rating scale (NRS) score ≥ 1 ; 2) pain localized to the surgical area, radiating to the innervated area, or referring to the skin or head (deep body and visceral tissues after surgery); 3) exclusion of other causes of pain, such as pre-existing pain conditions, infections, or malignancies. Patients were followed up by telephone to assess the presence and location of pain in the surgical area 3 months postoperatively. The NRS was used to evaluate the worst pain experienced. The degree of CPSP was defined by the NRS score: 0 (none), 1–3 (mild), ≥ 4 (moderate-to-severe). The 10-item Douleur Neuropathique 4 (DN4) Questionnaire was used to assess whether the nature of the chronic pain was consistent with neuropathic pain (NP), with a cutoff of 4 or greater.²¹ Finally, the Pain Self-Efficacy Questionnaire (PSEQ) was used to evaluate the impact of chronic pain on patients' lives.²² The PSEQ consists of 10 questions that assess the patient's confidence in performing activities such as housework, work, and socializing. Higher scores indicate greater confidence.

Statistical Analysis

Patients were divided into two groups based on the occurrence of CPSP. Continuous data with non-normal distribution were expressed as median (interquartile range [IQR]) and compared using the Wilcoxon test. Categorical data were expressed as number (percentage) and compared using the Chi-squared or Fisher's exact test. Logistic regression was used to analyze the associations between individual or categorical preoperative psychological symptoms and CPSP, adjusted for potential confounders, including sex, age, BMI, years of education, precordial pain, PSQI score before surgery, intraoperative hypothermia, and plasma infusion. Confounders for adjustment were selected based on prior studies and variables that showed significant differences in baseline comparisons.

A mediation analysis was conducted to assess whether and to what extent the TWA pain score mediated the association between preoperative psychological symptoms and CPSP. Three distinct effects were operationalized: The

indirect effect was defined as the difference in expected CPSP incidence when preoperative psychological symptoms were held constant while acute pain levels were modified as if the psychological symptom status had changed. The direct effect represented the difference in CPSP incidence when psychological symptoms were altered but acute pain levels were artificially maintained. The total effect, encompassing the complete impact of preoperative psychological symptoms on CPSP, was calculated as the sum of the direct and indirect effects. The analysis followed a two-stage modeling approach: First, a linear regression model was constructed with anxiety status (yes/no), depression status (yes/no), and psychological symptom categories (no symptoms, anxiety alone, depression alone, comorbid anxiety and depression) as independent variables, and TWA pain score as the dependent variable. Second, a logistic regression model was developed incorporating both preoperative psychological symptoms and TWA pain score as predictors of CPSP status. Effect estimates (total, indirect, and direct effects) with corresponding 95% confidence intervals (CIs) were obtained through nonparametric bootstrap resampling ($n = 5000$ iterations) using the ‘mediation’ package. All analyses were adjusted for the previously specified covariates through the mediation procedure.

Sensitivity analyses were performed using an ordinal regression model to assess the associations between preoperative psychological symptoms and CPSP severity. In addition, mediation analyses were conducted with acute pain as a mediator and CPSP severity as the outcome, adjusting for the aforementioned covariates. Additionally, exploratory analyses were carried out on patients who developed CPSP to investigate the potential influence of neuropathic pain components. Statistical significance was established at a two-tailed $P < 0.05$ threshold. All statistical procedures were implemented in R statistical software (version 4.3.1; The R Foundation for Statistical Computing).

A post hoc power analysis for logistic regression models was conducted using G*Power 3.1, given that the sample size determination was originally based on the primary study objectives. For preoperative anxiety (a binomial variable) with an OR of 3.64, a total sample size of 172, an R^2 of 0.225, and the $\alpha = 0.05$ (two-tailed), the analysis yielded a power of 0.908. Similarly, for preoperative depression (a binomial variable) with an OR of 3.26, a total sample size of 172, an R^2 of 0.153, and the $\alpha = 0.05$ (two-tailed), the analysis yielded a power of 0.821.

Results

Patient Characteristics

As detailed in Table 1, the majority of patients were male (73.8%), with median age 66 years (IQR, 60–70). Preoperative psychological evaluation revealed 30.2% ($n = 52$) of participants met criteria for clinical anxiety, while 22.7% ($n = 39$) exhibited depressive symptoms. According to the stratified analysis, 20.3% ($n = 35$) of the patients had anxiety alone and

Table 1 Baseline Data

	Total (n=172)	Participants with CPSP (n =65)	Participants with No CPSP (n = 107)	P-Value
Age in yrs., median (IQR)	66(60–70)	66(60–71)	66(60–70)	0.822
Female, n (%)	45(26.2)	24(36.9)	21(19.6)	0.012
BMI in kg/m ² , median (IQR)	25.7(23.7–27.8)	25.8(24.0–27.6)	25.6(23.3–28.3)	0.847
Years of education, median (IQR)	8(5–10)	7(4–9)	8(5–10)	0.182
Marital status (n, %)				
Married	168(97.7)	64(98.5)	104(97.2)	0.593
Death of a spouse	4(2.3)	1(1.5)	3(2.8)	
Working for the last 6 months (n, %)	47(27.3)	15(23.1)	32(29.9)	0.330
Smoking (n, %)	71(41.3)	25(38.5)	46(43.0)	0.559
Alcoholism (n, %)	23(13.4)	7(10.8)	16(15.0)	0.434
History of surgery (n, %)				
No history of surgery	119(69.2)	39(60.0)	80(74.8)	0.126
Surgery under general anesthesia	37(21.5)	18(27.7)	19(17.8)	
Surgery under local anesthesia	16(9.3)	18(12.3)	19(7.5)	

(Continued)

Table 1 (Continued).

	Total (n=172)	Participants with CPSP (n=65)	Participants with No CPSP (n=107)	P-Value
Medical history (n, %)				
Hypertension	118(68.6)	48(73.8)	68(63.6)	0.162
Diabetes	58(34.5)	25(38.5)	34(31.8)	0.370
Heart failure	9(5.2)	4(6.2)	5(4.7)	0.727
Old myocardial infarction	15(8.7)	5(7.7)	10(9.3)	0.709
Arrhythmia	5(2.9)	3(4.6)	2(1.9)	0.299
Cerebrovascular disease	36(20.9)	15(23.1)	21(19.6)	0.590
Diagnosis duration of CHD				
< one month	85(49.4)	33(58.0)	52(48.6)	0.388
One month to a year	38(22.1)	17(26.2)	21(19.6)	
> one year	49(28.5)	15(23.1)	34(31.8)	
After PCI surgery (n, %)	22(12.8)	10(15.4)	12(11.2)	0.427
Precordial pain (n, %)	81(47.1)	37(56.9)	44(41.1)	0.044
Recent myocardial infarction (n, %)	32(18.6)	11(16.9)	21(19.6)	0.742
Type of medication, median (IQR)	7(6–8)	6(6–8)	7(6–8)	0.988
Anxiety (HADS-A >7) (n, %)	52(30.2)	30(46.2)	22(20.6)	<0.001
Depression (HADS-D >7) (n, %)	39(22.7)	23(35.4)	16(15.0)	<0.001
Psychological symptoms (n, %)				
No symptoms	98(57.0)	23(35.4)	75(70.1)	<0.001
Anxiety alone	35(20.3)	19(29.2)	16(15.0)	
Depression alone	23(13.4)	13(20.0)	10(9.3)	
Combined anxiety and depression	16(9.3)	10(15.4)	6(5.6)	
Moca-B before surgery, median (IQR)	23(20–25)	22.5(20–25)	23(20–25)	0.944
PSQI before surgery, median (IQR)	4(2–6)	4(2–6)	4(2–6)	0.625

Notes: A *P* value < 0.05 was considered to indicate statistical significance.

Abbreviations: IQR, Interquartile Range; BMI, Body Mass Index; CHD, Coronary Heart Disease; PCI, Percutaneous Coronary Intervention; HADS-A, the Hospital Anxiety and Depression Scale-Anxiety; HADS-D, the Hospital Anxiety and Depression Scale-Depression; Moca-B, Montreal Cognitive Assessment Scale-Basic; PSQI, the Pittsburgh Sleep Quality Index.

13.4% (n = 23) had depression alone. The proportion of patients with combined anxiety and depression was 9.3% (n = 16). For cardiovascular manifestations, 47.1% (n = 81) of the patients suffered precordial pain at preoperative assessment, and 18.6% (n = 32) had documented acute myocardial infarction within the preceding 90-day period.

Patients were divided into two groups for comparison based on whether CPSP occurred. Patients with CPSP were more likely to be female (36.9%, *P* = 0.012) and experience preoperative precordial pain (56.9%, *P* = 0.044), anxiety (46.2%, *P* < 0.001) and depression (35.4%, *P* < 0.001) (Table 1). During the surgery, more patients with CPSP had hypothermia (23.1% vs 11.3%, *P* = 0.041) and less plasma was transfused (400 [200–463] vs 400 [400–600]; *P* = 0.024) than those without (Table 2). In the postoperative period, patients with CPSP had higher median TWA pain score within 5d (4.0 [IQR, 3.4–4.6] vs 3.0 [IQR, 2.4–3.9]; *P* < 0.001). For PSQI scores at POD 7, patients with CPSP had slightly higher scores than those without, but the difference did not reach statistical significance (9 [IQR, 6–12] vs 7 [IQR, 6–11]; *P* = 0.079) (Table 3).

Correlation Between Preoperative Psychological Symptoms and CPSP

The overall incidence of CPSP reached 37.8% (65/172), with 29.1% (50/172) classified as mild and 8.7% (15/172) as moderate-to-severe cases. In the Individual analysis, preoperative anxiety was associated with an increased odds of CPSP after adjusting for sex, age, BMI, years of education, precordial pain, PSQI before surgery, intraoperative hypothermia and plasma infusion (OR = 3.64; 95% CI, 1.68–7.89; *P* = 0.002). A comparable risk elevation emerged for preoperative depression (OR = 3.26; 95% CI, 1.47–7.24; *P* = 0.004) (Table 4). In the stratified analysis, compared with patients without psychological symptoms, a risk elevation of CPSP was observed among patients with anxiety alone (OR = 4.07;

Table 2 Intraoperative Data

	Total (n=172)	Participants with CPSP (n =65)	Participants with No CPSP (n = 107)	P-Value
Number of vascular grafts, median (IQR)	3(3–4)	3(3–4)	3(3–4)	0.444
Operation time (min), median (IQR)	255(230–285)	257.5(235–280)	255(230–290)	0.824
Anesthesia time (min), median (IQR)	320(300–355)	320(300–346.25)	320(295–360)	0.589
Hypotension (n, %)	60(34.9)	24(36.9)	36(33.6)	0.662
Hypothermia (n, %)	27(15.8)	15(23.1)	12(11.3)	0.041
Morphine equivalent consumption (mg), median (IQR)	320(265–370)	320(259–379)	320(265–365)	0.745
Blood loss (mL), median (IQR)	400(300–500)	400(300–400)	400(300–500)	0.475
Plasma transfusion (mL), median (IQR)	400(350–600)	400(200–463)	400(400–600)	0.024
Red cell transfusion (U), median (IQR)	0(0–0)	0(0–0)	0(0–0)	0.659
Autotransfusion (mL), median (IQR)	375(250–500)	375(250–500)	375(250–625)	0.954

Notes: morphine equivalent consumption was calculated: morphine (i.v.) 10mg=remifentanyl (i.v.) 100 mg=sufentanyl (i.v.) 10 mg=nalbuphine (i.v.) 10 mg=dizocin (i.v.) 10 mg=pentazocine (i.v.) 30 mg=tramadol (i.v.) 100 mg; A P value < 0.05 was considered to indicate statistical significance.

Abbreviation: IQR, Interquartile Range.

Table 3 Postoperative Data

	Total (n=172)	Participants with CPSP (n =65)	Participants with no CPSP (n = 107)	P-Value
TWA pain score within POD 5, median (IQR)	3.4(2.6–4.4)	4.0(3.4–4.6)	3.0(2.4–3.9)	<0.001
Cumulative morphine equivalent consumption during the POD 5 (mg), median (IQR)	180(120–198)	180(80–200)	180(165–255)	0.818
PSQI at POD 7, median (IQR)	8(5–11)	9(6–12)	7(6–11)	0.079
Postoperative complications (n, %)				
Pneumonia	49(28.5)	17(26.2)	32(29.9)	0.597
Pleural effusion	18(10.5)	5(7.7)	13(12.1)	0.354
Pneumothorax	5(2.9)	2(3.1)	3(2.8)	0.918
Wound infection	5(2.9)	2(3.1)	3(2.8)	0.918
Acute cerebral infarction	2(1.2)	1(1.5)	1(0.9)	0.720
Arrhythmia	2(1.2)	1(1.5)	1(0.9)	0.720
Intra-aortic balloon pump	2(1.2)	2(3.1)	0(0)	0.141
Re entering the ICU	3(1.7)	1(1.5)	2(1.9)	0.872
Postoperative blood transfusion, median (IQR)				
Red cell transfusion (U)	2(2–4)	2(2–4)	2(2–4)	0.583
Plasma transfusion (mL)	800(450–1200)	800(575–1200)	800(400–1150)	0.082
Albumin (g)	0(0–20)	0(0–20)	0(0–20)	0.838
Extubation time(h), median (IQR)	19(18–20)	19(18–24)	19(18–24)	0.114
Duration of ICU stay(h), median (IQR)	66(42–68)	66(44–84)	66(48–92)	0.844

Notes: morphine equivalent consumption was calculated: morphine (i.v.) 10mg=remifentanyl (i.v.) 100 mg=sufentanyl (i.v.) 10 mg=nalbuphine (i.v.) 10 mg=dizocin (i.v.) 10 mg=pentazocine (i.v.) 30 mg=tramadol (i.v.) 100 mg; A P value < 0.05 was considered to indicate statistical significance.

Abbreviations: TWA, Time-weighted Average; POD, Postoperative Day; IQR, Interquartile Range; PSQI, the Pittsburgh Sleep Quality Index; ICU, Intensive Care Unit.

95% CI, 1.64–10.06; $P = 0.002$), depression alone (OR = 4.14; 95% CI, 1.49–11.47; $P = 0.006$) and comorbid anxiety and depression (OR = 7.83; 95% CI, 2.10–29.16; $P = 0.002$). Sensitivity analyses incorporating CPSP severity gradients confirmed these associations, with marginally stronger effect estimates observed for moderate-to-severe CPSP compared with mild cases (Table 5).

Table 4 Association of Preoperative Psychological Symptoms with the Presence of CPSP

	Odds Ratio (95% CI)	P-Value
Individual analysis		
Anxiety	3.64(1.68–7.89)	0.002
Depression	3.26(1.47–7.24)	0.004
Stratified analysis		
No symptoms	Ref.	
Anxiety alone	4.07(1.64–10.06)	0.002
Depression alone	4.14(1.49–11.47)	0.006
Combined anxiety and depression	7.83(2.10–29.16)	0.002

Notes: Adjusted for sex, age, body mass index, years of education, precordial pain, the Pittsburgh Sleep Quality Index before surgery, intraoperative hypothermia and plasma infusion; A *P* value < 0.05 was considered to indicate statistical significance.

Abbreviations: CPSP, Chronic Postsurgical Pain; 95% CI, 95% Confidence Interval; Ref., Reference.

Table 5 Sensitivity Analysis of the Association of Preoperative Psychological Symptoms with the Severe of CPSP

	Mild CPSP		Moderate to Severe CPSP	
	Odds Ratio (95% CI)	P-Value	Odds Ratio (95% CI)	P-Value
Individual analysis				
Anxiety	2.73(1.19–6.27)	0.018	10.32(2.74–38.95)	<0.001
Depression	3.01(1.29–7.00)	0.011	4.01(1.14–14.14)	0.030
Stratified analysis				
No symptoms	Ref.		Ref.	
Anxiety alone	3.21(1.22–8.45)	0.018	10.76(2.07–55.80)	0.005
Depression alone	3.83(1.31–11.21)	0.014	6.78(1.05–43.68)	0.044
Combined anxiety and depression	5.58(1.37–22.82)	0.017	28.44(3.33–247.68)	0.002

Notes: Adjusted for sex, age, body mass index, years of education, precordial pain, the Pittsburgh Sleep Quality Index before surgery, intraoperative hypothermia and plasma infusion. A *P* value < 0.05 was considered to indicate statistical significance.

Abbreviations: CPSP, Chronic Postsurgical Pain; 95% CI, 95% Confidence Interval; Ref., Reference.

Mediation Analysis

In the adjusted analyses, preoperative anxiety (coefficient, 0.605; 95% CI, 0.259–0.951; *P* < 0.001; [Supplemental Table 1](#)) and preoperative depression (coefficient, 0.395; 95% CI, 0.020–0.770; *P* = 0.039; [Supplemental Table 2](#)), when analyzed individually, were both associated with acute pain, which, in turn, was associated with a higher incidence of CPSP ([Supplemental Table 3](#) and [Supplemental Table 4](#)). Mediation analysis revealed that the indirect effect of preoperative anxiety on CPSP mediated through acute pain was 7.7% (95% CI, 2.8%–14.0%; *P* = 0.002) after adjusting for covariates, accounting for 28.7% (95% CI, 9.8%–78.0%; *P* = 0.004) of the total effect. Similarly, the indirect effect of preoperative depression was 5.4% (95% CI, 0.4%–11.0%; *P* = 0.030), accounting for 21.6% (95% CI, 2.0%–66.0%; *P* = 0.036) of the total effect ([Table 6](#)).

In the stratified analysis, patients with anxiety alone (coefficient, 0.656; 95% CI, 0.259–1.054; *P* = 0.001) and those with both anxiety and depression (coefficient, 0.834; 95% CI, 0.260–1.407; *P* = 0.005) showed significant associations with acute pain, whereas no significant correlation was observed in those with depression alone (coefficient, 0.450; 95% CI, –0.013–0.914; *P* = 0.057; [Supplemental Table 5](#)). As observed in the individual analyses, acute pain was associated with a higher incidence of CPSP (OR, 1.849; 95% CI, 1.264–2.704; *P* = 0.002; [Supplemental Table 6](#)). Furthermore, mediation analysis revealed that the indirect effect of anxiety alone on CPSP, mediated through acute pain, was 7.3%

Table 6 Indirect, Direct, and Total Effect of Preoperative Psychological Symptoms with CPSP Mediated via Acute Pain

	Indirect Effect (95% CI)	Direct Effect (95% CI)	Total Effect (95% CI)	Proportion Mediated (95% CI)
Individual analysis				
Anxiety	7.7(2.8–14.0) **	19.2(1.8–35.0) *	26.9(10.3–42.0) **	28.7(9.8–78.0) **
Depression	5.4(0.4–11.0) *	19.5(2.8–37.0) *	24.9(7.0–42.0) **	21.6(2.0–66.0) *
Stratified analysis				
No symptoms	Ref.			
Anxiety alone	7.0(2.1–14.0) **	19.2(0.6–37.0) *	26.2(8.7–44.0) **	26.7(7.0–86.0) **
Depression alone	5.0(–0.1–11.0)	22.8(2.1–42.0) *	27.7(6.0–48.0) *	17.8(–2.6–60.0)
Combined anxiety and depression	9.0(2.0–18.0) **	30.5(3.9–52.0) *	39.5(14.9–58.0) **	22.8(4.6–74.0) **

Notes: Adjusted for sex, age, body mass index, years of education, precordial pain, the Pittsburgh Sleep Quality Index before surgery, intraoperative hypothermia and plasma infusion; *, $P < 0.05$; **, $P < 0.01$; A P value < 0.05 was considered to indicate statistical significance.

Abbreviations: CPSP, Chronic Postsurgical Pain; 95% CI, 95% Confidence Interval; Ref., Reference.

(95% CI, 2.3%–14.0%; $P = 0.004$), accounting for 26.8% (95% CI, 7.0%–86.0%; $P = 0.010$) of the total effect, whereas the indirect effect for patients with both anxiety and depression was 9.0% (95% CI, 2.0%–18.0%; $P = 0.005$), accounting for 22.8% (95% CI, 4.6%–74.0%; $P = 0.008$) of the total effect. No mediating role of acute pain was identified between depression alone and CPSP.

Sensitivity analyses using CPSP severity as the outcome confirmed the above mediation effect. Moreover, among patients with comorbid anxiety and depression, acute pain primarily mediated the development of moderate-to-severe CPSP. The proportion of mediation through acute pain was consistently higher for moderate-to-severe CPSP than for mild CPSP (Table 7).

Exploratory Analyses

NP is one of the principal types of CPSP following cardiac surgery; therefore, we conducted an exploratory analysis. The results showed that the incidence of NP was 41.5% (27/65), with the chest being the primary pain site (87.7%, 57/65). Patients with NP had a higher NRS score (3 [IQR, 2–4] vs 3 [IQR, 2–3]; $P = 0.030$) and a lower PSEQ score (54 [IQR, 52–56] vs 56 [IQR, 54–60]; $P = 0.004$) compared with those without (Table 8). In the adjusted analyses, NP was associated with worse pain (OR = 2.27; 95% CI, 1.18–4.35; $P = 0.014$) and lower self-efficacy (OR = 0.86; 95% CI, 0.76–0.97; $P = 0.016$; Table 8).

Discussion

Our study revealed that the presence of preoperative anxiety and depression in elderly off-pump CABG patients were associated with an increased risk of CPSP. Further analysis indicated that the relationship between preoperative anxiety and CPSP was partially mediated by acute postsurgical pain, although this mediation effect was modest. In contrast, the mediating role of acute pain in the association between preoperative depression and CPSP differed between individual and stratified analyses.

The incidence rates of preoperative anxiety and depression were 30.2% and 22.7%, respectively, consistent with previously reported prevalence in elderly cardiac surgery patients.^{8,23} Approximately one-tenth of patients exhibited both anxiety and depression, highlighting the complexity of preoperative psychological conditions. Although psychological symptoms are known to adversely affect recovery from cardiac surgery, evidence linking anxiety and depression with CPSP remains inconsistent.^{10,11} This inconsistency may be attributed to the physiological complexity of cardiac surgery; most procedures require cardiopulmonary bypass (CPB), which significantly impacts systemic inflammatory responses, organ perfusion, and coagulation function.²⁴ Current evidence identifies intraoperative CPB as an independent risk factor for CPSP;²⁵ however, previous studies that did not employ stratified analyses may have left potential confounding effects

Table 7 Sensitivity Analysis of the Indirect, Direct, and Total Effect of Preoperative Psychological Symptoms with CPSP Severity Mediated via Acute Pain

	Mild CPSP				Moderate to Severe CPSP			
	Indirect Effect (95% CI)	Direct Effect (95% CI)	Total Effect (95% CI)	Proportion Mediated	Indirect Effect (95% CI)	Direct Effect (95% CI)	Total Effect (95% CI)	Proportion Mediated
Individual analysis								
Anxiety	4.3(1.2–8.2) **	15.1(5.0–24.2) **	19.4(8.9–28.5) **	22.2	3.0(0.9–6.5) **	9.7(2.7–18.4) **	12.7(4.7–23.0) **	23.6
Depression	3.4(0.4–6.7) *	11.0(0.7–19.5) *	14.4(3.7–23.0) *	21.6	2.3(0.4–5.4) *	6.8(0.4–17.2) *	9.1(2.0–20.5) *	25.3
Stratified analysis								
No symptoms	Ref.				Ref.			
Anxiety alone	3.1(0.7–6.6) *	12.8(4.1–21.0) **	15.9(7.2–24.4) **	19.5	3.1(0.3–6.5) **	11.8(2.7–21.5) **	14.9(4.8–25.5) **	20.8
Depression alone	2.1(–0.3–5.4)	11.5(1.1–19.5) *	13.6(3.2–21.8) *	15.4	2.1(–0.2–5.1)	10.7(0.6–25.3) *	12.8(2.0–28.2) *	16.4
Combined anxiety and depression	3.4(–2.0–11.1)	13.3(0.8–19.8) *	16.7(5.1–22.9) **	20.4	6.0(1.3–12.5) **	19.3(1.9–40.2) *	25.3(5.8–48.1) **	23.7

Notes: Adjusted for sex, age, body mass index, years of education, precordial pain, the Pittsburgh Sleep Quality Index before surgery, intraoperative hypothermia and plasma infusion; *, $P < 0.05$; **, $P < 0.01$; A P value < 0.05 was considered to indicate statistical significance.
Abbreviations: CPSP, Chronic Postsurgical Pain; 95% CI, 95% Confidence Interval; Ref., Reference.

Table 8 Exploratory Analysis of Neuropathic Pain

	Total (n=65)	Participants with NP (n =27)	Participants with No NP (n = 38)	P-Value	Logistic Regression	
					OR (95% CI)	P-Value
NRS of the worst pain, median (IQR)	3(2–3)	3(2–4)	3(2–3)	0.028	2.27(1.18–4.35)	0.014
TWA pain score within POD 5, median (IQR)	4.00(3.38–4.86)	3.88(3.38–4.34)	4.43(3.31–4.91)	0.201	0.74(0.40–1.39)	0.349
Site of pain, n(%)						
Chest	57(87.7)	23(85.2)	34(89.5)	0.312	Ref.	
Leg	4(6.2)	1(3.7)	3(7.9)		0.48(0.04–6.34)	0.575
Both chest and leg	4(6.2)	3(11.1)	1(2.6)		3.89(0.27–56.69)	0.320
PSEQ score, median (IQR)	56(52–58)	54(52–56)	56(54–60)	0.004	0.86(0.76–0.97)	0.016

Notes: Adjusted for sex, age, body mass index, years of education, precordial pain, the Pittsburgh Sleep Quality Index before surgery, intraoperative hypothermia and plasma infusion. A P value < 0.05 was considered to indicate statistical significance.
Abbreviations: NP, Neuropathic Pain; OR, Odds Ratio; 95% CI, 95% Confidence Interval; NRS, Numerical Rating Scale; IQR, Interquartile Range; TWA, Time-weighted Average; POD, Postoperative Day; PSEQ, the Pain Self-Efficacy Questionnaire; Ref., Reference.

unaddressed. To minimize confounding by age, surgery type, and the use of CPB, our study focused on elderly patients undergoing off-pump cardiac surgery. In addition to analyzing the effects of anxiety and depression separately, we conducted a stratified analysis that further confirmed the association of preoperative anxiety and depression with CPSP, with patients exhibiting both conditions at higher risk for developing moderate to severe CPSP.

In our sample, approximately one-third of patients experienced varying degrees of pain at three months post-surgery, with about one-quarter reporting moderate to severe pain—a finding consistent with outcomes observed in other open-heart surgeries.^{10,26,27} Emerging evidence underscores the critical role of acute postsurgical pain as a modifiable risk factor for CPSP,^{7,10} a relationship that was also observed in our cohort. Unlike non-cardiac procedures, pain assessment in this population is complicated by prolonged ICU stays and variable timing of endotracheal extubation, which introduce significant temporal heterogeneity into conventional pain evaluations. To address this limitation, we employed the TWA pain score—a metric that integrates both pain intensity and duration—to more comprehensively quantify acute pain. The TWA pain score has been well established in clinical settings.^{20,28}

Mediation analysis revealed that acute pain acts as a significant mediator in the relationship between preoperative anxiety and CPSP. In contrast, the mediating effect of acute pain on the link between preoperative depression and CPSP showed contradictory results when comparing individual and stratified analyses: in stratified analyses, no statistically significant association was observed between preoperative depression and acute pain. This conflicting evidence regarding

the preoperative depression-acute pain relationship is reflected in previous studies: for instance, while preoperative anxiety demonstrated significant influence on postsurgical pain relief in abdominal surgery, preoperative depression showed no such effect;²⁹ conversely, both psychological factors were found to affect early postsurgical pain in bariatric surgery.³⁰ The inconsistency may also be attributed to the current study's limited sample size, necessitating further verification through large-scale multicenter studies. When interpreted with caution, our findings suggest distinct pathways: preoperative anxiety influences CPSP development through both direct and acute pain-mediated indirect effects, whereas preoperative depression's impact on CPSP appears predominantly direct. These insights underscore the importance of preoperative psychological interventions while proposing that a dual-strategy approach integrating psychological support with perioperative pain management may offer enhanced protection against CPSP—a hypothesis requiring further clinical validation. Similarly, the results may also inform the design of integrated care pathways involving anesthesiology, pain medicine, and mental health professionals. Multidisciplinary strategies that combine early psychological screening, targeted mental health interventions, and optimized perioperative analgesia could help reduce the transition from acute to chronic pain, ultimately improving both pain-related outcomes and overall postoperative recovery in elderly cardiac surgery patients.

The underlying mechanisms linking preoperative psychological symptoms to increased CPSP remain unclear. Mediation analyses suggest that preoperative anxiety may facilitate the conversion of acute pain into chronic pain through several pathways. Potential mechanisms include anxiety-induced hyperactivation of the sympathetic-adrenal axis leading to peripheral nociceptive sensitization;³¹ dysregulation of the hypothalamic-pituitary-adrenal axis, with excessive cortisol release crossing the blood-brain barrier to activate spinal glial cells and induce central sensitization in the dorsal horn;^{32,33} and anxiety-induced alterations in synaptic plasticity due to glutamatergic system dysfunction, which amplify the central transmission of acute pain signals.³⁴ In contrast, preoperative depression likely contributes to CPSP via mechanisms independent of acute pain mediation. Depressive symptoms may remodel central pain regulatory networks—manifesting as hyperexcitability of dorsal horn neurons or dysregulation of thalamo-cortical circuits—resulting in central sensitization and CPSP development.³⁵ Additionally, depression-induced neuroinflammation may provoke neuronal apoptosis, oxidative stress, and disruption of the blood-brain barrier, thereby directly facilitating the emergence of spontaneous pain and hyperalgesia.³⁶

This study has several limitations. First, the findings may be susceptible to chance variability due to the relatively small sample size in this study. Although a post hoc power analysis indicated sufficient statistical power (>80%), the results from stratified analyses should be interpreted with caution. Second, both psychological symptoms and pain outcomes were assessed via patient self-report. Despite standardized training of follow-up personnel, variability in patients' willingness or ability to accurately disclose their conditions may have introduced unmeasured bias. Additionally, the study did not evaluate other factors associated with CPSP, such as pre-existing chronic pain, pain catastrophizing, stress, or surgical fear, which could act as confounding variables. Finally, this single-center study recruited only older patients undergoing off-pump CABG, which limits the generalizability of the findings to broader surgical populations or clinical settings.

Conclusions

The study found that preoperative anxiety and depression, either independently or in combination, were associated with an increased risk of CPSP. Furthermore, acute pain was observed to partially mediate the relationship between preoperative anxiety and CPSP. These findings highlight the potential benefits of dual interventions targeting preoperative psychological symptoms and acute pain management, such as preoperative music therapy, mindfulness-based interventions, and relaxation training, together with perioperative multimodal analgesia, to prevent the development of chronic pain. Large-scale, multicenter studies are warranted to validate these findings.

Data Sharing Statement

The datasets supporting the findings of this study are accessible from the corresponding author on reasonable request.

Ethics Approval and Informed Consent

The prospective observational study adhered to the principles of the Declaration of Helsinki and received approval from the Institutional Ethics Committee of the Second Hospital of Hebei Medical University (2023-R628) and registered on the Chinese Clinical Trial Registry (ChiCTR2300079246). All participants provided written informed consent before enrollment.

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Disclosure

The authors report no conflicts of interest in this work.

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