

Preoperative Chronic Pain as a Risk Factor for Early Postoperative Cognitive Dysfunction in Elderly Patients Undergoing Hip Joint Replacement Surgery: A Prospective Observational Cohort Study

Xiaorong Huai

1.Second Affiliated Hospital of Soochow University. 2.Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital Jiaotong.

Yingfu Jiao

Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital

Xiyao Gu

Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital

Huichen Zhu

Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital

Lingke Chen

Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital

Bingwei Lu

Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital

Yichen Fan

Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital

Weifeng Yu

Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital

Diansan Su

Shanghai Jiao Tong University School of Medicine Affiliated Renji Hospital

Hong Xie (✉ hongxie2020@126.com)

The Second Affiliated Hospital of Soochow University <https://orcid.org/0000-0003-1190-5625>

Research

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Abstract

Background: Although there is high overall success rate of major joint replacement surgery, postoperative cognitive dysfunction (POCD) is a very common complication after surgery, increasing morbidity and mortality. Identifying POCD risk factors would be helpful to prevent and decrease the occurrence of POCD. We hypothesised that preoperative chronic pain increases the risk of POCD.

Methods: A single-centre, observational, prospective cohort study was conducted from January 2018 to March 2020. All consecutive elderly patients (>65 years) who underwent elective hemiarthroplasty or total hip arthroplasty with general anaesthesia by the same surgeon were enrolled. The patients underwent neuropsychological testing preoperatively and at 7 days and 2 months postoperatively. To determine POCD, a nonsurgical control group was recruited from the general community.

Results: Of the 141 patients who finished the neuropsychological testing 7 days after surgery, 61 (43.2%) had preoperative chronic pain. Of the 61 patients, 17 (27.9%) developed POCD; of the 79 patients with no chronic pain, 10 (12.7%) had developed POCD by 7 days after surgery. Multivariate logistic regression analysis identified preoperative chronic pain as a risk factor of POCD assessed 7 days after surgery (odds ratio, 3.335; $p = 0.022$). There was no significant difference in the POCD incidence 2 months after surgery between patients with and without preoperative chronic pain.

Conclusions: Preoperative chronic pain was a risk factor of developing POCD within 7 days after surgery in elderly patients following hip joint replacement surgery.

Clinical trial registration: NCT03393676. Registered 10 January 2018, <https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?id=S0006RLL&selectaction=Edit&uid=U0003WPM&ts=79&cx=llo35x>

Introduction

Major joint replacement surgery is one of the most common elective procedures and is performed primarily in older adults. After major joint replacement surgery, the majority of patients experience substantial relief from both pain and functional disability. Despite the overall success of major joint replacement surgery, patients undergoing this procedure still remain susceptible to cognitive decline, which is termed postoperative cognitive dysfunction (POCD), with reported rates ranging from 7% to 75% depending on the definition, patient population and assessment tools used.^{1,2} POCD can result in delayed mobilisation and discharge from the hospital, long-term cognitive dysfunction and potentially increased rates of re-hospitalisation and mortality.³

Several factors have been shown to be risk factors of POCD after hip and knee surgery, including general anaesthetics,^{4,5} cerebral microemboli caused by fat or marrow entering the blood during surgery,⁶ lower premorbid cognitive reserve (lower reading level or fewer formal education years), increased age, lower preoperative brain integrity and lower preoperative executive and memory functions.⁷⁻¹³ However, it is unclear if preoperative pain, which is one of the main reasons of major joint replacement surgery, is also a risk factor of POCD.

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”¹⁴ The IASP subcommittee on taxonomy defined it in 1986 as “pain without apparent biological value that has persisted beyond the normal tissue healing time usually taken to be three months.”

It is known that pain directly impairs cognitive function.¹⁵ Additionally, previous studies have established cross-sectional differences in cognition between older adults with and without pain.¹⁶⁻¹⁸ However, no studies have investigated the role of preoperative pain on the occurrence of POCD. In this study, we conducted a single-centre, observational, prospective cohort trial in elderly patients who planned to undergo hip joint replacement surgery with general anaesthesia to test our hypothesis preoperative chronic pain is a risk factor of POCD after major joint replacement surgery.

Methods

Study design

A single-centre, prospective, observational cohort study was conducted in Renji Hospital, School of Medicine, Shanghai Jiaotong University (Shanghai, China), from January 2018 to March 2020. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee (RJ198K) (registered at Clinicaltrials.gov; NCT03393676). Written informed consent was obtained from all patients. All investigators were well trained in neuropsychological testing and pain evaluation.

Patient selection

All consecutive patients who underwent elective hemiarthroplasty or total hip arthroplasty with general anaesthesia performed by a single surgeon were enrolled. The inclusion criteria were as follows: (1) >65 years old, (2) speaks Chinese Mandarin, (3) planned to undergo major low limb surgery like hemiarthroplasty or total hip arthroplasty with general anaesthesia, (4) signed the informed consent form and (5) assessed as American Society of Anesthesiologists classification(ASA) I to II.

The exclusion criteria included the following: (1) existing cerebral disease or a history of neurological and psychiatric disease, including Alzheimer's disease, stroke, epilepsy and psychosis; (2) existing cognitive impairment as evidenced by the Mini-Mental State Examination (MMSE) scores below 24; (3) severe hearing or visual impairment; (4) unwillingness to comply with the protocol or procedures; (5) inability to communicate in Chinese Mandarin; (6) presence of serious pulmonary, heart, liver or renal insufficiency; and (7) had undergone anaesthesia or surgery within the past 30 days.

To determine POCD and cognitive decline, it is necessary to use a nonsurgical control group.¹⁹ The selection criteria were the same for the subjects controls, where subjects were matched to the elective hemiarthroplasty or total hip arthroplasty replacement surgery sample by age, sex and education, but they had no chronic pain. The controls were recruited from the general community. Both groups were recruited over the same time frame and tested at the same time intervals.

All patients underwent hemiarthroplasty or total hip arthroplasty. All clinical care followed routine clinical practice. All surgical plans were decided and performed in a standard manner by the same orthopaedic surgeon. All patients received general anaesthesia according to routine clinical practice. All patients received standardised perioperative care, including preoperative and intraoperative care and postoperative pain control.

Neuropsychological testing, including a battery of six neuropsychological tests, was performed by a well-trained personnel at baseline (the day before surgery) and at 7 days and 2 months postoperatively. The neuropsychological tests consisted of the MMSE, Visual Reproduction Test, Digit Span Test, Digit Symbol Test, Colour Trail Tests 1 and 2 and Stroop Colour and Word Test. All tests were conducted in the same order at each time point. These measures are not only highly sensitive to the types of cognitive impairments but also have no cultural bias.

Since these tests are prone to the test–retest practice effect, a age-matched control group was tested at the same intervals, providing an indication of practice effect with this test battery for the given time intervals between sessions.

Statistical analysis

Continuous data are reported in the tables as means and standard deviation (SD) or as median and interquartile range, and categorical data were reported as frequency and percentage. We examined the demographic and health characteristics per dichotomous pain variable ('chronic pain' versus 'non-chronic pain'). Between-group differences were analysed by using analysis of variance or the Mann–Whitney rank sum test for continuous measures and the chi-squared test or Fisher's exact test for categorical measures. Cognitive test scores were examined per dichotomous pain variable. The association between continuously valued variables and POCD was assessed by the difference in medians of patients with or without POCD. The association between categorical variables and POCD was assessed by the difference in risk for POCD between the category and baseline category in percentage points, including the association between POCD identified at 7 days and 2 months after surgery. Univariate logistic regression analysis was performed. All clinically relevant and statistically significant preoperative variables were then entered into a multivariate logistic regression analysis using a forward entry method to identify independent preoperative risk factors for POCD. Data are presented as the odds ratio and 95% confidence intervals. Values of $p < 0.05$ were considered to be indicative of statistical significance.

POCD identification

The Z-score was calculated according to the methods of Rasmussen.²⁰ Briefly, the preoperative score was first subtracted from the postoperative score (7 days or 2 months) to obtain the difference, ΔX . Similarly, we calculated the difference in the scores for the healthy controls, $\Delta X_{\text{control}}$. The calculated difference, $\Delta X - \Delta X_{\text{control}}$, was then divided by the standard deviation for the changes in test results in the control group, $SD(\Delta X)_{\text{control}}$. The formula was as follows:

$$Z = \frac{\Delta X - \Delta X_{\text{control}}}{SD(\Delta X)_{\text{control}}}$$

where ΔX is the change in the neuropsychological test performance between different time points.

A combined Z-score was calculated as the sum of Z-scores divided by the standard deviation for this sum of Z-scores in the control group. POCD was defined as two individual Z-scores > 1.96 or a composite Z-score > 1.96 . Data from the healthy control group were used to gain information on the practice effect and normal distribution in the test results for this age group, and the Z-scores were calculated.²⁰

Sample size calculation

Pass (Version 15.0, NCSS, LLC, Kaysville, Utah, USA) software was used for the sample size calculation. Logistic regression tests for odds ratios with one binary X procedure were performed. With $\alpha = 0.05$, a power of 80% and an odds ratio = 3.0, the POCD incidence of major joint replacement was approximately 20%, and chronic pain prevalence in such patients was at nearly 50%.^{18,21} We then estimated that a total of 135 patients would be required for the study. To set the attrition rate at 10%, a total of 148 patients were required.

Results

A total of 155 consecutive patients were enrolled in this study. The trial profile is shown in Fig. 1A. Patients were excluded for the following reasons: three refused to sign the informed consent form, four baseline MMSE scores were < 24 , three declined to participate in a later test, two were admitted to an intensive care unit after surgery, and two underwent reoperation in the follow-up period. The remaining 141 (57.4% female) patients were included in the diagnosis of early POCD at day 7. Additionally, two patients failed to show up for their final evaluation at 2 months, two underwent further surgery prior to follow-up, and three had lost data. Hence, the remaining 134 patients' cognitive test results were included at 2 months.

Among the 104 age- and education-matched community adults enrolled for the POCD calculations in this study, nine refused to sign the informed consent, three did not complete the baseline neuropsychological testing, three underwent operations after baseline cognitive evaluation, five declined to continue and two had lost data. Finally, 82 subjects were included in the statistical analysis (Fig. 1B).

Patients' general characteristics

Table 1 presents the patients' general characteristics. At day 7 postoperatively, total 27 patients developed cognitive decline, 17 had chronic pain preoperatively (63.0%, $p < 0.05$). There was no difference in gender, education, ASA grade, surgery time, blood loss, blood transfusion, and length of hospital stay between patients with POCD and patients without POCD. For the pain stats, patients had similar Visual Analogue Scale (VAS) pain score before surgery and 7 days after surgery whether developed POCD or not. No significant difference in PCIA use (66.7 vs 78.1%) and analgesia drug use before (37.0 vs 45.6%) or after surgery (70.4 vs 63.2%, day 7). However, patients given additional opioids on request as rescue analgesia postoperatively had a significant higher incidence of POCD (55.6 vs 34.2, $p < 0.05$) (Table 1).

Of the 141 participants enrolled, 135 had cognitive testing completed at 2 months after surgery. Total 10 patients had cognitive decline at 2 months postoperatively. There was no difference between the patients who had POCD or not in education, ASA grade, surgery time, blood loss, blood transfusion, and length of hospital stay, and VAS score before or after surgery (day 3 and day 7). VAS score and analgesic use 2 months after surgery of patients with POCD were significantly higher than those of patients without POCD (Table 1).

Table 2 presents the general characteristics of the patients(non-chronic pain vs chronic pain). Table 3 presents the general characteristics of the community controls.

Patients with chronic pain were more likely to develop POCD

In total, the incidence of early POCD (7 days postoperative) was 27 (19.1%) per 141. The incidence of late POCD (2 months postoperative) was 10 (7.5%) per 134. Among all 141 patients, 61 (43.2%) had chronic pain preoperatively. Of the 61 patients, 17 (27.9%) developed POCD; of the 79 no chronic pain patients, 10 (12.5%) developed POCD at 7 days after surgery (Fig. 2). Among the 134 patients who finished the neuropsychological testing at 2 months after surgery, 60 (44.8%) had chronic pain preoperatively. Of the 60 patients, 4 (6.7%) developed POCD; of the 74 no chronic pain patients, 6 (8.1%) developed POCD at 2 months after surgery.

Chronic pain preoperatively was a risk factor of POCD within 7 days after surgery

In the univariate logistic analysis, we found that preoperative chronic pain ($p = 0.003$), rescue opioid medicine ($p = 0.049$), and the VAS score at 3 days after surgery ($p = 0.042$) were risk factors of POCD within 7 days after surgery. In the multivariate logistic analysis, only preoperative chronic pain was a risk factor of POCD within 7 days after surgery (odds ratio, 3.335; 95% CI, 1.188–9.364, $p = 0.022$; Table 4).

In the univariate logistic analysis, we found that the VAS score at 2 months after surgery ($p = 0.037$) and pain medication usage 2 months after surgery ($p = 0.035$) were risk factors of POCD within 2 months after surgery. In the multivariate logistic analyses, no risk factor was found to be a risk factor for POCD within 2 months after surgery (Table 5).

Discussion

Our study demonstrated that preoperative chronic pain was a potent risk factor (odds ratio, 3.335) for POCD within 7 days postoperatively in elderly patients who had undergone major joint replacement surgery but not for POCD at 2 months after surgery. Previous study showed that chronic preoperative pain impaired recovery of attention after surgery in non-elderly patients.²² To the best of our knowledge, the present study is the first to identify chronic preoperative pain as a risk factor of POCD in elderly patients.

Many studies have demonstrated that chronic pain impaired memory.^{16,17,23,24} Guusje and colleagues found that high-level pain led to cognitive decline and that elderly adults with chronic pain had a higher risk of developing cognitive decline.²⁵ Preoperative chronic pain might affect basic physiological functioning of the brain. Eccleston and colleagues²⁶ proposed in the cognitive–affective theory stating that the pain experience demands attention and takes precedence over other attention-demanding cognitive processes. Alternatively, in a demonstration of the competing effects of pain on the brain, it has been reported that the distraction of demanding cognitive tasks led to reduced pain intensity and reduced activation of multiple pain-related brain areas in healthy young and middle-aged adults. Thus, it may be that some older persons who have chronic pain are unable to draw their attention away from their pain and thereby have difficulty performing cognitive tasks while others are able to use distraction to manage their pain.^{27,28}

Many factors might contribute to the easier development of POCD in patients with chronic pain. Although there was no difference in major cognitive functioning between patients with and without chronic pain before surgery, cognitive reserve was lower in the patients with chronic pain.²⁹ This finding might be one of the reasons why POCD developed more easily in the chronic pain patients. However, another reason might be that patients with chronic pain after surgery experience greater intensity of pain. In a meta-analysis of 29 993 patients who had undergone total knee arthroplasty that exclusively examined preoperative risk factors, preoperative pain was most commonly significantly associated with persistent postsurgical pain.³⁰ The present study demonstrated that the VAS scores before surgery and at 7 days after surgery were significantly higher in the chronic pain group than in the non-chronic pain group. Compared with the patients without early POCD, the patients who developed POCD had significantly higher VAS scores 3 days after surgery and more often requested additional opioids as rescue analgesia postoperatively. Several studies have demonstrated that postoperative pain was associated with the development of POCD.^{5,31,32} Further research is required to understand how preoperative chronic pain affects POCD.

Chronic pain is very common in patients who undergo major joint surgery. Since patients with chronic pain before surgery are more likely to develop POCD, more attention should be given to these groups of patients. Pain management starting in the preoperative

period and high-quality anaesthesia should be implemented if possible.

This study had some limitations. Individuals with significant cognitive impairment (MMSE < 24) were excluded from our research cohort. Therefore, our results cannot be generalised to elderly persons with moderate-to-severe cognitive impairment. We did not assess several factors, such as low postoperative oxygen saturation and inflammatory mediators in blood. Inflammation plays a central role in osteoarthritis pathogenesis. Those factors potentially could have diluted the effect of preoperative chronic pain on the incidence of POCD. In this study, there were more osteoarthritis patients in the chronic pain group than in the non-chronic pain group. Osteoarthritis is a type of autoimmunity disease; thus, it can potentially affect the occurrence of POCD.³³⁻³⁸ In the present study, we did not evaluate the presence of postoperative delirium (POD). However, many studies have demonstrated that in general, POD only occurred ≤ 5 days after surgery. In this study, the second neuropsychological testing was performed on day 7 after surgery. In theory, POD should disappear ≤ 7 days after surgery in most patients. Actually, the data analysed in this study were from the patients who had finished the second neuropsychological test, which indicated that all patients had no delirium at least by day 7 after surgery.

In conclusion, our study revealed that preoperative chronic pain was associated with an increased risk of early POCD in elderly patients after major joint replacement surgery. High-quality perioperative pain management might be helpful to reduce POCD.

Declarations

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Authors' contributions

Yingfu Jiao and Weifeng Yu conceived of the study, and participated in its design and coordination. Hong Xie and Diansan Su participated in the design of the study and contributed content to the writing of the review. Xiaorong Huai, Lingke Chen, Huichen Zhu, Bingwei Lu and Yichen Fan participated in the investigation of the study and data Curation. Xiaorong Huai and Xiyao Gu analysed the data, and helped to draft the manuscript. All other authors designed the study and approved the manuscript before submission. All authors read and approved the final manuscript.

Declare of interests

The authors declared they had no conflict of interests.

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The funders had no role in the analyses and interpretation of the results or writing of the manuscript.

Availability of data and materials

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

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethics committee (RJ198K) (registered at Clinicaltrials.gov; NCT03393676).

Abbreviations

POCD: postoperative cognitive dysfunction; IASP: The International Association for the Study of Pain; ASA: American Society of Anesthesiologists; MMSE : Mini-Mental State Examination; SD: standard deviation; VAS: visual analogue scal; PCIA : patient controlled intravenous analgesia; POD : postoperative delirium.

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Tables

Table 1. General characteristics of patients

Characteristic	Total, n=141	Non-Chronic pain, n=80(56.7%)	Chronic pain, n=61(43.2%)	p value
Mean (SD) or Median(IQR) or N (%)				

Age(yr)	69.6(6.2)	69.1(6.2)	70.1(6.1)	0.347
Gender (male/female)	60/81	34 /46	26 /35	1.000
BMI(kg/m ²)	24.3(3.7)	23.1(3.4)	25.9(3.4)	<0.001
Education Level(yr)	9.0(9.0-12.0)	9.0(8.0-12.0)	9.0(6.0-12.0)	0.079
History of hypertension	68(48.2)	34(42.5)	34(55.7)	0.129
History of diabetes	28(20.6)	16(20.0)	12(19.7)	1.000
History of smoking	14(9.9)	9(11.2)	5(8.2)	0.586
ASA grade I/II	57 /84	35/45	22/39	0.390
Diagnosis				<0.001
Osteoarthritis	48(34.0)	2(2.5)	46(75.4)	
Femoral neck fracture	84(59.6)	77(96.2)	7(11.5)	
Aseptic necrosis of femoral head	9(6.4)	1(1.2)	8(13.1)	
Surgery type				
Total hip arthroplasty	86(61.0)	37(46.2)	49(80.3)	<0.001
Hemiarthroplasty	55(49.0)	43(53.8)	12(19.7)	
Surgery time[min]	120.0(90.0-150.0)	111.3(89.1-150.0)	150.0(99.6-180.0)	<0.001
Blood loss[ml]	400.0(200.0-600.0)	400.0(200.0-600.0)	400.0(300.0-600.0)	0.312
Blood transfusion[ml]	400.0(0.0-600.0)	400.0(0.0-600.0)	400.0(0.0-700.0)	0.282
Length of hospital stay(days)	7.0(7.0-11.0)	7.0(7.0-9.0)	8.0(7.0-13.0)	0.014
Pain Stats				
Chronic pain peroid[yr]	0.0(0.0-2.0)	0.0(0.0-0.0)	3.0(1.0-5.0)	<0.001
VAS score before surgery	5.0(4.0-5.0)	4.0(4.0-5.0)	5.0(4.5-6.0)	0.001
VAS score after surgery				
3 days	4.0(4.0-5.0)	4.0(4.0-5.0)	4.0(4.0-5.0)	0.477
7 days	2.0(1.0-3.0)	1.0(1.0-3.0)	3.0(1.0-3.0)	0.018
2 months	1.0(1.0-1.0)	1.0(1.0-1.0)(n=74)	1.0(1.00-1.75)	0.386
POCD 7day	27(19.1)	10(12.5)	17(27.9)	0.030
POCD 2months	10(7.5)	6(8.1)	4(6.7)	1.000

SD: standard deviation

IQR: interquartile range

BMI: body mass index

ASA: American Society of Anesthesiologists

VAS: visual analogue scal

POCD: postoperative cognitive dysfunction

Table 2. General characteristics of the community people not receiving surgery.

Characteristic	N = 82
Age (yr)	67.5 (65–82)
Gender (male/female)	29/53
Education Level(yr)	9.5 (2.7)
History of hypertension	40 (48.8)
History of diabetes	17 (20.7)
History of smoking	6(7.3)
ASA grade I/II	32/50

Values are median(min–max), numbers, mean (SD) or number(proportion)

SD: standard deviation

ASA: American Society of Anesthesiologists

VAS: visual analogue scal

POCD: postoperative cognitive dysfunction

Table 3. Logistic analysis for the POCD occurred at 7 days after surgery

Characteristic	Univariate analysis	Multivariate analysis	
	p	Odds ratio (95% CI)	p
Chronic pain preoperative	0.003	3.335 (1.188–9.364)	0.022
Pain period	0.136	0.960(0.846-1.091)	0.534
Gender	0.137	1.582(0.598-4.183)	0.356
History of smoking	0.144	1.726(0.425-7.001)	0.445
VAS score 3 days After surgery	0.042	1.585(0.598-4.183)	0.369
Rescue opioid medicine	0.049	1.378(0.371-5.109)	0.632

POCD: postoperative cognitive dysfunction

VAS: visual analogue scale

Table 4. Logistic analysis for the POCD occurred at 2 months after surgery

	Univariate analysis	Multivariate analysis	
	P	Odds ratio (95% CI)	p
Gender	0.101	3.491(0.812-15.009)	0.093
History of diabetes	0.120	0.000	0.998
VAS score 2 months after surgery	0.037	0.616(0.184-2.069)	0.434
Pain killer medicine usage 2 months after surgery	0.035	10.128(0.472-217.177)	0.139
Day 7 POCD	0.115	3.491(0.812-15.009)	0.258

POCD: postoperative cognitive dysfunction

VAS: visual analogue scale

Figures

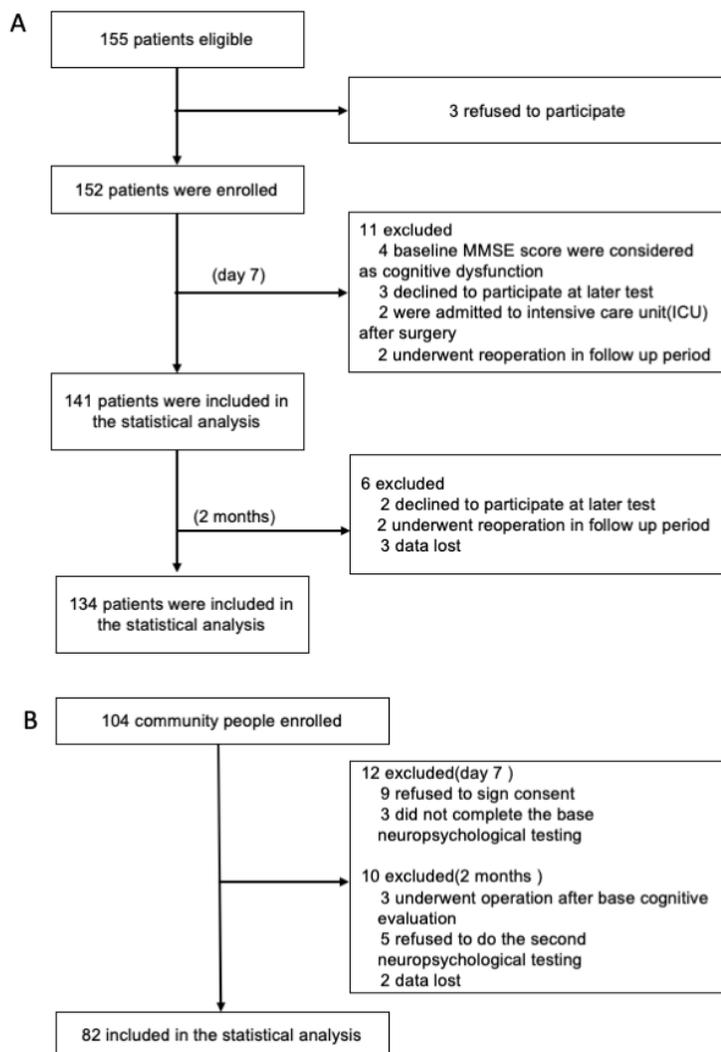


Figure 1

The flow chart of this study. A: patients flow chart B: health community people flow chart

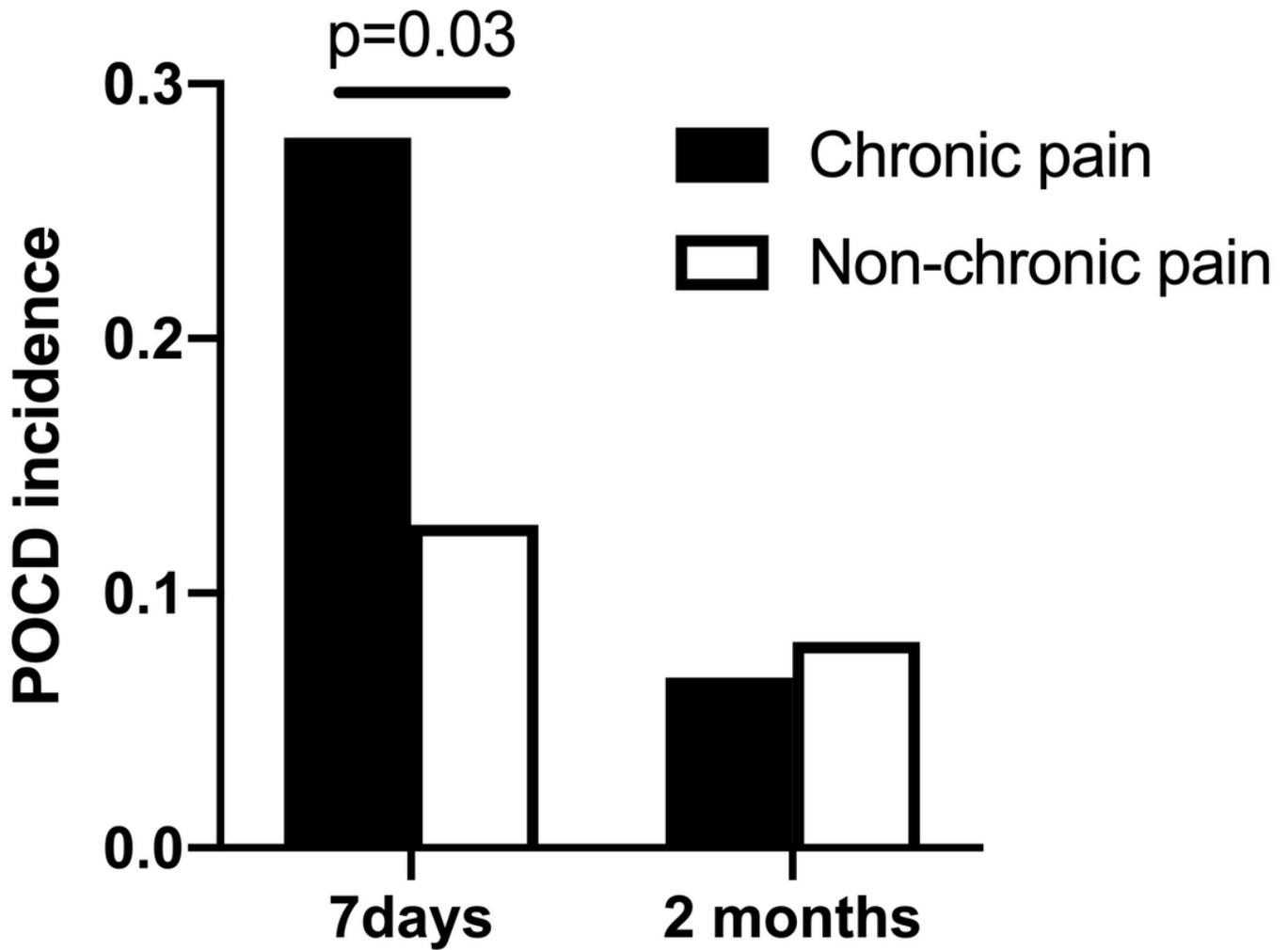


Figure 2

POCD incidence at 7 days and 2 months after surgery (Chronic pain patients vs non-chronic pain patients). POCD: postoperative cognitive dysfunction