DISSERTATION

Postoperative delirium and chronic pain
Postoperatives Delir und chronische Schmerzen

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List of abbreviations

ASA PS	American Society of Anesthesiologists Physical Status
CAM	Confusion Assessment Method
CCI	Charlson Comorbidity Index
CI	Confidence Interval
DASS-21	Depression Anxiety Stress Scale-21
DSF	Deutscher Schmerzfragebogen (German Pain Questionnaire)
DSM	Diagnostic and Statistical Manual of Mental Disorders
IASP	International Association for the Study of Pain
IBM	International Business Machines Corporation
ICD	International Classification of Diseases
IQR	Interquartile Range
NRS	Numerical Rating Scale
Nu-DESC	Nursing Delirium Screening Scale
OPS	Operation and Procedure Classification System
OR	Odds Ratio
PACU	Post Anesthesia Care Unit
POCD	Postoperative Cognitive Dysfunction
POD	Postoperative Delirium
RASS	Richmond Agitation-Sedation Scale
SAP®	System Applications and Products in Data Processing
SPSS®	Statistical Product and Service Solutions
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
VAS	Visual Analog Scale
3D-CAM	3-Minute Diagnostic Interview for CAM-defined Delirium

Abstract

Background: Postoperative delirium (POD) is characterized by an acute change in attention, awareness, and cognition. It is a common complication after surgery. There is evidence that preoperative pain can contribute to POD, but previous studies also suggest an association between several pain medications and POD. The influence of chronic pain on POD is not entirely clear. Thus, we investigated the association between chronic pain lasting ≥ 6 months and POD in an adult cohort.

Methods: This secondary analysis of a prospective observational cohort study examines adults ≥ 18 years without preexisting delirium undergoing elective non-cardiac surgery. Two hundred participants were enrolled between January 2017 and January 2018 at the Department of Anesthesiology and Operative Intensive Care Medicine, Charité – Universitätsmedizin Berlin CCM/CVK. The primary outcome was the occurrence of POD. POD was defined as meeting diagnostic criteria for delirium during study visits, or by delirium diagnosis of the responsible physicians. We used validated delirium screening tests, diagnostic criteria of delirium according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition, and conducted a medical record review. Multivariable logistic regression was used to identify risk factors. We analyzed 176 participants due to early dropouts. A subgroup analysis included 69 participants with chronic pain ≥ 6 months.

Results: POD occurred in 39 out of 176 participants (22%). Chronic pain was not an independent risk factor for POD (Odds Ratio, 95% Confidence Interval, 2.216 [0.968;5.070], P = 0.060) when controlling for confounding factors (American Society of Anesthesiologists Physical Status, duration of anesthesia and anxiety according to the Depression Anxiety Stress Scale-21). Preoperative current pain intensity in chronic pain patients was higher in those who developed POD than in those who did not.

Conclusions: Chronic pain was not associated with POD, but chronic pain patients who developed POD had a higher current pain intensity preoperatively. These findings suggest that undertreated chronic pain might be a modifiable risk factor, which could have implications for an adequate perioperative pain therapy. This is relevant in an aging population with a rising incidence of chronic pain and surgical procedures. Further research should be conducted to confirm our findings, to develop optimized perioperative pain management strategies, and to consider the current pain classification of the International Association for the Study of Pain.

Zusammenfassung

Hintergrund: Das postoperative Delir (POD) ist eine akute Störung der Aufmerksamkeit, des Bewusstseins und der Kognition. Es gilt als häufig. Einige Studien weisen auf einen Zusammenhang zwischen präoperativen Schmerzen und POD; ebenso gibt es Hinweise zum Einfluss einiger Schmerzmedikamente auf das POD. Der Einfluss chronischer Schmerzen ist jedoch unzureichend untersucht. Daher untersuchten wir den Zusammenhang zwischen chronischen Schmerzen mit einer Dauer ≥ 6 Monaten und POD.

Methodik: Diese sekundäre Analyse einer prospektiven Beobachtungsstudie rekrutierte 200 Erwachsene ≥ 18 Jahre ohne präoperatives Delir mit elektivem nicht-kardiochirurgischen Eingriff an der Klinik für Anästhesiologie und Intensivmedizin der Charité – Universitätsmedizin Berlin CCM/CVK von Januar 2017 bis Januar 2018. Der primäre Endpunkt war das Erfüllen der diagnostischen Kriterien für POD während einer Studienvisite oder die Diagnose durch die behandelnden Ärzt*innen. Angewendet wurden validierte Tests, die diagnostischen Kriterien gemäß Diagnostic and Statistical Manual of Mental Disorders, 5. Ausgabe, eine Kurvenvisite sowie die Sichtung des Arztbriefes. Zur Analyse der Risikofaktoren diente eine multivariable logistische Regression. Aufgrund früher Dropouts wurden 176 Proband*innen analysiert. Die Subgruppenanalyse umfasste 69 Personen mit chronischen Schmerzen ≥ 6 Monaten.

Ergebnisse: Von 176 Proband*innen erfüllten 39 (22%) die Kriterien für ein POD. Chronische Schmerzen waren kein unabhängiger Risikofaktor (Odds Ratio, 95%-Konfidenzintervall, 2.216 [0.968;5.070], $p = 0.060$) nach Berücksichtigung der Klassifikation gemäß American Society of Anesthesiologists, Anästhesiedauer und Angst gemäß Depression Anxiety Stress Scale-21. In der Subgruppenanalyse war die aktuelle Schmerzstärke bei Proband*innen mit POD präoperativ höher als bei Proband*innen ohne POD.

Schlussfolgerung: Es gab keinen Zusammenhang zwischen chronischen Schmerzen und POD. Die aktuelle Schmerzstärke war jedoch höher bei chronischen Schmerzpatient*innen, die ein POD entwickelten. Dies deutet darauf, dass unzureichend behandelte chronische Schmerzen ein modifizierbarer Risikofaktor sein könnten, was eine adäquate perioperative Schmerztherapie beeinflussen könnte. Dies ist relevant angesichts einer alternden Bevölkerung. Zukünftige Studien sind nötig, um diese Hypothese zu bestätigen, das perioperative Schmerzmanagement zu optimieren, und die aktuelle Klassifikation von Schmerzen der International Association for the Study of Pain zu berücksichtigen.

1. Introduction

For a long time, the common understanding of an anesthesiologist's role was limited to the task of anesthetizing patients for surgery and waking them up again after the procedure, Lewandowski et al. wrote in an article that was published in 2021 to commemorate the 175th anniversary of the first public ether anesthesia.[1] Today, anesthesiology is dedicated to much more than anesthesia, as it also encompasses intensive care, emergency and pain medicine. The perspective has widened from a narrow focus on the immediate perioperative period. Research on long-term effects related to patient health and well-being long after anesthesia is becoming increasingly important.[2] In this context, studies on potentially adverse effects of anesthesia on cognition and an association with cognitive decline play an important role.

1.1 Postoperative delirium

1.1.1 Definition and epidemiology

Postoperative delirium (POD) is a common complication following surgical procedures, especially in older adults. The first description of delirium may be well over 2000-2500 years old.[3–5] With evolving knowledge of this condition, its description and definition have been refined over time. The current diagnostic criteria for delirium are outlined in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).[6] According to these, delirium is characterized by an acute change of attention and awareness. These disturbances cannot be better explained by another neurocognitive disorder or by coma, differ from baseline cognition and are accompanied by an additional cognitive dysfunction, such as hallucinations or memory disorders. Symptoms typically develop over a few hours to a few days, are usually already present in the recovery room and tend to fluctuate.[7] Moreover, there is evidence of an underlying organic cause or a medical condition, such as substance intoxication or withdrawal. All criteria must be met simultaneously within five days after surgery for a diagnosis of POD.[7]
What was once referred to as "acute confusional state" or even "subacute befuddlement"[8] – implicating a temporary disturbance that would soon subside – is now acknowledged as a neurotoxic event that may cause long-term effects.[9] Studies have found an association of POD with functional and cognitive decline, an increased risk for dementia, as well

as with impaired activities of daily living.[10–15] Length of hospital stay is increased in patients with POD.[16] POD is also associated with an increased perioperative mortality[17], but it does not seem to be associated with an increased five-year mortality.[18]

The varying incidence depends on several factors such as age, or the type of surgery: approximately 3% of patients with elective surgeries of the extremities are affected, compared with 10-20% of patients with elective surgeries of the trunk, 20-45% of patients with emergency surgeries and up to 70% of patients with hip fractures.[17] In 2021, around 15.8 million inpatient surgeries were performed in Germany.[19] Assuming an overall incidence of 20%[20], this would result in 3.16 million cases of POD per year in German hospitals alone. To put this into perspective, the population of Berlin was approximately 3.68 million people in 2021.[21]

1.1.2 Prevention and risk factors

Prevention includes non-pharmacological measures to facilitate orientation, such as offering glasses or hearing aids if needed, restoring day-night rhythm, and early mobilization after surgery.[7,17,22] Since treatment options are limited, prevention is an important component of delirium management. It is estimated that more than 40% of delirium cases could be preventable.[9]

For an effective prevention of POD, it is necessary to know what promotes it – or in other words, to recognize its risk factors. Previous observational studies have already identified many risk factors. These can be divided into predisposing and precipitating factors.[23] Predisposing factors are patient-related, for example preexisting cognitive impairment and dementia, sensory deficits, reduced functional status and severe comorbidities.[7] These risk factors overlap with advanced age. Precipitating factors are treatment-related, for example emergency and/or major surgery.[7] These examples illustrate that some risk factors are modifiable, and some are not.

Modifiable risk factors are particularly important for clinical practice. Ideally, preoperative risk stratification can help to identify patients with an increased vulnerability towards POD. In these groups, special attention must be paid to the preventive non-pharmacological interventions described above. Subsequent risk reduction can be achieved by eliminating modifiable risk factors.

1.2 Pain as a risk factor for postoperative delirium

Many studies have investigated the association between pain and delirium in general. The following discussion focuses on relevant studies specifically on the association between pain and POD.

The association between uncontrolled **postoperative** pain and POD is long known and has been found in many studies.[24–29] Especially in frail patients with hip fractures, undertreated perioperative pain seems to be a risk factor for delirium.[30] One study found that aggressive treatment of pain within the first two postoperative days contributes to a fast recovery from POD.[31] Based on all this evidence, the current guideline on POD recommends adequate assessment of postoperative pain as a risk factor for POD, and suggests a multimodal pain therapy in the perioperative setting.[7]

The association between **preoperative** pain and POD however is inconclusive. There is not much evidence on this topic, and some of it is contradictory. Some studies found no association between preoperative pain and POD.[26,32] Others found an association only in bivariate analyses, but not in a logistic regression after adjustment for confounders.[27,33,34] Others again found an association between preoperative pain and POD in a logistic regression model when controlling for confounders.[25,35,36] Some studies included general information about the type of pain, such as “pain at rest” or “pain with movement”, as well as “pain intensity”. However, there was no description of other important pain characteristics such as onset, duration or course, which could allow further differentiation or distinguish different types of pain.

To our knowledge, no study has analyzed chronic pain defined as pain lasting ≥ 6 months to assess a possible influence on POD. Specific characteristics of chronic pain have not been investigated yet.

1.3 Aim of the study

We aimed to examine the association of preoperative chronic pain and POD in an adult cohort undergoing elective surgery.[37] Also, we wanted to examine the subgroup of chronic pain patients in more detail to investigate whether characteristics of chronic pain are associated with POD. Thus, our goal was to examine chronic pain as a potentially modifiable risk factor to prevent POD.

2. Methods

2.1 Study design

This is a secondary analysis of data collected in a prospective observational cohort study to validate the 3-minute Diagnostic Assessment for CAM-defined Delirium (3D-CAM) in the recovery room.[38] Two hundred adults undergoing elective surgery were recruited from January 2017 to January 2018. Each participant provided written informed consent. Patients who were unwilling or incapable to provide written informed consent were excluded. The study took place at the Department of Anesthesiology and Operative Intensive Care Medicine of the Charité-Universitätsmedizin Berlin, Campus Virchow-Klinikum. Approval for the study was obtained on 29 September 2016 by the ethics committee of the Charité-Universitätsmedizin Berlin (ref.: EA1/261/16, chairman Prof. Dr. med. R. Morgenstern). The study was conducted in compliance with the Declaration of Helsinki. It was registered under ClinicalTrials.gov: NCT02992717. We considered the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines when reporting our results.[39]

2.2 Study population

Inclusion and exclusion criteria are presented in table 1.

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Age ≥ 18 years • Elective surgery • General anesthesia • Expected admission to recovery room or Post Anesthesia Care Unit (PACU) • Expected length of stay in the hospital ≥ 24 hours after surgery	• Severe auditory and/or severe visual impairment • Illiteracy • Psychiatric disorders • Cognitive impairment • Insufficient German language skills • Simultaneous participation in a clinical trial • Employment at the Charité-Universitätsmedizin Berlin • Accommodation in an institution due to an official or judicial order

Table own representation

2.3 Preoperative assessment

2.3.1 Patient characteristics

After enrollment, we conducted an interview with every participant. This usually took place on the day before hospital admission when patients came to see the anesthesiologist for preanesthesia evaluation. During this interview, we collected patient characteristics such as demographics: age, sex, current occupation and education (in school years). Medical information was obtained from the electronic health record, including the American Society of Anesthesiologists Physical Status (ASA PS, table 2) and the code of principal diagnosis according to the International Classification of Diseases, 10th edition (ICD-10). Comorbidities were recorded and later assessed using the Charlson Comorbidity Index (CCI).[40] Each participant was screened for symptoms indicating stress, anxiety or depression using the Depression Anxiety Stress Scale-21 (DASS-21).[41]

Table 2: American Society of Anesthesiologists Physical Status Classification System

Class	Definition
I	Healthy patients without any abnormalities
II	Patients with a mild systemic disease
III	Patients with a severe systemic disease that is not life-threatening
IV	Patients with a severe systemic disease that is continuously life-threatening
V	Moribund patients that are not expected to survive without surgery
VI	Brain-dead patients whose organs are being removed for donation

Table modified from the American Society of Anesthesiologists, 2020[42]

2.3.2 Pain assessment

Patients were asked whether they experienced chronic pain (defined as pain lasting ≥ 6 months). All chronic pain patients were assessed further using the German Pain Questionnaire (Deutscher Schmerzfragebogen, DSF).[43] We extracted the following items from the questionnaire: duration of pain, course of pain over the last four weeks, current pain intensity, average and worst pain intensity over the last four weeks, chronic pain diagnosis, and effectiveness of previous pain treatment (table 3).

Table 3: Items extracted from the German Pain Questionnaire

Variable	Description
Duration of pain	Choose one option that fits best: 6 months to 1 year 1 to 2 years 2 to 5 years > 5 years
Course of pain over the last four weeks	Choose one option that fits best: Permanent pain, little variation Permanent pain, great variation Painful attacks Permanent pain and painful attacks
Pain intensity (assessed with the NRS)	Choose on a scale from 0 (no pain) to 10 (worst pain): Current pain intensity Average pain intensity over the last four weeks Worst pain intensity over the last four weeks
Chronic pain diagnosis	Choose one option: Present Not Present
Effectiveness of previous pain treatment	Choose one option that fits best: Ineffective Temporarily effective Effective

NRS = Numerical Rating Scale

Table modified from Pfingsten et al., 2015[43]

2.3.3 Delirium assessment

Preoperative testing also implicated to rule out the presence of preexisting delirium. This was achieved with several tests. We evaluated diagnostic criteria for delirium using the criteria for delirium according to the DSM-5 (table 4).[6] If all criteria listed in table 4 occurred simultaneously, a patient was rated as delirious. We also employed the Nursing

Delirium Screening Scale (Nu-DESC)[44], which consists of five items that are each rated with zero to two points (table 5). A patient was considered delirious with a total score of ≥ 2 points. Third, the Confusion Assessment Method (CAM) was used (table 6).[45] Since the CAM requires at least a brief cognitive assessment to detect the presence of delirium[46], we also conducted the Mini-Cog©.[45,47] The Mini-Cog© requires memorizing three words, drawing a clock, and recalling the three words afterwards. A maximum score of five points can be achieved with this test, since each recalled word yields one point, drawing the clock correctly yields two points.

Table 4: Diagnostic and Statistical Manual of Mental Disorders, 5th edition criteria for delirium

Criteria	Description
A	Main characteristics: Inability to direct, sustain, focus and shift attention **and** Impaired awareness (= altered orientation to the environment)
B	Course: Symptoms develop usually within hours to a few days Symptoms tend to fluctuate in severity during the day Disturbances represent a change from baseline attention and awareness
C	Additional cognitive disturbances, e.g.: Memory deficits Disorientation Language disorders Impaired visuospatial ability Altered perception
D	Exclusion of differential diagnoses: Criteria A and C cannot be attributed to another preexisting, established, or developing neurocognitive disorder **and** Criteria A and C do not occur in the context of a coma
E	Etiology: Patient history, physical examination, or laboratory findings indicate a cause Underlying causes may be a medical condition, substance intoxication or withdrawal E.g., drug abuse, exposure to a toxin or medication, multiple etiologies

Table modified from the American Psychiatric Association, 2013[6]

Table 5: Nursing Delirium Screening Scale

Symptom	Description
I	Impaired orientation: Verbal or behavioral expressions indicating disorientation to time or place or misperception of surrounding people
II	Inadequate behavior: Inappropriate behavior for this person or in this context, such as pulling on tubes or dressings, or attempting to get out of bed despite contraindication
III	Inadequate communication: Inappropriate communication for this person or in this context, such as incoherent, nonsensical or incomprehensible speech, or lack of communication
IV	Illusions: Distorted vision of existing objects or audiovisual hallucinations
V	Psychomotor delay: Delayed responses and little or no spontaneous behavior or speech, such as deferred reaction or impaired arousal following stimulation

Table modified from Gaudreau et al., 2005[44]

Table 6: Short Confusion Assessment Method

Box 1	
I	Sudden onset or fluctuation: Is there an acute change from the patient's baseline mental status? Does the (abnormal) behavior fluctuate in severity during the day?
II	Impaired attention: Does the patient have difficulty to focus attention, e.g., being easily distractible or having difficulty to follow a conversation?
Box 2	
III	Disorganized thinking: Is the patient's thinking disorganized or incoherent, e.g., rambling or irrelevant conversation, unclear or illogical flow of thought, or unpredictable switching from one topic to another?
IV	Altered consciousness: What is the patient's level of consciousness? Alert and calm (normal), hyperalert (vigilant), lethargic (sleepy but easily aroused), stupor (difficult to arouse), coma (unarousable)

Table modified from Inouye et al., 2003[45]

2.4 Postoperative assessment

2.4.1 Perioperative data

The first postoperative study visit was planned to take place within 30 minutes after extubation in the recovery room. Study personnel assessed postoperative delirium in immediate successive measurements. These tests were conducted by different members of the research team. We employed the same methods as in the preoperative assessment to detect delirium: DSM-5, Nu-DESC and CAM. These are validated in the recovery room in adults. In accordance with the German current guideline,[48] we assessed vigilance with the Richmond Agitation-Sedation Scale (RASS, table 7). Delirium assessment was postponed in case of insufficient vigilance (RASS <-2) due to prolonged effects of anesthesia.

Table 7: Richmond Agitation-Sedation Scale

Score	Description
+4	Aggressive: Aggressive or violent behavior that imposes an immediate danger
+3	Very agitated: Pulling on tubes or catheters, aggressive behavior toward staff
+2	Agitated: Frequent undirected movements or patient-ventilator dyssynchrony
+1	Restless: Anxious behavior, but movements are not aggressive or vigorous
0	Alert and calm: Normal response and behavior
-1	Drowsy: Not fully alert, but responds to voice with sustained awakening (≥ 10 seconds) and eye contact
-2	Lightly sedated: Responds to voice with brief awakening (< 10 seconds) and eye contact
-3	Moderately sedated: Responds to voice with any movement or eye opening but with no eye contact
-4	Deeply sedated: No response to voice, but any movement or eye opening to physical stimulation
-5	Unarousable: No response to voice or physical stimulation

Table modified from Sessler et al., 2002[49]

Subsequent postoperative study visits on the ward were repeated once daily up to three days after the surgical procedure took place. If the patient was discharged earlier than three days after surgery, study visits took place until the patient was discharged. Hence, patients were examined up to four times for the presence of postoperative delirium (table 8). Patients were examined separately by two members of the research staff that were blinded against each other's test results (examiner 1 and 2). We also conducted a chart review to detect fluctuating symptoms of delirium that were not present during any of the study visits.

Table 8: Summary of postoperative study visits and delirium assessments

	Recovery Room	Day 1	Day 2	Day 3
Examiner 1	DSM-5	DSM-5	DSM-5	DSM-5
Examiner 2	Nu-DESC, CAM	Nu-DESC, CAM	Nu-DESC, CAM	Nu-DESC, CAM

DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th edition; Nu-DESC = Nursing Delirium Screening Scale; CAM = Confusion Assessment Method

Table own representation

After discharge, information about the surgical procedure was extracted from the medical record software COPRA: duration of anesthesia and type of anesthesia. Further data was collected using the System Applications and Products in Data Processing® Electronic Medical Record system (SAP® Deutschland SE & Co. KG, Walldorf, Germany). Operative severity was derived using the Physiological and Operative Severity score for the Enumeration of Mortality and Morbidity (POSSUM).[50] The hospital discharge letter included information on length of stay in the hospital and delirium diagnosis during the study period, if applicable. We also recorded the procedure code according to the Operation and Procedure Classification System (OPS) in order to summarize the site of surgery (table 9).

2.4.2 Primary outcome

The primary outcome was defined as the occurrence of POD. This included all patients with at least one positive delirium screening test result (Nu-DESC and/or CAM) during any of the study visits, all patients fulfilling DSM-5 criteria during any of the study visits, and all patients that were diagnosed with postoperative delirium by medical personnel other than the study personnel. This approach was employed to ensure identification of all cases of postoperative delirium despite its fluctuating course.

2.5 Statistical analysis

Sample size was determined for the primary aim of the study – validation of the 3D-CAM in an adult cohort in the recovery room – for which a sample size of n = 200 participants was calculated.[38] Patient characteristics were reported as median [interquartile range, IQR] or as frequencies [percentages, %]. All statistical analyses were approved by the statistician Jochen Kruppa from the Institute for Biometry and Clinical Epidemiology, Charité – Universitätsmedizin Berlin.

For **bivariate analysis**, participants were grouped based depending on whether postoperative delirium was present or not. Differences between the two groups were then assessed. Non-parametric continuous and ordinal variables were analyzed using Mann-Whitney-U-test. Categorical variables were analyzed using Chi-Square test (or Fisher's exact test in case of a small sample size). A significance level of $P \leq 0.05$ was considered statistically significant (two-sided testing).

Variables that were significantly associated with postoperative delirium in our bivariate analysis were then introduced into a **multivariable logistic regression model**. This included ASA PS score, duration of anesthesia and DASS-21 anxiety score. We also entered chronic pain into the model since this was our research interest. We did not include operative severity since this variable was strongly correlated with duration of anesthesia.

Finally, we performed a **subgroup analysis** that included all patients that had reported chronic pain. We used the same approach as described above: stratification of chronic pain patients into two groups based on the occurrence of postoperative delirium, and subsequent assessment of group differences using Mann-Whitney-U-test, Chi-Square test, or Fisher's exact test, respectively. This subgroup analysis also included all variables that were extracted from the German Pain Questionnaire.

All statistical analyses were performed using International Business Machines Corporation SPSS® Statistics 28.0 (IBM Corp. Released 2021. IBM SPSS® Statistics for Macintosh, Version 28.0. Armonk, NY: IBM Corp).

3. Results

We recruited a total of 200 participants for this study (figure 1). Of these, 24 participants were early dropouts. Thus, 176 participants were included in the analysis for the primary outcome: the occurrence of POD. Sixty-nine out of 176 participants (39%) reported chronic pain. These were also included in the subgroup analysis.

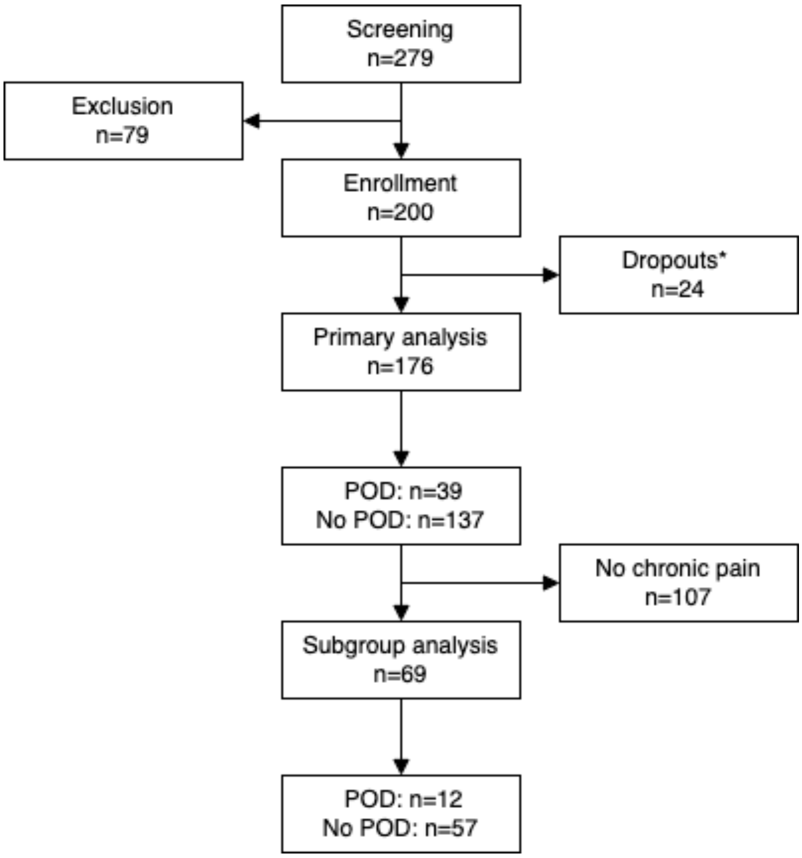

Figure 1: Flowchart showing recruitment and analysis of participants for the occurrence of post-operative delirium; POD = postoperative delirium; * = Dropouts due to cancelled surgery (n = 12), withdrawal of consent (n = 6), postoperative assessment not possible, e.g., due to prolonged mechanical ventilation (n = 5), invalid informed consent (n = 1); modified from Eckert et al., 2023[37]

3.1 Primary analysis

Thirty-nine out of 176 participants (22%) developed POD. In a bivariate analysis, we assessed known and presumed predisposing and precipitating risk factors (table 9 and table 10). There were no significant group differences regarding chronic pain. We found that participants who developed POD had a significantly higher ASA PS score, DASS-21 anxiety score and operative severity, and a significantly longer duration of anesthesia. We found no significant differences in patients with and without POD regarding age, sex, current occupation, education in school years, grouped CCI, DASS-21 depression and stress scores, and type of anesthesia. Table 11 shows the surgical sites.

The multivariable logistic regression analysis included ASA PS score, duration of anesthesia and DASS-21 anxiety score. We also entered chronic pain into the model since this was our research interest. After adjustment for confounding factors, duration of anesthesia and DASS-21 anxiety score were significantly associated with POD (table 12). Chronic pain was not significantly associated with POD (Odds Ratio [OR], 95% Confidence Interval [CI], 2.216 [0.968;5.070], P = 0.060).

Table 9: Bivariate analysis of predisposing risk factors for postoperative delirium (n = 176)

Variable	No POD (n = 137)	POD (n = 39)	P value
Age [in years]	63 [53;73]	72 [59;79]	0.108
Sex			0.150
Female	67 (49%)	14 (36%)	
Male	70 (51%)	25 (64%)	
Current occupation			0.338
Working or in training	55 (40%)	11 (28%)	
Unemployed	7 (5%)	3 (8%)	
Retired	75 (55%)	25 (64%)	
Education [in school years]	10 [10;11]	10 [9;11]	0.484
ASA Physical Status			0.006
I	13 (9.5%)	5 (13%)	
II	91 (66%)	15 (38%)	
III	31 (23%)	19 (49%)	
IV	2 (1.5%)	0 (0%)	
Charlson Comorbidity Index			0.254
0	14 (10%)	3 (8%)	
1-2	49 (36%)	9 (23%)	
3-4	39 (28.5%)	11 (28%)	
≥ 5	35 (25.5%)	16 (41%)	
DASS-21 score			
Depression score	2 [0;5]	3 [1;6]	0.312
Anxiety score	1 [0;3]	3 [1;5]	0.002
Stress score	5 [2;7]	3 [2;6]	0.483
Chronic pain			0.221
Present	57 (42%)	12 (31%)	
Not present	80 (58%)	27 (69%)	

ASA = American Society of Anesthesiologists; DASS-21 = Depression Anxiety Stress Scale-21; POD = Postoperative delirium

Table modified from Eckert et al., 2023[37]

Table 10: Bivariate analysis of precipitating risk factors for postoperative delirium (n = 176)

Variable	No POD (n = 137)	POD (n = 39)	P value
Type of anesthesia			0.572
Balanced anesthesia	89 (65%)	23 (59%)	
Total intravenous anesthesia	48 (35%)	16 (41%)	
Operative severity			0.002
1	77 (56%)	10 (26%)	
2	33 (24%)	12 (31%)	
3	20 (15%)	15 (38%)	
4	7 (5%)	2 (5%)	
Duration of anesthesia [in minutes]	124 [81;184]	161 [100;245]	0.021

POD = Postoperative delirium

Table modified from Eckert et al., 2023[37]

Table 11: Surgical sites based on the Operation and Procedure Classification System (n = 176)

Variable	n (%)
Musculoskeletal system	60 (34%)
Visual system	37 (21%)
Digestive system	22 (13%)
Facial bones and oral cavity	13 (7%)
Nervous system	10 (6%)
Respiratory system	10 (6%)
Integumentary system	7 (4%)
Endocrine system	6 (3%)
Diagnostic procedures	6 (3%)
Cardiovascular system	2 (1%)
Genitourinary system	2 (1%)
Hematopoietic and lymphatic system	1 (1%)

Table modified from Eckert et al., 2023[37]

Table 12: Multivariable logistic regression analysis of risk factors for postoperative delirium (n = 176)

Variable	OR [95%-CI]	P value
ASA Physical Status	1.551 [0.851;2.824]	0.152
Duration of anesthesia [in minutes]	1.005 [1.001;1.010]	0.018
DASS-21 anxiety score	1.152 [1.006;1.319]	0.041
Chronic pain	2.216 [0.968;5.070]	0.060

ASA = American Society of Anesthesiologists; CI = Confidence Interval; DASS-21 = Depression Anxiety Stress Scale-21; OR = Odds Ratio

Table from Eckert et al., 2023[37]

3.2 Subgroup analysis of patients with chronic pain

The subgroup analysis included all 69 participants who reported chronic pain ≥ 6 months. Twelve out of these (17%) developed POD. In a bivariate analysis, we assessed the same risk factors as before in the entire patient sample (table 13 and table 14). Participants who developed POD had significantly higher DASS-21 depression and anxiety scores, as well as a significantly longer duration of anesthesia and a significantly higher operative severity. No significant differences were found in patients with and without POD regarding age, sex, current occupation, education in school years, ASA PS score, grouped CCI, DASS-2 stress score, and type of anesthesia.

We conducted a more detailed pain assessment. The most frequently reported localizations were back pain and shoulder pain (table 15). In a bivariate analysis, we found that current pain intensity was higher in patients who developed POD (figure 2). We did not find any differences regarding duration of pain, course of pain over the last four weeks, average and worst pain intensity over the last four weeks, presence of a chronic pain diagnosis, and effectiveness of previous treatment (table 16).

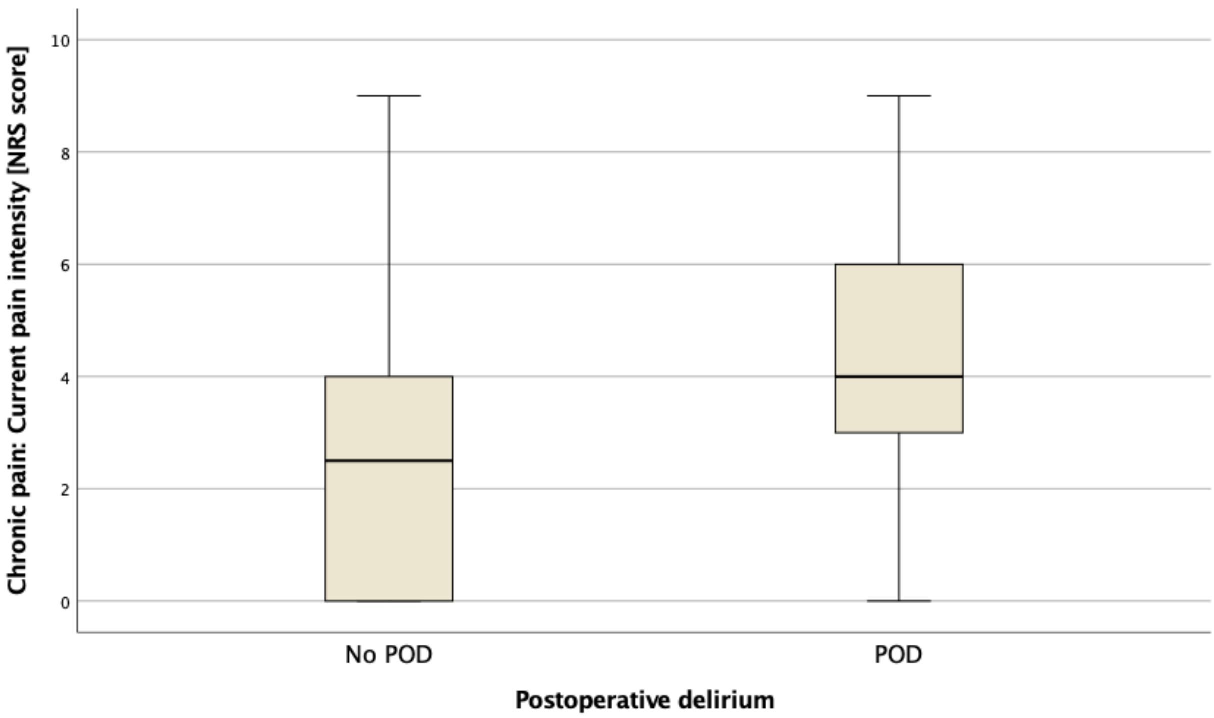

Figure 2: Boxplot showing preoperative current pain intensity in chronic pain patients with and without postoperative delirium (n = 68); NRS = Numerical Rating Scale, POD = Postoperative delirium; median NRS score in chronic pain patients without POD = 3 [0;4], median NRS score in chronic pain patients with POD = 4 [3;7], own representation

Table 13: Subgroup analysis of predisposing risk factors for postoperative delirium (n = 69)

Variable	No POD (n = 57)	POD (n = 12)	P value
Age [in years]	63 [55;75]	74 [59;78]	0.367
Sex			0.224
Female	30 (53%)	4 (33%)	
Male	27 (47%)	8 (67%)	
Current occupation			0.071
Working or in training	18 (32%)	1 (8%)	
Unemployed	2 (3%)	2 (17%)	
Retired	37 (65%)	9 (75%)	
Education [in school years]	10 [9;10]	10 [9;13]	0.785
ASA Physical Status			0.256
I	3 (5%)	0 (0%)	
II	37 (65%)	5 (42%)	
III	16 (28%)	7 (58%)	
IV	1 (2%)	0 (0%)	
Charlson Comorbidity Index			0.120
0	4 (7%)	1 (8%)	
1-2	22 (38%)	1 (8%)	
3-4	17 (30%)	4 (33%)	
≥ 5	14 (25%)	6 (50%)	
DASS-21 score*			
Depression score	3 [1;8]	7 [4;9]	0.029
Anxiety score	1 [1;4]	5 [3;6]	0.004
Stress score	5 [2;8]	4 [2;9]	0.910

ASA = American Society of Anesthesiologists; DASS-21 = Depression Anxiety Stress Scale-21; POD = Postoperative delirium

*n = 68 (due to missing data in questionnaire)

Table modified from Eckert et al., 2023[37]

Table 14: Subgroup analysis of precipitating risk factors for postoperative delirium (n = 69)

Variable	No POD (n = 57)	POD (n = 12)	P value
Type of anesthesia			0.289
Balanced anesthesia	43 (75%)	7 (58%)	
Total intravenous anesthesia	14 (25%)	5 (42%)	
Operative severity			0.038
1	27 (47%)	1 (8%)	
2	13 (23%)	4 (33%)	
3	15 (26%)	7 (58%)	
4	2 (4%)	0 (0%)	
Duration of anesthesia [in minutes]	136 [94;201]	172 [129;267]	0.047

POD = Postoperative delirium

Table modified from Eckert et al., 2023[37]

Table 15: Localization of pain (n = 69)

Variable	n (%)
Back pain	24 (35%)
Joint pain	
Shoulder	13 (19%)
Fingers	1 (1%)
Hip	5 (7%)
Knee	7 (10%)
Ankle	1 (1%)
Neck	1 (1%)
Jaw	1 (1%)
Multiple joints	8 (12%)
Generalized pain	3 (4%)
Abdominal pain	2 (3%)
Headache or facial pain	2 (3%)
Chest pain	1 (1%)

Table modified from Eckert et al., 2023[37]

Table 16: Subgroup analysis of pain characteristics (n = 69)

Variable	No POD (n = 57)	POD (n = 12)	P value
Duration of pain*			0.597
6 months to 1 year	11 (20%)	1 (8%)	
1 to 2 years	9 (16%)	1 (8%)	
2 to 5 years	13 (23%)	5 (42%)	
> 5 years	23 (41%)	5 (42%)	
Course of pain over the last four weeks**			0.966
Permanent pain, little variation	8 (14.5%)	2 (17%)	
Permanent pain, great variation	19 (34.5%)	5 (42%)	
Painful attacks	21 (38%)	4 (33%)	
Permanent pain and painful attacks	7 (13%)	1 (8%)	
Pain intensity (NRS)*			
Current pain intensity	3 [0;4]	4 [3;7]	0.026
Average pain intensity over the last four weeks	5 [3;6]	4 [3;6]	0.578
Worst pain intensity over the last four weeks	7 [5;8]	8 [6;9]	0.260
Chronic pain diagnosis			0.679
Present	48 (84%)	11 (92%)	
Not present	9 (16%)	1 (8%)	
Effectiveness of previous pain treatment***			0.165
Ineffective	2 (4%)	2 (17%)	
Temporarily effective	21 (39%)	2 (17%)	
Effective	29 (54%)	8 (67%)	

NRS = Numerical Rating Scale; POD = Postoperative delirium

*n = 68 (due to missing data in questionnaire); **n = 67 (due to missing data in questionnaire); ***n = 66 (not all patients received treatment)

Table modified from Eckert et al., 2023[37]

4. Discussion

4.1 Short summary of results

4.1.1 Key findings

A prospective observational cohort study was conducted to investigate the presumed association between preoperative chronic pain lasting ≥ 6 months and the occurrence of POD as primary outcome. It included adult patients ≥ 18 years undergoing elective non-cardiac surgery under general anesthesia. This primary analysis did not find a significant association between chronic pain and POD.

A subgroup analysis examined specific characteristics of chronic pain. The aim was to determine potentially modifiable risk factors for POD that can be treated preoperatively. This subgroup analysis included all patients from the cohort who reported chronic pain. It showed that current pain intensity was higher in chronic pain patients who later developed POD.

As we hypothesized to find an association between chronic pain and POD, these results are somewhat surprising, but they do not question the assumption that pain is a risk factor for delirium in general. Instead, they might indicate that the relationship is more complex: the mere presence of chronic pain might not be as important as certain pain characteristics, such as current pain intensity.

4.1.2 Additional findings

Our bivariate analysis showed that patients who developed POD had significantly higher ASA PS scores, DASS-21 anxiety scores, a higher operative severity, and a longer duration of anesthesia. Multivariable analysis showed that a longer duration of anesthesia and higher DASS-21 anxiety scores were significantly associated with POD.

4.2 Interpretation of results

This analysis suggests that the mere presence of chronic pain lasting ≥ 6 months is not a modifiable risk factor for POD. This is to some extent surprising given our hypothesis, as we expected to find an association between chronic pain and POD. There could be several reasons for this:

First, the definition of chronic pain employed here might have influenced the outcome. Previous clinical studies usually described lasting or recurring pain over 3 to 6 months as chronic pain.[51] Choosing a cut-off of six months might be more restrictive, but on the other hand, assessment was based on the answer of the participant to the question "Do you experience chronic pain lasting six months or longer?". Self-report is considered the gold standard to measure pain since it is a subjective experience.[52] With this approach, 69 out of 176 patients (39%) reported chronic pain. In the general adult population in Europe, the prevalence is only 19%.[53] But this difference is plausible, because study participants were both hospitalized and older than the average population. Older people are more likely to experience chronic pain. In our cohort, 59 out of 69 patients had a clinical diagnosis of chronic pain documented in their medical record and were mostly treated for it. Thus, it seems unlikely that the definition employed here had flaws, leading to many over-diagnosed or false-positive cases of chronic pain.

Second, a relatively low delirium incidence (compared to other studies) may suggest that some cases of POD were not adequately detected. The definition of delirium has changed significantly over time in the literature[8] and the evaluation varies in prior studies. Different diagnostic tools – with varying sensitivity and specificity – can be employed to detect POD. Our approach might have yielded a lower incidence than other measurements. DSM-5 criteria for delirium diagnosis have been described as being more restrictive as previous DSM versions.[8] A strict adherence to DSM-5 criteria might therefore produce a higher proportion of false-negative cases. Only 16 patients fulfilled DSM-5 criteria for POD during any study visit, which could have impacted the outcome of this study. To address this, we also conducted a medical record and chart review and included all patients with a positive delirium test result, which yielded 39 cases of POD (22%). Hence, it seems unlikely that the definition employed here had flaws, leading to many undetected or false-negative cases of POD.

Third, the interaction between chronic pain and POD might be more complex than expected initially. It might be moderated or mediated by certain pain characteristics, such as current pain intensity. Similar studies have investigated preoperative pain and POD, and some have found an association between a higher current pain intensity and the occurrence of POD in older adults. Although these studies were not specifically focused on chronic pain patients, it is enlightening to summarize their results in detail:

Some studies did not find an association between preoperative pain and POD. Leung et al. (2009)[26] investigated 335 patients undergoing noncardiac surgery, primarily to find out whether postoperative delirium might restrict the use of patient controlled analgesia, but they also assessed preoperative pain at rest < 48 hours before surgery using a verbal version of the Visual Analog Scale (VAS). They did not find a significant difference regarding preoperative resting pain in patients who later developed POD compared to those who did not. Greene et al. (2009)[32] examined 100 patients undergoing major noncardiac surgery. The preoperative evaluation took place within 14 days prior to surgery and contained the Numerical Rating Scale (NRS) to assess pain. They found no significant group differences regarding preoperative pain either.

Several studies found an association only in bivariate analyses, but not after controlling for confounders. Leung et al. (2013)[27] included 581 patients > 65 years undergoing scheduled noncardiac surgery to assess how preoperative risk for delirium moderates the influence of other risk factors for POD (namely postoperative pain and opioid use). They conducted a preoperative interview that usually occurred < 1 week before surgery, which also included assessment of preoperative pain at rest using the NRS. A high score was found to be associated with POD in a bivariate analysis, but they did not explore this further. Leung et al. (2005)[33] examined 219 patients ≥ 65 years scheduled for major noncardiac surgery and conducted an interview < 48 hours before surgery in the preoperative clinic. Preoperative pain at rest and with movement were assessed via VAS. Both scores were significantly associated with POD in a bivariate, but not in a multivariate logistic regression analysis. Tan et al. (2008)[34] included 53 patients undergoing cardiac surgery and found mildly increased preoperative pain rating as a significant predictor for POD.

Lastly, some studies found an association between preoperative pain and POD also when controlling for confounders. Vaurio et al. (2006)[25] assessed preoperative pain at rest and with movement in 333 patients ≥ 65 years undergoing scheduled noncardiac surgery. They used a verbal version of the VAS and found both pain scores to be significantly increased in patients with POD using bivariate analysis. A multivariate logistic regression showed an association between moderate to severe preoperative resting pain and POD. Behrends et al. (2013)[35] assessed 472 patients > 65 years undergoing major noncardiac surgery. They conducted an interview < 48 hours before surgery and found that higher NRS pain scores (defined as scores ≥ 4) were an independent risk factor for POD. This was found using a multivariable logistic regression. Kosar et al. (2014)[36] enrolled 459 patients to assess whether preoperative pain and depressive symptoms have a cumulative effect to increase risk for POD. An association of preoperative pain and POD was found in a multivariable analysis. Preoperative pain interacted with depressive symptoms as well, which was in line with their hypothesis.

These results are obviously not transferable to each other and inconsistent. The underlying cause why our results are consistent with some of these studies and diverge from others is hard to assess. It could be attributed to restrictions of the patient sample. Notably, most previous studies included older adults ≥ 65 years. In one study, the sample was restricted to a certain surgical field. This could have produced different results than in our study sample of adults ≥ 18 years, but it does not explain the mixed results in general.

Different outcomes could also be attributed to the fact that preoperative pain was not characterized any further. Different types or features of preoperative pain could produce different results. All previous studies discussed here do not provide any more specific information on the type of preoperative pain that they measured. Some studies mention general information to characterize it, such as “pain at rest” or “pain with movement”. Likewise, “pain intensity” is sometimes described (e.g., current, average, or worse pain) using the VAS or NRS. But they do not mention whether they assessed acute or chronic pain, or the localization, duration, and other important characteristics of pain.

To conclude this comparison with similar studies, it is interesting to consider a recent study from 2020 that analyzed 60 patients for POD. The authors found an association with acute pain lasting < 1 month, whereas chronic pain lasting > 1 month was not found to be associated.[54] This is consistent with our results.

In sum, these considerations demonstrate the importance to characterize preoperative pain further and differentiate between various types of pain. However, they do not question the general association of pain and delirium.

4.3 Embedding of results into the current state of research

The preceding section provided an interpretation of our results that does not refute a general relationship between pain and POD. In the following, this will be further elaborated by reviewing the current state of research.

Current research largely agrees on the association between pain and POD. But there are not many recent studies that investigate this any further. Sampson et al. pointed out the need for more research on this topic.[55] Our study contributes to closing this research gap. It highlights the importance to differentiate between pre- and postoperative pain when examining an association of pain and POD. When investigating preoperative pain, it is important to note that the pathophysiology is different in acute and chronic pain. Therefore, it makes sense to differentiate between these types of pain.

This study focused on chronic pain because of the growing evidence linking the pathophysiology of chronic pain and POD. Earlier studies have pointed out that certain conditions enhance the brain's susceptibility to external stressors, thereby increasing the risk for POD.[56] Chronic pain might be involved in – or contribute to – these underlying mechanisms. The transition from acute to chronic pain is mediated by activated microglia and astrocytes that induce the release of inflammatory mediators such as cytokines and chemokines.[57–59] This leads to central sensitization, increased neuroinflammation and neurodegeneration.[60] These inflammatory changes can also promote neurocognitive disorders.[60–62] Accordingly, neuroinflammation has been proposed as a therapeutic target for perioperative neurocognitive disorders.[63] While the pathophysiology of POD is still largely unknown, several mechanisms have been proposed that are mostly based on animal studies.[17,64] These include an imbalance of neurotransmitters, impaired cerebral perfusion and neuroinflammation.[62] Interestingly, a meta-analysis of observational studies found that POD is indeed associated with increased central and peripheral inflammatory markers: C-reactive protein and interleukin 6.[65]

Chronic pain can impair cognition, including attention, memory, information processing and executive function. All these aspects are important in the diagnosis of POD. A systematic review from 2018 investigates the relationship between chronic pain and neurocognitive function and supports this argument.[66] Another meta-analysis from 2021 also found an association between chronic pain and cognitive decline, depending on the cognitive assessment method.[67] Moreover, chronic pain is associated with neurocognitive disorders that are similar to POD, such as dementia.[61] Lately, there has been a possible causal explanation how chronic pain impairs memory.[68] To support this hypothesis, a recent study found that chronic pain is associated with postoperative cognitive dysfunction (POCD) in patients > 65 years undergoing elective hip surgery.[69]

To conclude, accumulating evidence is in line with a plausible hypothesis for the underlying pathophysiology that connects chronic pain and POD; and clinical studies have found an association between chronic pain and impaired cognitive function or even neurocognitive disorders. Despite this evidence and in contrast to the underlying hypothesis, this study did not find an association between chronic pain and POD. This implies that the mere presence of chronic pain might not be the crucial factor. Instead, current pain intensity shortly before surgery might be more relevant.

4.4 Strengths and weaknesses of the study

This study has several strengths and weaknesses that both affect the validity of our results. Validity includes two domains: internal and external validity.[70] Internal validity describes the extent to which our results are credible in the context of this study. It depends on thoughtful study design and methodology, including accurate measurements with valid test instruments, careful data collection, and appropriate statistical analysis. A high internal validity indicates that changes in the outcome variable can be attributed to the independent variable, whereas a low internal validity indicates that changes in the outcome variable are rather caused by a systematic error.[71] External validity describes the generalizability of our results to other situations, locations, patients and times. It is limited by the internal validity of the study.

4.4.1 Internal validity

So far, this is the first study to systematically assess in depth the relationship between chronic pain lasting ≥ 6 months and POD. To detect POD, we used only validated delirium tests and instruments with a high sensitivity and specificity. Specific pain characteristics in the subgroup of chronic pain patients were assessed with items from a standardized and validated pain questionnaire. Together, these items provide a relatively comprehensive picture of chronic pain that was present in our cohort.

All examinations were conducted by trained study personnel. Data were carefully collected and there was no restrained access to relevant data for the study. Because many previous studies investigated potential risk factors for POD, we could rely on this extensive body of literature.

Since our research question was not suitable for an experimental study design, we conducted an observational cohort study. Our study design implies that that we cannot infer a causal relationship between chronic pain and POD. Confounding is also an important issue to consider in observational studies, as opposed to randomized controlled trials.[72] Confounders may enhance, weaken or mask an association. There are two possibilities to reduce confounding in an observational cohort study: first, by limiting the study population to participants with a specific expression of the confounding factor and second, by controlling for confounders with multivariable analysis or stratification.[73] The first strategy involves for example inclusion of a specific age group, but the disadvantage of this strategy is a limited generalizability of the results. Here, multivariable analysis was used to control for confounders. Propensity score methods can also help to reduce the effects of confounding in non-experimental research, but we did not employ this here.[74] Despite striving for comprehensiveness – aiming to measure and report all important confounding variables – we cannot be certain that there was an unrecognized and unmeasured confounding variable that influenced the outcome.

Selection bias is a common hazard in case-control studies, but less common in cohort studies.[73] In our cohort study, a selection bias would occur if there was a systematic difference between patients with and without chronic pain (= exposure), and if this systematic difference was associated with POD (= outcome). There was no random selection of participants since we only screened patients that presented themselves for preanesthesia evaluation at the Charité Berlin. Not all patients could be contacted due to limited personnel capacity. To avoid handpicked candidates, we always approached the first ones on the waiting list. In this context, the proportion of analyzed cases must also be discussed. We included 200 patients, but only 176 were analyzed due to early dropouts (figure 1). Surgery was cancelled in 12 cases, six patients withdrew their consent preoperatively during the first assessment, five patients could not be assessed postoperatively (due to prolonged mechanical ventilation or severely impaired consciousness), and one patient was discovered to suffer from mild dementia during the first assessment and thus excluded. In sum, every patient that was assessed postoperatively was also included in our analysis. Hence, we are confident that there is no systematic difference in the two groups with and without chronic pain.

4.4.2 External validity

The generalizability of our results to the general population and across different situations is limited since the occurrence of POD depends on many factors and situational aspects.

Our patient cohort consisted of adults ≥ 18 years undergoing elective surgery under general anesthesia. We aimed to achieve generalizability for an adult cohort by recruiting patients ≥ 18 years, whereas many other studies only investigate delirium in older people ≥ 65 years. Since patients were included regardless of the type of surgery, our results are not limited to a specific surgical discipline. But we excluded patients with severe visual or auditory impairments, language barriers and dementia. Patients with mild cognitive impairments were also less likely to participate in the study. Sensory deficits and preexisting cognitive impairment are among the most important risk factors for POD. Thus, our cohort did not have some designated risk factors and was less prone to develop POD. We would have probably observed a higher number of POD cases if we had restricted our patient cohort to more risk factors or to another setting (e.g., advanced age, emergency surgery). Our patient cohort is most likely a non-representative sample of the entire adult patient population undergoing elective surgery. But it is relatively more representative than previous studies.

Importantly, our findings are limited by a small sample size. This study included 200 patients. Due to early dropouts, 176 of these patients could be evaluated. Thirty-nine out of 176 patients (22%) fulfilled criteria for POD. A larger study with more participants would be more representative and provide more accurate or reliable results. It would also enable a more advanced analysis of other pain-related risk factors for POD in chronic pain patients. With only 69 patients in our subgroup, we could not conduct a multivariable but only a bivariate analysis.

Situational aspects such as the place and timing of the study must also be considered.[71] Data collection took place from January 2017 to January 2018. As this period covered an entire year of normal surgical routine, we are confident that timing of the study had no influence. A multi-centric study would be preferable to confirm our results. POD is mostly already present in the recovery room, but can develop up to the fifth postoperative day[7]. In this regard, our results are limited because patients were assessed preoperatively, postoperatively, and once daily throughout postoperative day 1 to 3 (or until discharge, if they were discharged earlier than on postoperative day 3). However, most patients were already discharged around postoperative day 3 (median length of hospital stay = 4 days [3;7]), so even if we had intended to visit them from postoperative day 1 to 5, this would not have been possible in many cases. Another patient cohort with more cases of major surgeries and longer periods of hospitalization would have enabled longer visits in order to make sure the required assessment throughout postoperative day 5 is guaranteed. Also, more than one study visit per day would have been favorable as POD is known to fluctuate. To detect fluctuating symptoms that were not present during any study visit, we conducted a chart review and reviewed the medical record as well as the discharge letter in order to not miss any cases of POD.

4.5 Implications for practice and future research

4.5.1 Implications for practice

Since treatment options for POD are still limited, its management mainly consists of prevention. This requires a careful preoperative risk stratification and risk reduction.[17]

We aimed to identify modifiable risk factors for POD by investigating the influence of chronic pain. We hypothesized that chronic pain was a risk factor for POD, but we did not find an association between chronic pain and POD. Our subgroup analysis showed that current pain intensity was higher in chronic pain patients who later developed POD. If future studies confirm that a high current pain intensity is indeed a risk factor for POD in chronic pain patients, this could have implications for clinical practice.

The current guideline on POD recommends general measures to minimize the risk of all patients for POD, as well as identification of vulnerable patients.[7] Figure 3 extends these recommendations to the assumption that a high current pain intensity was a risk factor. It is important to note that due to a limited generalizability and a small sample size, the suggested algorithm in figure 3 cannot be implemented in clinical practice based on the findings in this study. No direct conclusions can be drawn from our results as far as recommendations for clinical practice are concerned. Nevertheless, a few clinical implications can be derived from the interpretation of our results and considering previous studies.

Since current pain intensity was higher in chronic pain patients who later developed POD, our results could be interpreted to consider chronic pain patients as a vulnerable group for POD if they experience intense pain preoperatively. Chronic pain is often underdiagnosed und undertreated.[53] In an aging population such as in Germany, this is especially important as age, comorbidities and chronic pain are associated.[75] Undertreated pain is an unfavorable condition that should be addressed adequately in the hospital setting, but especially in emergency settings, it was sometimes not paid enough attention to, or even regarded as unavoidable in the past.[76,77] Previous research has pointed out that severe pain is associated with delirium in the emergency department.[78] This underlines the importance to treat it adequately.

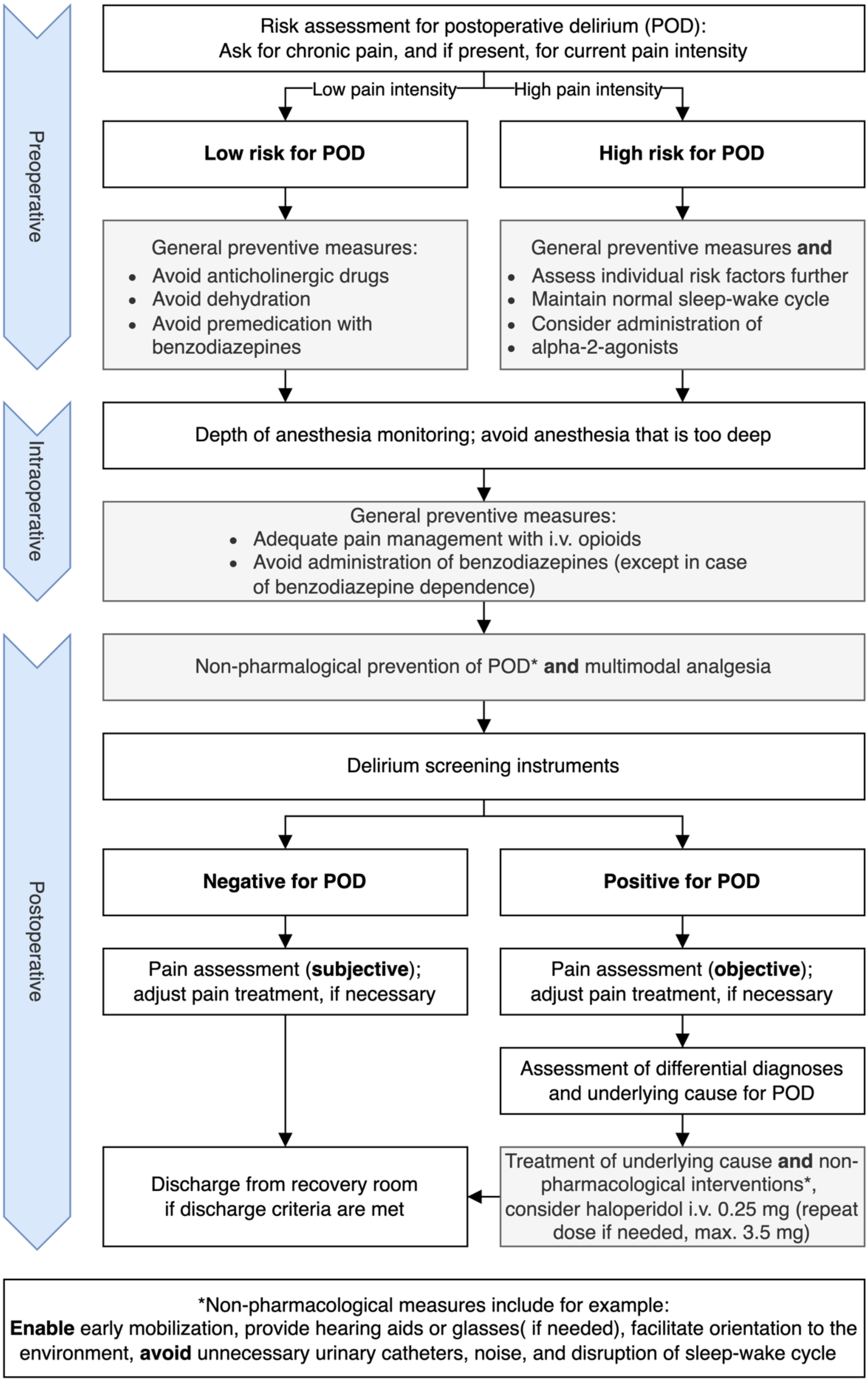

Figure 3: Flowchart showing guideline-conform recommendations for the prevention and treatment of postoperative delirium (POD), modified for the case that a high current pain intensity in chronic pain patients was a risk factor for POD, modified from Aldecoa et al., 2017[7]

In clinical practice, adequate treatment of acute pain is sometimes avoided due to the fear that opioids may cause delirium. There are more reasons why one could be reluctant to use opioids for acute pain, but if we only consider delirium, the underlying consideration for this is a presumptive dilemma: "Pain causes delirium, but opioids also cause delirium, so what shall I do?" It is long known that avoiding opioids or using minimal doses of opioids increases the risk for patients with acute pain.[30]

Thus, a possible implication for clinical practice from our study could be that – aiming to reduce risk for POD – patients with chronic pain should be asked for their current pain intensity preoperatively. If they report intense pain, they should be treated appropriately before surgery to optimize their preoperative status in accordance with the current guideline.[7] An adequate perioperative pain management with a multimodal pain strategy should be implemented. Perioperative pain management can be challenging in patients with chronic pain, especially in patients with long-term opioid use, who often face stigma and underestimation of their actual pain.[79] But there are efforts to improve the situation with a multidisciplinary and patient-centric approach that considers pre-, intra-, and postoperative periods alike.[80] These suggestions should be adapted in clinical practice.

4.5.2 Implications for future research

Future research should evaluate chronic pain according to the current International Association for the Study of Pain (IASP) classification, which has been recently revised for the first time since 1979. Pain is now defined as:

> *"An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage".*[81]

Several notes accompany the definition for further elaboration. The following note reflects the fundamental difference between acute and chronic pain:

> *"Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being".*[81]

This aspect is important to mention since chronic pain is not only characterized by a longer duration, but also by its maladaptive nature. It does not serve as a warning sign like acute pain, but rather comprises a condition itself that often goes along with functional limitations. The ICD-11 states that chronic primary pain

> *"[…] has persisted for more than 3 months and is associated with significant emotional distress and/or functional disability, and the pain is not better accounted for by another condition".*[82]

Previous studies usually described lasting or recurring pain over 3 to 6 months as chronic pain.[51] But future research should employ these new definitions.

Future research should also consider investigating specific subtypes of chronic pain as defined by the IASP. These are chronic primary pain and the 6 subgroups of chronic secondary pain: cancer-related pain, postsurgical or posttraumatic pain, secondary musculoskeletal pain, secondary visceral pain, neuropathic pain, secondary headache or orofacial pain.[51] Since these are different types of pain, their association with POD may vary.

Furthermore, it is interesting to consider our results and those of a previous study that found an association between POD and acute pain lasting < 1 month, but not with chronic pain lasting > 1 month.[54] This finding should be tested with a larger cohort and as mentioned above, with a definition of chronic pain as pain that persists or recurs for more than 3 months. One should also be aware that acute pain may mediate other risk factors for POD such as preoperative cognitive impairment, as shown in a recent study on the effect of postoperative acute pain.[29]

Further investigations could also focus on the reciprocal effects of preoperative pain and perioperative pain management. Undertreated acute pain, not opioid use, was found to increase risk for delirium in patients with hip fractures.[30] Hence, when examining chronic pain and POD, evaluation of pain management including the type and dosage of analgesics would also be interesting.

It is important to mention that our findings are limited by a small number of cases. Future research should carefully consider selecting a patient sample and aim to challenge our findings with more cases. Some inclusion and exclusion criteria could be revisited and optimized in order to include patients that are more prone to develop POD. With more cases of POD, one can also conduct a logistic regression of the subgroup.

Regarding data collection, daily study visits should be conducted up to the fifth postoperative day, preferably more than once daily. A multi-centric study would be preferable as well.

5. Conclusions

The results of this study implicate several conclusions. First, this study did not find a significant association between chronic pain and the occurrence of POD. This result must be interpreted with caution. There are both accumulating evidence and a plausible hypothesis how chronic pain is associated with pathophysiological changes that impose a risk factor for postoperative delirium. Our cohort had a high prevalence of chronic pain and a low incidence of POD, which might have influenced our results. Due to the heterogeneity of chronic pain and the recent advancements in the definition of chronic pain,[81] further investigation would be an interesting research topic.

Second, a subgroup analysis of chronic pain patients found that current pain intensity could be associated with POD. This finding suggests that undertreated chronic pain might be a modifiable risk factor. We could not investigate this further due to a low number of cases. But it would be very interesting to explore the differences between acute pain and chronic pain, and other characteristics of pain further.

Third, certain features of chronic pain might be more influential than others. This study highlights the need for a more differentiated approach. This is particularly important since perioperative management of chronic pain patients is complex, and since an adequate perioperative pain treatment should be a cornerstone in every anesthesiologist’s routine.

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Statutory declaration

„I, Sophie Charlotte Eckert, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic “Postoperative delirium and chronic pain” (“Postoperatives Delir und chronische Schmerzen”), independently and without the support of third parties, and that I used no other sources and aids than those stated.

All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.og) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me. “

May 23, 2023

Date Signature

Declaration of own contribution to the publications

Sophie Charlotte Eckert hatte folgenden Anteil an den folgenden Publikationen:

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Curriculum Vitae

My curriculum vitae does not appear in the electronic version of my paper for reasons of data protection.

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