

# BMJ Open Prediction of chronic postsurgical pain in adults: a protocol for multivariable prediction model development

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## ABSTRACT

**Introduction** Chronic postsurgical pain (CPSP) is a condition that affects an estimated 10%–50% of adults, depending on the surgical procedure. CPSP often interferes with activities of daily living and may have a negative impact on quality of life, emotional and physical well-being. Clinical prediction models can help clinicians target preventive strategies towards patients at high-risk of CPSP. Therefore, the objective of this study is to develop a clinically applicable and generalisable prediction model for CPSP in adults.

**Methods and analysis** This research will be a prospective single-centre observational cohort study in Denmark spanning approximately 1 year or until a predefined number of patients are recruited (n=1526). Adult patients aged 18 years and older scheduled to undergo surgery will be recruited at Aarhus University Hospital. The primary outcome is CPSP 3 months after surgery defined as average pain intensity at rest or on movement  $\geq 3$  on numerical rating scale (NRS) within the past week, and/or average pain interference  $\geq 3$  on NRS among any of seven short-form Brief Pain Inventory items in the past week (general activity, mood, walking ability, normal work (including housework), relations with other people, sleep and enjoyment of life). Logistic regression will be used to conduct multivariate analysis. Predictive model performance will be evaluated by discrimination, calibration and model classification.

**Ethics and dissemination** This research has been approved by Central Region Denmark and will be conducted in accordance with the Danish Data Protection Act and Declaration of Helsinki. Study findings will be disseminated through conference presentations and peer-reviewed publication. A CPSP risk calculator (CPSP-RC) will be developed based on predictors retained in the final models. The CPSP-RC will be made available online and as a mobile application to be easily accessible for clinical use and future research including validation and clinical impact assessments.

**Trial registration number** NCT04866147.

## INTRODUCTION

Chronic postsurgical pain (CPSP) is a condition that affects an estimated 10%–50% of adults who undergo surgery, depending on the type of surgical procedure.<sup>1</sup> In 2019, the International Association of the Study of Pain

## Strengths and limitations of this study

- We will recruit 1526 surgical patients based on a sample size calculation independent of events per variable to minimise potential model overfitting.
- The analysis will include patients from a broad range of surgical procedures to increase generalisability of the prediction model at the cost of reduced specificity.
- We will employ logistic regression to develop a simple and clinically applicable prediction model from which a risk calculator will be developed.
- Some possible limitations to the study design include the single-centre nature of the study, the observed incidence rate of chronic postsurgical pain may be lower than accounted for in the sample size calculation, outcome measurement will be patient-reported without physical confirmation and limited to 3 month follow-up and response rates to electronic (emailed) follow-up questionnaires may be lower than expected.

(IASP) redefined CPSP as pain that develops or increases in intensity after a surgical procedure, persists for at least 3 months and is localised to the surgical field.<sup>2,3</sup> Other causes of CPSP must be ruled out (ie, pre-existing conditions, infections).<sup>2</sup> It is estimated that over 300 million surgical procedures are performed globally each year.<sup>4</sup> Given the total volume of surgical procedures performed annually, the number of affected surgical patients and potential burden of CPSP are likely to be large.

CPSP often interferes with activities of daily living and has a negative impact on quality of life, emotional and physical well-being.<sup>5–8</sup> Several different mechanisms may contribute to the severity of CPSP, including mechanisms in relation to peripheral (the site of tissue trauma) and central (spinal and supraspinal) sensitisation and the psycho-social context in which the pain is experienced.<sup>9,10</sup> The wide scope of factors involved makes pain management complex and highlights the importance

of tailored treatment plans with a focus on long-term health rather than short-term resolution.<sup>9</sup> Thus, clinical prediction models are necessary to identify patients at high risk of developing CPSP and to support preoperative and postoperative clinical decision-making based on individual patient risk profiles.

Prediction models are equations that convert a combination of predictor values to estimate the individual risk of experiencing a future outcome within a specific period of time.<sup>11–13</sup> In surgery, prediction models are commonly used to predict the risk of adverse outcomes following an intervention.<sup>12</sup> In order for prediction models to be clinically useful, they must have adequate discrimination, calibration, face validity and clinical applicability. Ideally, prediction models will be developed using clinically relevant predictors that are selected based on a review of the literature in combination with clinical knowledge, rather than individual predictor-outcome associations in order to limit model overfitting.<sup>14</sup>

There is evidence to suggest the need for higher quality and more generalisable prediction models for CPSP. In our recent systematic review of prediction models for CPSP,<sup>15</sup> existing models posed several statistical and practical limitations for use in clinical settings. Most notably, small sample sizes, poor reporting or inappropriate handling of missing data, lack of model performance measure evaluation and absence of model validation.<sup>15</sup> There was also significant heterogeneity in tools used to measure CPSP, pain intensity cut-off values to distinguish between individuals with and without CPSP and length of follow-up times. Additionally, the majority of models were limited to specific populations and surgical procedures and therefore lack generalisability.

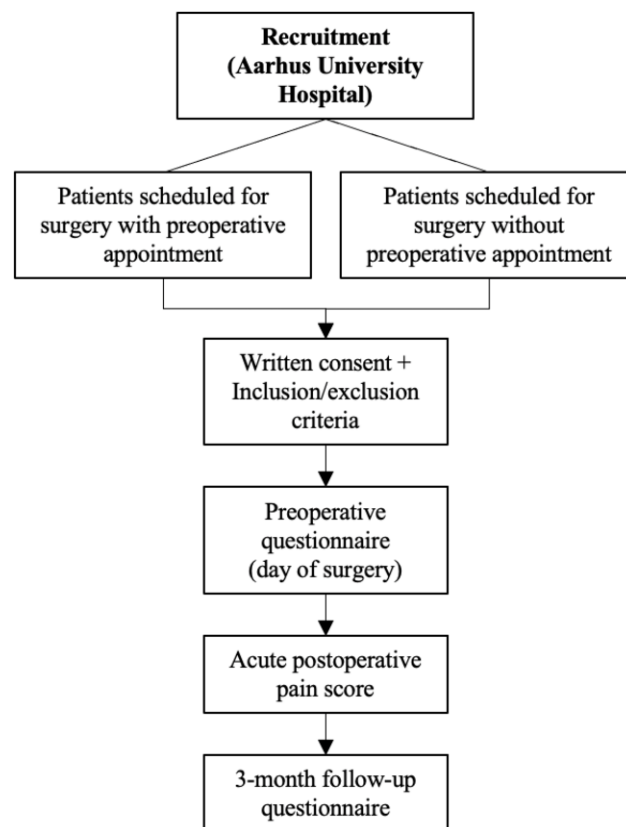
## OBJECTIVE

The primary objective of this study is to develop a clinically relevant and pragmatic prediction model for CPSP utilising preoperative, intraoperative and postoperative predictors for CPSP among a broad range of surgical patients who will provide a relatively high degree of generalisability to a variety of surgical procedures. Implementation of a high-quality prediction model could help facilitate shared decision-making, result in more efficient and effective postoperative pain management and contribute to CPSP prevention.<sup>14</sup>

## METHODS AND ANALYSIS

### Study design

The proposed research will be a prospective single-centre observational cohort study in Aarhus, Denmark, spanning approximately 1 year or until a predefined number of patients are recruited. Standard of care will not be affected and there is no intervention. All patients will be followed-up with electronically 3 months after surgery. A patient recruitment flow diagram is illustrated in [figure 1](#).



**Figure 1** Patient recruitment flow diagram.

Two prediction models will be developed. A model for preoperative prediction of CPSP will aid preoperative and intraoperative anaesthetic decision-making and acute postsurgical pain management. A model for postoperative prediction of CPSP, including preoperative, intraoperative and acute postoperative predictors, will support short-term and long-term postoperative pain management.

This study will follow the Prognosis Research Strategy (PROGRESS) framework<sup>13</sup> and Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) guidelines<sup>16</sup> for prediction model development.

### Setting and participants

Consenting Danish-speaking adults aged 18 years and older who are scheduled to undergo surgery will be recruited at Aarhus University Hospital (AUH). AUH is one of the largest hospitals in Northern Europe with 41 clinical departments, 854 beds, 9699 employees and 82585 annual surgeries. Patients who undergo common elective surgical procedures within the following major categories will be recruited into the study: cardiothoracic surgery, breast surgery, abdominal surgery (gastrointestinal, genitourinary and obstetrics) and orthopaedic surgery.

All patients will be asked to provide written informed consent in-hospital prior to their scheduled surgery in order to participate in the study. Patients who are scheduled for a preoperative check-up appointment will be

informed of the study during the preoperative appointment. For patients who are scheduled for a surgical procedure without a preoperative check-up appointment, it may not be possible to provide a recommended reflection time of 24 hours. In such cases, patients may be asked to provide informed consent on the day of their surgery. On providing consent, patients will be asked to complete a 10-min questionnaire prior to their surgery and a 5-min online questionnaire 3 months following their surgery.

Patients who refuse or are unable to provide informed consent will be excluded from the study. Individuals with a cognitive impairment will be excluded based on clinical judgement. Patients who undergo reoperation in the same surgical area within 3 months of their initial surgery will be excluded.

### Outcome

The primary outcome of interest is CPSP defined by the IASP as: (1) pain that develops or increases in intensity after a surgical procedure, (2) persists or recurs for 3 months and (3) is localised to the surgical field.<sup>2</sup> CPSP will be measured 3 months after the surgical procedure using an 11-point numerical rating scale (NRS; 0–10) where 0 is no pain and 10 is the worst pain imaginable. Based on the literature, an NRS cut-off value of  $<3$  will indicate no or mild CPSP, while NRS values  $\geq 3$  will indicate the presence of moderate to severe CPSP.

In addition to the previously defined IASP criteria, fulfilment of one of the following conditions will be required to define CPSP: (1) average pain intensity on rest or movement  $\geq 3$  on NRS within past 1 week, and/or (2) average pain interference  $\geq 3$  on NRS among any of seven short-form Brief Pain Inventory (BPI) items (general activity, mood, walking ability, normal work (including housework), relations with other people, sleep and enjoyment of life) in past 1 week. Average pain in the past week was chosen as the primary endpoint for CPSP since it has been found to better reflect the overall experience of pain and its impact on function in patients with persistent pain, compared with current pain ratings.<sup>17</sup> A case definition for CPSP and an algorithm to illustrate how patients will be categorised are illustrated in online supplemental files 1 and 2.

### Candidate predictors

We identified 10 candidate predictors to be considered for inclusion in the multivariable models based on clinical knowledge and a review of the literature. The preoperative model will include age, sex, body-mass index (BMI), marital status, preoperative opioid consumption, preoperative pain intensity in the surgical area, presence of other preoperative pain, surgical technique (invasive/open, minimally invasive) and the postoperative model will include the aforementioned predictors in addition to surgery duration and acute postoperative pain intensity. See online supplemental file 3 for a list of candidate predictors to be included in preoperative and

postoperative models and handling of candidate predictors in the multivariable models.

### Data collection

Preoperative demographic and clinical characteristics will be collected using standardised questionnaires and from the electronic medical record (EMR). Data obtained from the electronic medical record will include date of birth (age), sex, height and weight (BMI), physical comorbid conditions and ASA physical status score. Data obtained from patient questionnaires will include ethnicity, smoking status, alcohol use, preoperative pain in the operative area, presence of other preoperative pain conditions, current pain treatment and medications, pain-related symptoms (ie, numbness, sensitivity), pain catastrophising, anxiety and depression scores.

Intraoperative characteristics will be collected postoperatively from the electronic medical record. These will include the surgical procedure, type of surgery (primary, removal, revision), surgical technique (invasive/open, minimally invasive), central/peripheral nerve block (yes, no), remifentanyl infusion (yes/no), intraoperative handling of nerves, if relevant (preserved, partly preserved, sectioned), duration of surgery (time from incision to skin closure) and patient type (inpatient or outpatient).

Postoperative characteristics will be collected from the responsible nurse in the postanesthesia care unit and from the electronic medical record. These will include acute postoperative pain intensity, postoperative analgesics, dose and formulation, postoperative complications, time to discharge readiness, analgesics at discharge (both provided and prescribed), postsurgical opioid use at 3 months, postsurgical pain intensity at 3 months and impact of pain on daily life at 3 months. All patients will be emailed the same standardised questionnaire for self-reported outcome measurement at 3 months via REDCap.

Presurgical and postsurgical pain intensity and impact of pain on daily life will be measured using a NRS with questions adapted from the BPI.<sup>18</sup> Preoperative anxiety and depression scores will be measured using the Hospital Anxiety and Depression Scale (HADS).<sup>19</sup> Pain catastrophising will be measured using the Pain Catastrophising Scale (PCS).<sup>20</sup> Possible neuropathic pain components will be measured using questions adapted from the pain-DETECT questionnaire.<sup>21</sup> REDCap will be used for data collection and management.

### Sample size calculation

A sample size calculation for prediction models with binary outcomes was conducted according to Riley *et al.*<sup>22</sup> Based on an external validation study by Montes *et al.*,<sup>23</sup> an estimated Cox-Snell  $R^2$  value of 0.074, CPSP prevalence rate of 20.6% and 10 degrees of freedom, we require a minimum sample size of 1174 participants and 24 events per variable to ensure a global shrinkage factor of  $\geq 0.9$ , a small absolute difference of  $\leq 0.05$  in the apparent and adjusted Nagelkerke  $R^2$  value and precise estimate of



overall risk within a margin of error of 0.05. Using these parameters, we expect 242 patients to develop CPSP within our study sample. To account for anticipated withdrawals, incomplete data or losses to follow-up, we added 30% bringing the targeted enrolment to 1526 participants.

Based on proportions of patients undergoing surgical procedures at AUH, we will aim to recruit the following number of patients from each major surgical group between June 2021 and July 2022: thoracic (n=294, 19.3%), breast (n=136, 8.9%), gastrointestinal (n=206, 13.5%), genitourinary (n=400, 26.2%), obstetrics (n=148, 9.7%) and orthopaedics (n=342, 22.4%).

### Statistical analyses

Means, standard deviations, medians and proportions will be used to describe the study sample. Possible missing data patterns will be investigated and reported. Appropriate data imputation techniques will be considered depending on the type and extent of missingness (missing completely at random, missing at random or not missing at random).<sup>14 24</sup> Logistic regression will be used to conduct multivariable analysis. All candidate predictors will be entered into the model and backwards selection will be used to determine predictors for the final prediction models. Since sex is likely strongly correlated with specific procedures, we will either conduct a stratified analysis stratifying by sex or a sensitivity analysis restricted to female sex, dependent on sample size.

Predictive model performance will be evaluated by discrimination and calibration. Receiver-operating curves will be assessed to evaluate the models' discriminative abilities (how accurately predictions discriminate between individuals with and without the outcome). Calibration plots and Hosmer-Lemeshow test will be assessed to evaluate the agreement between observed and predicted outcomes (how close the model estimates are to the true probability of the population under study). Model classification (sensitivity and specificity) and overall performance ( $R^2$ ) will also be assessed.

Possible model overfitting will be corrected by shrinkage of predictor weights and optimism will be assessed through internal validation by bootstrapping to ascertain the best-fitted and most stable model while correcting for bias. Similar to Montes *et al*, a post-hoc analysis will be conducted to examine the effects of pain catastrophising and anxiety and depression on predictive performance.<sup>23</sup> All analyses will be conducted using R (R Foundation for Statistical Computing, Vienna, Austria).

### Model simplification

There are both strengths and limitations to simplified prediction methods. Simplified prediction models may demonstrate a greater degree of generalisability and are relatively easier to implement clinically.<sup>25 26</sup> However, simplification may risk loss of specificity to predict outcomes in particular situations.<sup>27 28</sup> We will

consider simplification of the final models by transforming continuous variables to binary variables and re-evaluate model performance for significant changes. If there is no or little change in model performance, we will consider the simplified models as the final models.

### Patient and public involvement

Patients, family members and hospital nursing staff were involved in questionnaire development. No patients were involved in study planning. There are no current plans to involve patients in analysis, however we plan to include patient representatives from relevant patient organisations for the interpretation and dissemination of results.

## ETHICS AND DISSEMINATION

### Ethical aspects and informed consent

This research has been approved by Central Denmark Region and will be conducted in accordance with the Danish Data Protection Act and Declaration of Helsinki.

There is a recommended reflection time for patients to consider participation in a study of 24 hours. However, since not all patients have a preoperative appointment and due to restrictions on calling patients who are scheduled for surgery, it will not be possible to provide the recommended 24-hour reflection period for all patients.

### Dissemination plan

Representatives of the included surgery departments and patient representatives from relevant pain organisations will be provided an opportunity to review and comment on the study results. Study findings will be disseminated through conference presentations, peer-reviewed publication and relevant patient organisations.

A CPSP risk calculator (CPSP-RC) will be developed based on predictors retained in the final models. Since this tool is intended for clinical use, we intend to obtain input from clinicians through focus groups to ensure adequate design and usability of the final prediction tool. The CPSP-RC will be made available online and as a mobile application to be easily accessible for clinical use and researchers to conduct future validation and clinical impact assessments.

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**Contributors** NP-P conceived the study. NP-P designed the data analysis and statistical modelling with input from LN, SH and CFC. LN will facilitate data collection among the various surgical departments. All authors contributed and approved the design of the final study protocol. NP-P drafted the manuscript. All authors read, revised and approved the final manuscript.

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