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Pain

Development and validation of a multivariable prediction model for early prediction of chronic postsurgical pain in adults: a prospective cohort study

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Abstract

Background: Early identification of patients at risk of developing chronic postsurgical pain (CPSP) is an essential step in reducing pain chronification in postsurgical patients. We aimed to develop and validate a prognostic model for the early prediction of CPSP including pain characteristics indicating altered pain processing within 2 weeks after surgery.

Methods: A prospective cohort study was conducted in adult patients undergoing orthopaedic, vascular, trauma, or general surgery between 2018 and 2019. Multivariable logistic regression models for CPSP were developed using data from the University Medical Centre (UMC) Utrecht and validated in data from the Erasmus UMC Rotterdam, The Netherlands.

Results: In the development (n=344) and the validation (n=150) cohorts, 28.8% and 21.3% of patients reported CPSP. The best performing model (area under the curve=0.82; 95% confidence interval [CI], 0.76–0.87) included preoperative treatment with opioids (odds ratio [OR]=4.04; 95% CI, 2.13–7.70), bone surgery (OR=2.01; 95% CI, 1.10–3.67), numerical rating scale pain score on postoperative day 14 (OR=1.57; 95% CI, 1.34–1.83), and the presence of painful cold within the painful area 2 weeks after surgery (OR=4.85; 95% CI, 1.85–12.68). Predictive performance was confirmed by external validation.

Conclusions: As only four easily obtainable predictors are necessary for reliable CPSP prediction, the models are useful for the clinician to be alerted to further assess and treat individual patients at risk. Identification of the presence of painful cold within 2 weeks after surgery as a strong predictor supports altered pain processing as an important contributor to CPSP development.

Keywords: chronic pain; model validation; nociplastic pain; postoperative pain; postsurgical pain; prediction model; prognostic factor; risk assessment

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Editor's key points

- Chronic postsurgical pain (CPSP) is a major health issue and remains difficult to predict. Yet identifying risk factors for CPSP is the best way to prevent pain chronicity after surgery.
- In this prospective large scale study of patients undergoing various types of surgery, a prognostic model for postsurgical pain was developed and validated.
- The model retained only four items: orthopaedic surgery, preoperative use of opioids, pain intensity and painful cold within the painful area (using the DN4 questionnaire) two weeks after surgery.
- The relevance of this model to predict chronic postsurgical pain at one year and its impact on therapeutic management must now to be determined.

Chronic postsurgical pain (CPSP), commonly defined as pain that develops after a surgical procedure and persists at least 3 months, constitutes a widely underdiagnosed and often poorly treated medical problem affecting 10–50% of all postsurgical patients.[1–3] CPSP leads to significant disease burden and reduced quality of life.[4,5] Difficulty of treating the transitioned pain has contributed to opioid analgesic overuse in some countries introducing an increased risk of misuse, and abuse.[6]

Early identification of patients at risk of developing CPSP is an essential step in reducing pain chronification. Prediction of CPSP has received increasing attention over the past decade. Most studies on predicting CPSP, however, have investigated isolated risk factors in specific surgical procedures rather than explaining the interaction and independency of risk factors by predictive modelling in a wide range of surgical interventions. A systematic review appraising the quality and performance of prediction models for CPSP has described fair performing models which were generally hampered by a high risk of bias owing to poor reporting and the lack of external validation.[7] The need for a simple, high-quality clinical prediction model with greater reliability to predict individual outcomes in the early postoperative period remains.

A common feature of CPSP is that the painful sensations change from the familiar acute postoperative pain to a complex pain syndrome with nociplastic characteristics, neuropathic characteristics, or both.[8,9] Preclinical studies have revealed that the transition from acute to chronic pain starts early within the first 2 weeks after nociception by peripheral and central inflammatory processes and activation of spinal glial cells.[10–13] We hypothesise that the ability to predict CPSP improves by including pain characteristics that occur with nociplastic and neuropathic pain at this critical time-point in the transition from acute to chronic pain. The predictive value of seven signs and symptoms was assessed in preparatory to develop and validate generic postoperative prediction models based on easily obtainable data for the early identification of patients at risk for CPSP.

Methods

After approval by the local medical ethics committees of the University Medical Centre Utrecht (UMCU) and Erasmus University Medical Centre Rotterdam (EMC), this prospective cohort study was nested in PAIN OUT (Improvement in postoperative PAIN OUTcome), an international quality improvement and registry project providing an information system for assessing and optimising postoperative pain management (ClinicalTrials.gov: NCT02083835). Further details of this registry have previously been described.[14]

Study population

Between January 2018 and December 2019, adult patients undergoing orthopaedic, vascular, trauma, or general surgery at the UMCU and EMC included in PAIN OUT were enrolled. Because the goal was to develop generic prediction models, there was no restriction to surgery type.

On the first day after surgery, eligible patients were approached by a research assistant for further explanation and definitive inclusion. Depending on the requirements of the local ethics committee, a written or oral informed consent was obtained. Patients were retrospectively excluded if there was a need for reoperation within 3 months after primary surgery.

Study design and data collection

Study participants were asked to complete the validated self-reporting International Pain Outcome Questionnaire (IPOQ) supplemented by a questionnaire addressing pain characteristics on postoperative days 1 (POD1), 14 (POD14), and 90 (POD90). To minimise loss to follow-up, initial nonresponders received reminders by mail, telephone, or both a week after receipt of the original survey.

The IPOQ addresses severity of pain, its interference with activities and affect, adverse effects, whether the patient received information about pain management, use of non-pharmacological treatment, existence of chronic pain before surgery and its severity by 11-point numerical rating scales (NRS).[15] The questionnaire addressing pain characteristics was derived from the first two questions of the Douleur Neuropathique en 4 (DN4) questionnaire comprising seven items (i.e. burning, painful cold, electric shock, pins and needles, tingling, numbness, and pruritus) with a dichotomous yes–no scale. These pain descriptors have a high specificity in discriminating pain associated with an injury of the nervous system and pain related to other somatic lesions.[16,17]

Patient characteristics and clinical data were extracted from the patients' electronic medical records. These included age, sex, BMI, pain-related comorbidities, use of anti-neuropathic drugs before admission, type and duration of surgery, type of perioperative anaesthesia, and cumulative doses of analgesics given.

Outcome measure

The outcome of interest was CPSP, defined as pain with a NRS of 4 or higher 3 months after surgery.

Statistical analysis

No formal sample size calculation was conducted. The sample size was based on the available data. Based on the overall cohort, two datasets were constructed: the first containing solely patients from the UMCU for model development, the second only including patients from the EMC for external validation.

Potential risk factors for the development of CPSP were selected based on published data, clinical expertise, pathophysiological reasoning, and practical considerations for future implementation in clinical practice. The clinical candidate predictors studied included: age, sex, BMI, surgery type, the use of opioids and anti-neuropathic drugs before admission, the

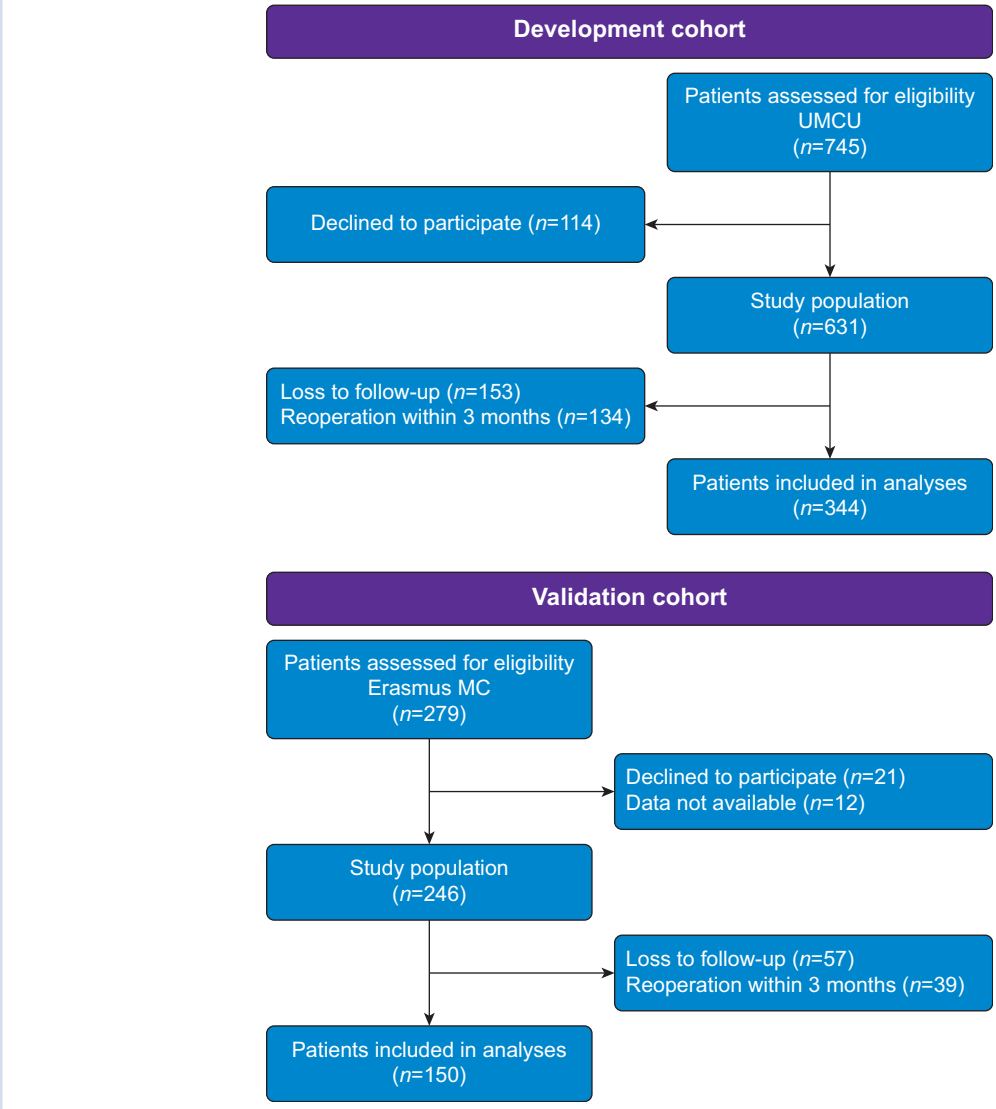

Fig 1. Flowchart. MC, Medical Centre; UMCU, University Medical Centre Utrecht.

presence of chronic pain before surgery, pain scores on POD1 and POD14, the presence of certain pain characteristics (i.e. burning, painful cold, electric shock, pins and needles, tingling, numbness and pruritus) on POD1 and POD14.

Age, BMI, and pain scores were coded as continuous variables. The predictor 'surgery type' was dichotomised into bone surgery yes/no, because the impact of bone surgery on postoperative pain severity is hypothesised to be different compared with surgery in soft tissue only.[18]

Two prediction models for the occurrence of CPSP based on information available on respectively POD1 and POD14 were developed in five steps:

1. The initial set of clinical candidate predictors consisted of 14 items. All demographic and surgery related factors were directly selected for inclusion in multivariable modelling.
2. To limit collinearity caused by inclusion of closely related predictors, the predictive adjusted association between each pain characteristic and CPSP was tested using logistic regression in patients without missing values for each pain characteristic. Pain characteristics that turned out significant on a significance level of $P<0.1$ in adjusted analyses were preselected for inclusion in multivariable modelling. As the DN4 has not been validated in the postoperative setting, and the two DN4 items requiring physical examination reduce clinical applicability, the predictive value of the DN4 score was not assessed.
3. To minimise bias attributable to selective loss to follow-up, imputation techniques were used to impute missings in the predictors entered in the model. In this procedure, 10 imputed datasets were created as the maximum number of missings was approximately 10% per predictor. The models were estimated on the 10 imputed datasets and the results were combined using Rubin's rules.[19]
4. Multivariable logistic regression on the selected candidate predictors was used to develop the prediction models. Candidate predictors yielding a P-value greater than 0.05 in the logistic regression analysis were removed from the final

Table 1 Demographic and clinical data of patients. *Values are median (IQR). IQR, inter-quartile range; ME, morphine equivalent; NRS, numerical rating scale; POD, postoperative day; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

	Development cohort		Validation cohort	
	Total (n=344)	Missing values, n (%)	Total (n=150)	Missing values, n (%)
Age (yr)		0		0
Mean (SD)	59 (16)		55 (14)	
Range	18–94		18–81	
Male sex (%)	188 (55)	0	74 (51)	0
BMI (kg m^{-2})		10 (2.9)		2 (1.3)
Mean (SD)	26.7 (4.4)		27.0 (4.9)	
Range	16.9–43.8		17.9–42.9	
Comorbidities	258 (75.2%)	1 (0.3)	103 (68.7%)	1 (0.7)
Cancer	73 (21.2%)		57 (38.0%)	
Cardiovascular comorbidity	146 (42.4%)		42 (28.0%)	
Pulmonary disease	39 (11.3%)		10 (6.7%)	
Renal insufficiency	33 (9.6%)		4 (2.7%)	
Gastrointestinal disease	21 (6.1%)		4 (2.7%)	
Psychiatric comorbidity	67 (19.5%)		8 (5.3%)	
Pre-existing chronic pain	203 (59.7%)	4 (1.2)	67 (44.7%)	0
• Site of surgery	110 (55.6%)	5 (2.5)	42 (63.6%)	1 (1.5)
• Elsewhere	21 (10.6%)		9 (13.6%)	
• Both	67 (33.8%)		15 (22.7%)	
Drug use before admission				
Opioids	76 (22.1%)	0	17 (11.3%)	0
Opioid dose (ME)*	30.0 (10.0–52.5)		30.0 (10.0–40.0)	
Antineuropathic drugs	32 (9.3%)	0	6 (4.0%)	0
• TCA	13 (3.8%)		1 (0.7%)	
• Antiepileptic drugs	13 (3.8%)		3 (2.0%)	
• SSRI	0 (0.0%)		1 (0.7%)	
• Alternatives	1 (0.3%)		0 (0.0%)	
• TCA+antiepileptic drug	5 (1.5%)		1 (0.7%)	
Type of surgery		0		0
Orthopaedic surgery	156 (45.3%)		40 (26.7%)	
Trauma surgery	49 (14.2%)		22 (14.7%)	
General surgery	72 (20.9%)		84 (56.0%)	
Vascular surgery	67 (19.5%)		4 (2.7%)	
Duration of surgery (min)*	94 (63–139)	1 (0.3)	123 (85–179)	0
Type of anaesthesia		0		0
General anaesthesia (GA)	273 (79.4%)		114 (76.0%)	
Regional anaesthesia (RA)	31 (9.0%)		1 (0.7%)	
GA+RA	37 (10.8%)		35 (23.5%)	
Local anaesthesia	3 (0.9%)		0 (0.0%)	
Other candidate predictors POD1				
Worst pain score (NRS 0–10)	5.84 (2.8)	1 (0.3)	6.23 (3.0)	0 (0.0)
Presence of burning	129 (38.4%)	8 (2.3)	58 (38.9%)	1 (0.7)
Presence of painful cold	30 (8.9%)	8 (2.3)	13 (8.8%)	3 (2.0)
Presence of electric shock	28 (8.3%)	8 (2.3)	23 (15.5%)	2 (1.3)
Pins and needles	99 (29.5%)	8 (2.3)	60 (40.5%)	2 (1.3)
Tingling	76 (22.6%)	8 (2.3)	41 (27.7%)	2 (1.3)
Numbness	81 (24.1%)	8 (2.3)	29 (19.5%)	1 (0.7)
Pruritus	50 (14.9%)	8 (2.3)	28 (19.0%)	3 (2.0)
Other candidate predictors POD14				
Pain score (NRS 0–10)	2.85 (2.2)	40 (11.6)	2.59 (2.3)	0 (0.0)
Presence of burning	143 (46.7%)	38 (11.0)	68 (45.3%)	0 (0.0)
Presence of painful cold	33 (10.8%)	38 (11.0)	12 (8.0%)	0 (0.0)
Presence of electric shock	52 (17.0%)	38 (11.0)	24 (16.0%)	0 (0.0)
Pins and needles	105 (34.3%)	38 (11.0)	67 (44.7%)	0 (0.0)
Tingling	73 (23.9%)	38 (11.0)	41 (27.3%)	0 (0.0)
Numbness	77 (25.2%)	38 (11.0)	37 (24.7%)	0 (0.0)
Pruritus	63 (20.6%)	38 (11.0)	46 (30.7%)	0 (0.0)

models. The number of predictors put in the prediction model was guided by the effective sample size. The final models were presented as model formulas, which allows estimation of the individualised probability for developing CPSP within 3 months based on an individual's characteristics on POD1 and POD14, respectively.

5. In a fifth step, the performance of the constructed models was evaluated. The discriminatory performance was

According to the logistic regression derived β coefficients, an individual's risk of CPSP might be calculated as follows:

$$\text{the risk of CPSP} = \frac{1}{1 + e^{-\text{predictors}}}$$

Model POD1

In order to predict a patient's individual risk of developing CPSP on POD1, the model could be represented in the form of the following formula:

$$P(\text{CPSP}) = \frac{1}{1 + e^{-(-2.540 + \text{bonesurgery} \times 0.785 + \text{preop. opioids} \times 1.023 + \text{worst pain score} \times 0.123 + \text{pruritus} \times 0.732)}}$$

Where P(CPSP) denotes the probability for a patient to have CPSP within 3 months after surgery. Bone surgery has value of 1 if the patient underwent surgery on bone tissue. Preop. Opioids is 1 if the patient has used opioids prior to admission for surgery. Worst pain score denotes the NRS score (0-10) indicated by the patient for the worst experienced pain since surgery. Pruritus has value 1 if the pain is associated with itching in the same area.

Applying this model formula to a hypothetical 60-yr-old woman who used oxycodone prior to admission for orthopaedic surgery and rated her worst pain score since surgery with a 4 without itching will result in a predicted probability for CPSP within 3 months of:

$$P(\text{CPSP}) = \frac{1}{1 + e^{-(-2.540 + 0.785 + 1.023 + 4 \times 0.123)}} = 0.440 = 44.0\%$$

Model POD14

The predicted probability of developing CPSP within 3 months after surgery could be calculated on POD14 using the following formula:

$$P(\text{CPSP}) = \frac{1}{1 + e^{-(-2.540 + \text{bonesurgery} \times 0.696 + \text{preop.opioids} \times 1.397 + \text{pain on POD14} \times 0.449 + \text{painful cold on POD14} \times 1.578)}}$$

Where P(CPSP) denotes the probability for a patient to have CPSP within 3 months after surgery. Predictor value for bone surgery, preop. Opioids and *painful cold on POD14* is one when present and zero when absent. *Pain score on POD14* denotes the NRS score (0-10) indicated by the patient for the experienced pain 2 weeks after surgery. Applying this model formula to a hypothetical 60-yr-old woman who used oxycodone prior to admission for orthopaedic surgery and rated her pain characterised by a painful cold experience on POD14 with a 4 will result in a predicted probability for CPSP within 3 months of:

$$P(\text{CPSP}) = \frac{1}{1 + e^{-(-2.540 + 0.696 + 1.397 + 4 \times 0.449 + 1.578)}} = 0.95 = 95\%$$

Fig 2. Predicting a patient's individual risk of developing CPSP with an example. CPSP, chronic postsurgical pain; NRS, numerical rating scale; *P*, probability; POD, postoperative day.

quantified by calculating the area under the receiver operating characteristics curve (AUC). A calibration plot was constructed to examine the agreement between the predicted probabilities and the observed frequencies.

Internal validation of the final models was performed by calculating discrimination and calibrations measures using bootstrapping. To assess the models' external validity, discrimination and calibration were assessed in the validation dataset using complete cases by calculating the AUC. A calibration plot was computed to assess graphically the agreement between the probability of developing CPSP within 3 months as predicted by the internally and externally validated models.

Unless otherwise stated, statistical significance is considered when the two-sided *P*-value is less than 0.05. All analyses were performed using R version 3.6.2 (R Core Team [2021], https://www.R-project.org) with the package MICE for the imputation and pooling procedures and psfmi for model estimation and validation.[20] Results were reported according

Table 2 Final prediction models for chronic postsurgical pain. Results are presented as β coefficients and odds ratios (95% CI). CI, confidence interval; CPSP, chronic postsurgical pain; OR, odds ratio; POD, postoperative day; NRS, numerical rating scale.

Predictor	Model POD1			Model POD14		
	β coefficient	OR (95% CI)	P-value	β coefficient	OR (95% CI)	P-value
(Intercept)	−2.540	0.08 (0.04–0.17)	0.000	−2.540	0.08 (0.04–0.17)	0.000
Surgery type, bone surgery	0.785	2.19 (1.29–3.74)	0.004	0.696	2.01 (1.10–3.67)	0.024
Preoperative treatment with opioid	1.023	2.78 (1.60–4.85)	0.000	1.397	4.04 (2.13–7.70)	0.000
Worst pain score (NRS) on POD1	0.123	1.13 (1.02–1.25)	0.015	–	–	–
Presence of pruritus within the painful area on POD1	0.732	2.08 (1.08–4.02)	0.030	–	–	–
Pain score (NRS) on POD14	–	–	–	0.449	1.57 (1.34–1.83)	0.000
Presence of painful cold within the painful area on POD14	–	–	–	1.578	4.85 (1.85–12.68)	0.002

to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines.[21]

Results

From a consecutive sample of 1024 patients, a total of 494 patients – 344 in the development cohort and 150 in the validation cohort – were included in the analysis (Fig 1, Table 1). There were no significant differences in baseline data between responders and patients lost to follow-up (Supplementary Table S1).

Occurrence and characteristics of chronic postsurgical pain

Three months after surgery, 99 (28.8%) patients in the development cohort and 32 (21.3%) patients in the validation cohort experienced CPSP. Presence of CPSP influenced functionality as higher median score for pain interference with activities in and out of bed were reported. Patients acquiring CPSP in the development cohort were more likely to have preoperative chronic pain (69.7% *vs* 54.7%, $P=0.010$), used more opioids before admission (15.9% *vs* 37.4%, $P<0.001$), and were more often exposed to bone surgery (i.e. orthopaedic and trauma surgery) ($P=0.023$; Supplementary Table S2).

Predicting chronic postsurgical pain on POD1

Variable screening of pain characteristics on POD1, indicated presence of pruritus within the painful area as the only pain characteristic possibly associated with CPSP (odds ratio [OR]=1.82; 95% confidence interval [CI], 0.95–3.43) (Supplementary Table S3).

In multivariable logistic regression bone surgery, preoperative treatment with opioids, NRS score for worst pain and the presence of pruritus within the painful area on POD1 emerged as significant predictors of CPSP (Supplementary Table S5) and were included in the final prediction model (Table 2). In Fig 2, an example of an absolute individualised risk calculation is presented.

Discriminative ability was acceptable (area under the curve [AUC]=0.71; 95% CI, 0.65–0.77). The calibration plot showed an overall good agreement between the predicted and observed CPSP cases as estimated by the newly developed model (Fig 3a). Predictive performance was confirmed by external validation (Fig 3c).

Predicting chronic postsurgical pain on POD14

Assessment of the predictive association between the pain characteristics until POD14 and CPSP resulted in selection of presence of pruritus on POD1 (OR=2.01; 95% CI, 0.95–4.16), presence of a painful cold on POD14 (OR=3.67; 95% CI, 1.54–9.00), and tingling on POD14 (OR=1.81; 95% CI, 0.91–3.57) (Supplementary Table S4).

Bone surgery, preoperative treatment with opioids, NRS pain score on POD14, and a painful cold within the painful area on POD14 proved to be significantly associated with CPSP in multivariable logistic regression analysis (Supplementary Table S5). In the prediction model, presence of a painful cold within the painful area on POD14 was the largest contributor to the risk of developing CPSP, followed by preoperative treatment with opioids before admission for surgery. The risk further increased with bone surgery and higher pain scores on POD14 (Table 2, Fig 2).

The final model showed good internally validated discrimination (AUC=0.82; 95% CI, 0.76–0.87) and nearly perfect calibration, which was confirmed by almost identical performance in external validation (Fig 3).

Discussion

In the present study, two models for the prediction of CPSP within 2 weeks after surgery were developed and externally validated. The models showed good performance in both the development and the validation cohorts. Transition of acute pain into CPSP could most reliably be predicted 2 weeks after surgery by the model including preoperative treatment with opioids, bone surgery, the NRS pain score, and the presence of a painful cold within the painful area on POD14. Therefore, this model is recommended for clinical practice.

The observed prevalence of CPSP (21.3% and 28.8%) falls within the range previously reported.[2] The variation across studies may be attributed to different definitions for CPSP, varying follow-up times, and diverse surgical procedures. Certain types of surgical procedures are more likely to generate CPSP, such as surgery on bones.[22] Bone surgery is often associated with severe acute postoperative pain[18] and higher rates of preoperative pain. Preoperative pain has been identified as risk factor for CPSP across a range of surgical procedures.[6–8,18–25] Although it is reasonable to argue that preoperative pain

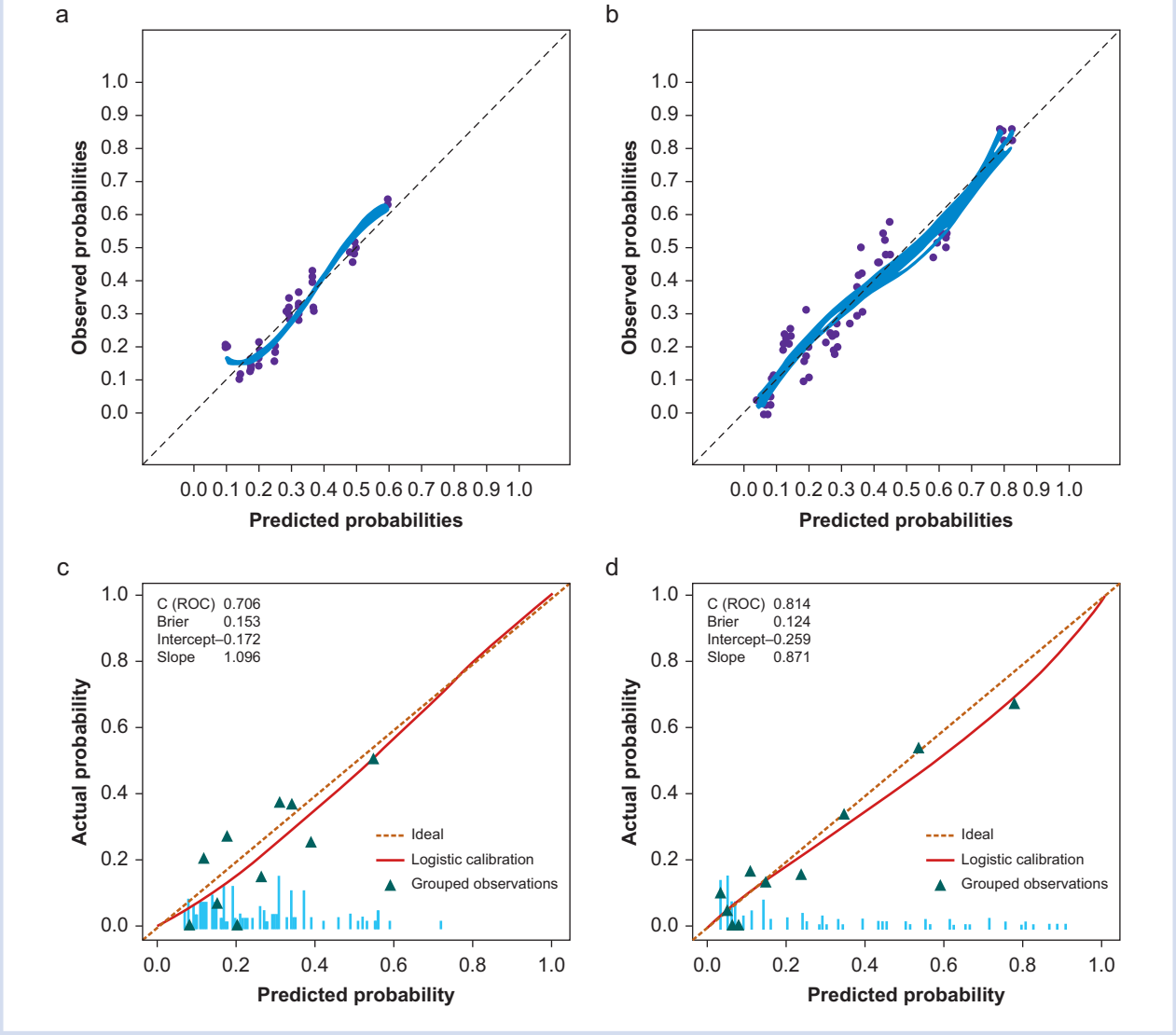

Fig 3. Calibration plots for internal and external validation of Model POD1 (left, a and c) and Model POD14 (right, b and d). The blue triangles in plots (c) and (d) denote the mean predicted and observed event probabilities for patients grouped into tenths using deciles. The dashed line denotes perfect calibration. The calibration curve is presented as a red solid line. The distribution of calculated predicted probabilities is overlaid along the horizontal axis. A subset of various statistics useful for validating the models are also shown.

stimuli may sensitise the nociceptive system thereby predisposing the patient to CPSP,[26] the presence of preoperative pain was not a significant predictor for CPSP in this study. This may be explained by its association with preoperative opioid use, which was a strong predictor of CPSP (Supplementary material, *post-hoc* analysis 1). Long-term high-dose opioid treatment may increase the risk of CPSP caused by opioid-induced hyperalgesic priming.[6,27] Moreover, tolerance from preoperative opioid use may reinforce pain chronification by complicating acute postoperative pain management. This study supports the frequently replicated finding by prior studies that high-intensity acute postsurgical pain is one of the strongest predictors for CPSP in different surgical fields.[2,22,28–31]

Besides pain intensity, presence of pruritus on POD1 and presence of a painful cold on POD14 within the painful area were strong predictors associated with the development of CPSP. A systematic comparison of patients with neuropathic or non-neuropathic pains has shown that presence of pruritus and a painful cold within the painful area are characteristics associated with a definite neurological lesion.[17] The role of these neuropathic pain characteristics in predicting CPSP suggests that postsurgical chronic pain is a manifestation of neuropathic pain with both peripheral and central nervous system sensitisation starting in the early postoperative period.

Pain, cold, and pruritus have similar pathways with overlapping pro-inflammatory mediators, neurotransmitters, and neuropeptides to transduce the signal that eventually arouses the body to potential harm. All are transmitted by unmyelinated slow conducting C-fibres and utilise the same brain regions when comprehending their stimuli.[32,33]

Although predictive for CPSP on POD1, presence of pruritus within the painful area on POD1 loses its impact when predicting CPSP on POD14. Pruritus is a common side-effect of opioids administered in the early postoperative period. However, additional analyses performed to investigate this potential association showed no statistically significant difference in total cumulative opioid dose between patients experiencing pruritus and patients without pruritus within the painful area on POD1 (Supplementary material, *post-hoc* analysis 2).

Cold pain sensitivity has recently been identified as a risk factor for CPSP after spine surgery and breast cancer surgery.[34,35] Although the experimentally induced cold hypersensitivity differs from spontaneously reported cold pain sensations in our study, we hypothesise a common pathway.[36] Unravelling whether reduced tissue perfusion, small fibre neuropathies, or both are responsible for these cold pain sensations may be a topic of further research.

The evidence regarding age and sex as risk factors for CPSP is inconsistent. Although various studies suggest that a younger age and female sex may be associated with an increased risk of developing CPSP,[28,30,31,37,38] age and sex were not found to be significant predictors in our models.

This may be explained by the wide range of surgical procedures included in this study, with varying sex and age distributions per surgery type, diluting possible effects of age and sex on CPSP development as was seen in previous work.[39]

This study has strengths and limitations. Strengths include the prospective population-based design, the relatively large sample size, the use of high-quality data, and adherence to the TRIPOD statement's recommendations. The data for model development and validation were derived from one of the world's largest registry projects on postoperative pain that provides patient-reported outcome data and clinical data in a highly standardised way after surgical procedures. A strict operationalised outcome criterion was used to define symptomatic outcomes. Furthermore, the models were externally validated in an independent dataset from a different university medical centre with a different surgical case mix (Supplementary material, *post-hoc* analysis 3). Despite differences in the case mix between the development and validation cohort, external validation showed similar performance.

Several limitations need to be addressed. The small number of patients who consented to participate (48% of eligible patients) might have affected the generalisability of the prediction models to all postsurgical patients. Study compliance was moderate with 69% and 72% of patients providing follow-up data. Effects of loss to follow-up are small, as patients lost to follow-up and those completing follow-up had comparable characteristics at baseline (Supplementary Table S1).

Another potential limitation concerning generalisability is that this study was exclusively based on patients receiving surgery at university medical centres. The reproducibility of our findings in non-university hospitals was not assessed.

Furthermore, in this study it was not ruled out whether CPSP was a continuation of already existing preoperative pain, as recommended by Macrae.[1] Other definitions of CPSP, however, propose to include pain that has different characteristics or increases in intensity compared with preoperative pain as well.[40] As the endpoint CPSP was not confirmed by a pain specialist, there is a probability of misclassification.

Despite evidence that psychologic factors (e.g. anxiety and catastrophising) might improve CPSP prediction,[40] their added contribution was not assessed in this study. Nevertheless, predictive performance of our models without psychologic factors compares well with those including them.[7] Besides, assessing psychological status by questionnaires would reduce clinical applicability by increasing the burden for patients and clinicians.

Finally, several issues concerning the implementation of our best performing model, that is model POD14, in clinical practice. It requires an active follow-up strategy up to 2 weeks after surgery to assess pain intensity and presence of a painful cold. A web-based screening application including the four easily obtainable predictors, calculating the risk for CPSP would simplify use in clinical practice. Based on the calculated risk, patients may be invited to the outpatient clinic for additional screening for neuropathic pain possibly resulting in alterations in their pain management. Additional research will have to show whether this leads to a reduction in CPSP prevalence.

In conclusion, this prospective study in patients undergoing a variety of surgical procedures has resulted in the development and validation of two prediction models for the early identification of patients at risk for CPSP to alert the clinician to undertake further assessment. Interestingly, two neuropathic pain characteristics – pruritus and painful cold within the painful area within 2 weeks after surgery – are highly predictive for CPSP development. This suggests that CPSP often is a manifestation of neuronal damage or altered nociceptive processing by the nervous system.

Authors' contributions

Conception and design: FJPMGH, MR
Acquisition, analysis, or interpretation of data: all authors
Drafting of the article: MECD, MR
Critical revision of article for important intellectual content: all authors
Statistical analysis: MECD, SJB, MR
Administrative, technical, or logistic support: MECD, JFMD
Supervision: WM, FJPMGH, MR

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Declarations of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.04.030.

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