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ORIGINAL ARTICLE

Chronic postsurgical pain

A European survey

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BACKGROUND Chronic postsurgical pain (CPSP) is a clinical problem, and large prospective studies are needed to determine its incidence, characteristics, and risk factors.

OBJECTIVE To find predictive factors for CPSP in an international survey

DESIGN Observational study

SETTING Multicentre European prospective observational trial

PATIENTS Patients undergoing breast cancer surgery, sternotomy, endometriosis surgery, or total knee arthroplasty (TKA).

METHOD Standardised questionnaires were completed by the patients at 1, 3, and 7 days, and at 1, 3, and 6 months after surgery, with follow-up via E-mail, telephone, or interview.

MAIN OUTCOME MEASURE The primary goal of NIT-1 was to propose a scoring system to predict those patient likely to have CPSP at 6 months after surgery.

RESULTS A total of 3297 patients were included from 18 hospitals across Europe and 2494 patients were followed-up for 6 months. The mean incidence of CPSP at 6 months was 10.5%, with variations depending on the type of surgery: sternotomy 6.9%, breast surgery 7.4%, TKA 12.9%, endometriosis 16.2%. At 6 months, neuropathic characteristics were frequent for all types of surgery: sternotomy 33.3%, breast surgery 67.6%, TKA 42.4%, endometriosis 41.4%. One-third of patients experienced CPSP at both 3 and 6 months. Pre-operative pain was frequent for TKA (leg pain) and endometriosis (abdomen) and its frequency and intensity were reduced after surgery. Severe CPSP and a neuropathic pain component decreased psychological and functional wellbeing as well as quality of life. No overarching CPSP risk factors were identified.

CONCLUSION Unfortunately, our findings do not offer a new CPSP predictive score. However, we present reliable new data on the incidence, characteristics, and consequences of CPSP from a large European survey. Interesting new data on the time course of CPSP, its neuropathic pain component, and CPSP after endometriosis surgery generate new hypotheses but need to be confirmed by further research.

TRIAL REGISTRATION clinicaltrials.gov ID: NCT03834922

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KEY POINTS

- Our findings do not offer a new chronic postsurgical pain (CPSP) predictive score.
- We offer reliable new data on the incidence, characteristics, and consequences of CPSP from a large European survey.
- We found interesting new data on the time course of CPSP, its neuropathic pain component, and CPSP after endometriosis surgery.

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Introduction

The results from a recent large prospective international cohort study described a 3.3% incidence of chronic postsurgical pain (CPSP) at 12 months after non-cardiac surgery.[1] In 2019, the International Association of the Study of Pain 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.[2,3] It is estimated that over 50 million surgical procedures are performed in Europe each year and the potential burden of CPSP is likely to be large.[4]

CPSP has a negative impact on the quality of life, as well as on emotional and physical well being.[5,6] Thus, clinical prediction models are needed to identify patients at high risk of developing CPSP and to support pre-operative and postoperative clinical decision-making based on an individual patient's risk profile. To reach this goal, we need large prospective studies to determine the CPSP risk factors, incidence and characteristics.

In a recent systematic review of existing prediction models for CPSP, the models posed several statistical and practical limitations for use in clinical settings. These included, most notably, small sample sizes, poor reporting or inappropriate handling of missing data, lack of model performance measure evaluation, and absence of model validation.[7] There was also significant heterogeneity in the 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, most models were limited to specific populations and surgical procedures and therefore lack generalisability.

The IMI-PainCare project, targeting improved care of patients suffering from acute or chronic pain, is supported by the IMI-PainCare consortium, a public–private partnership supported by the European Union's Horizon2020 research and innovation program and the European Federation of Pharmaceutical Industries and Associations (EFPIA) within the Innovative Medicines Initiative 2 (IMI-PainCare, 2018: https://www.imi-paincare.eu). PROMPT (Providing Standardised Consented PROMs (Patient Reported Outcome Measures) for Improving Pain Treatment), a subsidiary study of the IMI-PainCare project, aims at improving management of acute and chronic pain by identifying a core set of PROMs that are predictive indicators of treatment success, in both clinical practice and controlled trials. To achieve this aim, an extensive literature search and a consensus process on core outcome domains were executed then completed by a review of literature on factors of pain persistence after surgery.[8] As an integral part of the PROMPT study, the current study (Non-Interventional Trial-1, NIT-1), was conducted as a large prospective, non-interventional, multicentre study to collect clinical and PROM data from hospitals across Europe. The primary goal of NIT-1 was to use these data to propose a score to predict those patients likely to having CPSP at 6 months after surgery. Secondary endpoints were the differences in the incidence and characteristics of CPSP for the four types of surgery as well as pain-related functional impairment at 6 months.

Methods

Recruitment of European participants centres

To ensure sufficient inclusion numbers, we advertised participation in our study throughout Europe, using a network of former study sites and the webpage of the well established projects PAIN OUT and QUIPS.[9,10] If the estimated number of procedures of interest and potential patient recruitment were sufficient, conclusion of a co-operation-agreement was the next step. This co-operation agreement ensured adherence to the standard operating procedure, confidentiality, data exploitation rules, and regulated the remuneration.

Ethical considerations

Approval for the study was obtained from the local ethics committee at each centre, and General Data Protection Regulation clearance was needed for all participating hospitals. Patients' consent could be oral or written, depending on the local requirements. Ethics requirements vary considerably across Europe.[11] Ethics approval for the study was obtained at Jena University Hospital's Ethics Board (Reg. No. 2019-1298-Bef on 06.02.2019). The PROMPT NIT-1 study was registered (clinicaltrials.gov ID: NCT03834922)

Population of patients included

Patient inclusion criteria in NIT-1 were as follows: the patient was due to undergo elective surgery of one of the four different types (i.e., breast surgery for cancer, total knee arthroplasty (TKA), sternotomy and endometriosis surgery); was $\geq$18 years old; fluent in one of the languages of the available questionnaire; and agreed to participate in the study (Table 1). A pre-existing chronic pain condition at the site of surgery or as a comorbidity was not an exclusion criterion. The four types of surgery were chosen to cover surgery with or without pre-operative pain, pain in both sexes, and visceral pain after endometriosis surgery.

Technical implementation

We used five main components for data management and processing: a subject-ID-generator, OpenClinica (OpenClinica LLC and collaborators, Waltham, MA, USA), an address tool, a follow-up survey tool and LimeSurvey (LimeSurvey GmbH, Hamburg, Germany). After patients had given their informed consent, the study team generated a subject-ID and recorded the patient's contact details (name, e-mail-address, phone number and OpenClinica-ID). Survey invitations were generated and sent to patients as a private link. Most patients then completed the questionnaires online in LimeSurvey.

Table 1 Specific surgical inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
Breast surgery	Woman ≥18 years old Diagnosis of breast cancer Lumpectomy with axillary node dissection Lumpectomy with sentinel node dissection Mastectomy with axillary node dissection Mastectomy with sentinel node dissection	Secondary surgery due to complications Surgery performed for cosmetic purposes only
Sternotomy	Patient is ≥18 years Median sternotomy for CABG with use of a heart lung machine (HLM) Median sternotomy for CABG without use of a HLM Partial sternotomy for CABG with and without use of a HLM Median sternotomy for heart valve surgery with and without use of a HLM Partial sternotomy for heart valve surgery with and without use of a HLM Median sternotomy for combined CABG and heart valve surgery with and without use of a HLM Partial sternotomy for combined CABG and heart valve surgery with and without use of a HLM	Secondary surgery due to complications
Endometriosis surgery	Woman is ≥18 years Primary surgery because of pelvic/abdominal pain with a suspected diagnosis of and with the aim of confirming endometriosis Elective abdominal surgery in women with pelvic/abdominal pain and confirmed endometriosis	Secondary surgery due to complications Endometriosis surgery due to infertility only
Total knee arthroplasty (TKA)	Patient is ≥18 years old Unilateral, elective TKA secondary to osteoarthritis TKA with patellar resurfacing TKA without patellar resurfacing	Previous surgery in the same area: same side or collateral knee surgery <6 months pre-operatively

CABG, coronary artery bypass grafting; CPSP, chronic postsurgical pain; HLM, heart lung machine; TKA, total knee arthroplasty.

If patients did not respond or did not have an e-mail address, the invitation link was sent to the hospital where the patient was recruited, so that the study team could contact the patient by telephone. In this case, the information was obtained verbally and entered into LimeSurvey by the study staff.

Evaluation around surgery

NIT-1 was conducted as a multicentre, noninterventional study in 18 hospitals across Europe in patients undergoing one of four surgical procedures: these were sternotomy, total knee arthroplasty (TKA), breast cancer surgery, and endometriosis surgery. The patients completed questionnaires about their pain at seven time points: pre-operatively (the patients were interviewed the day before surgery or the morning of surgery when surgery was ambulatory), on postop day (POD)1, POD3, POD7 and postop month (POM)1, POM3 and POM6. At these time points, patients were evaluated with established instruments measuring patient-reported outcomes, modified questionnaires, and selected single items. The data, timing of data collection and modality of analysis (i.e., continuous or dichotomous) are presented in Table 2. Twenty-eight different questionnaires in eight languages were used (7 time-points × 4 procedure specific questionnaires in English, French, German, Italian, Serbian, Finnish, Spanish and Portuguese). Three types of items were incorporated into the PROMPT NIT-1 questionnaires: existing questionnaires, modified existing questionnaires, and newly developed items. Translations were available for most of the existing questionnaires whereas modifications and new questions required translation. Translations were carried out according to a defined forward-backward-procedure with double-checks as previously reported.[12,13]

Statistical analysis

The primary end point was the incidence of moderate to severe CPSP (NRS > 3/10) at 6 months using the average pain on the BPI (Brief Pain Inventory) questionnaire ('Please rate your pain by circling the one number that best describes your pain on the average'). Secondary outcome measures were the incidence of moderate to severe CPSP at 1 and 3 months; and neuropathic pain characteristics and pain interference with daily activities for patients with CPSP at 6 months. The neuropathic component of pain was evaluated with the DN4 interview questionnaire which has been validated previously to distinguish neuropathic pain (positivity if score on the DN4 questionnaire ≥ 3/7).[14,15] This questionnaire was used both pre-operatively and postoperatively to create a dichotomous variable. The functional interference with daily activities was evaluated with the pain interference total scores (PITS) obtained from the BPI questionnaire.[16] The psychological interference was evaluated with the Hospital Anxiety and Depression Scale (HADS).[17] The quality-of-life interference was evaluated with the EQ-5D-5L questionnaire.[18] The location of

Table 2 Questionnaires used in IMI PROMPT NIT1 observational study

Questionnaires	Pre-op	Intra-operative	POD1	P0D3	POD7	M1	M3	M6
Demographics	X							
Educational level	X							
Comorbidities	X							
Clinical data								
- ICD-10-CM		X						
- Anaesthesia		X						
- Type of surgery		X						
IPO (modified)	X		X	X	X			
PROMs (WP2)	X		X	X	X			
ASES adapted			X					
Pain								
- BPI	X					X	X	X
- DN4 interview	X		X		X	X	X	X
- NPSI	X		X					
Analgesic use	X	X	X	X	X	X	X	X
PSQ	X							
Adverse events			X					
Psychological profile								
- HADS	X							
- PCS	X							
- Pain expectation	X							
QOL (EQ-5D-5L)	X					X	X	X
Laboratory values								
- WBC, CRP		X	X					

ASES adapted, 11-point scale using a modified version of the Arthritis Self-Efficacy Scale and used as a continuous scale; BPI, Brief Pain Inventory used as a dichotomous variable with the pain interference total score; CRP, C-reactive protein; DN4, Douleur Neuropathique 4 questions questionnaire used as a dichotomous variable; HADS, Hospital Anxiety and Depression scale used as a continuous variable; ICD-10-CM, International Classification of Diseases – Tenth Revision – Clinical Modification; IPO, International Pain Outcome Questionnaire; NPSI, neuropathic pain symptom inventory used as a continuous variable; Pain expectation, questionnaire on pain expectation used as a continuous variable; PCS, Pain catastrophising scale used as a continuous variable; PROMs,patient related outcome measures; PSQ, Pain sensitivity questionnaire used as a continuous variable; QOL, quality of life; WBC, white blood cell; X, indicates that the questionnaire was used at the time point.

pain in the pre-operative and the postoperative period was identified in the BPI diagram with the question 'the area that hurts the most' since we considered it was the most problematic type of pain for the patient. The CPSP was defined according to this area that hurts the most whatever the location

The power calculation was based on an expected incidence of 15% for moderate-to-severe CPSP and an expected follow-up rate of 67%.[19,20] Thus, 4000 data sets (1000 for each surgical procedure) had to be included to result in 400 patients with CPSP.

We applied the least absolute shrinkage and selection operator (LASSO) regression as the method of variable selection for the primary outcome of CPSP after 6 months with all potential predictors as independent variables.[21] Most demographic and clinical variables collected before surgery and at the other time points after surgery were included in the model before variable selection. LASSO is a regression analysis method, which performs variable selection in order to minimise the prediction error. This is achieved by imposing a constraint on the model parameters shrinking the regression coefficients towards zero: this is achieved by forcing the sum of the absolute value of the regression co-efficients to be less than a fixed value λ. Considering a linear regression with p potential predictors x_{ij} and outcome values y_i for $i = 1, \ldots, n$ and $j = 1, \ldots, p$ the LASSO algorithm performs the minimisation of

$$\sum_{i=1}^{n}\left(y_i - \sum_{j=1}^{p} x_{i,j}\beta_j\right)^2 + \lambda \sum_{j=1}^{p}|\beta_j|,^{21}$$

For the binary outcome CPSP a logit link function was applied in the model. Variables with a regression coefficient $ß_j$ of zero after shrinkage are excluded from the model. In this way the complexity of the model will be reduced, including only the variables that are predictive for the outcome variable. Reducing the number of variables in the final model also prevents the issue of overfitting. Traditional approaches like stepwise selection methods (e.g. backward elimination and forward selection procedures) are also capable of identifying a subset of relevant variables, however, the resulting final model depends on the order of the variables which are entered or removed. In LASSO regression all potential variables are entered simultaneously, which avoids this problem and therefore should be preferred for variable selection instead of conventional approaches.[22]

Results

Sample characteristics

The data collection took almost 3 years (first patient in was August 2019, last patient out was June 2022) as the

number of elective surgical procedures was significantly reduced due to the COVID-19 pandemic. However, despite the pandemic, the 6 consortium and 12 non-consortium hospitals included a total of 3297 patients during this period. Sufficient case numbers were reached and follow-up rates on POM1, POM3 and POM6 were very good (70 to 80%). The flow chart is described in Fig. 1. Demographic characteristics are listed in Table 3 and missing values are listed in Table 4.

Incidence and characteristics of chronic postsurgical pain

Chronic postsurgical pain incidence at 3 and 6 months

Moderate to severe CPSP at 6 months was reported by 10.5% of the whole patient cohort with variations across the four surgical models: 6.9% for sternotomy, 7.4% for breast surgery, 12.9% for TKA and 16.2% for endometriosis (Fig. 1 and Table 5).

Data was obtained from 2178 patients for the change of CPSP between M3 and M6: 1861 (85.4%) had no pain at either time point and 317 (14.6%) had CPSP at M3 and/or M6. Of these 317 patients, 115 (36.3%) had pain at M6 but not at M3, 102 (32.2%) had CPSP at M3 but not at M6 and 100 (31.5%) had CPSP at both M3 and M6. The percentage of patients without CPSP at M3 but having CPSP at M6 was not statistically different in the four types of surgery: 3.5% for breast surgery, 8.4% for endometriosis, 4.5% for sternotomy, and 7.4% for TKA.

Sites of chronic postsurgical pain for the four types of surgery

The various sites of CPSP are shown in Fig. 2 based on the BPI diagram and the question 'the area that hurts the most'. The most frequent sites for CPSP were the thorax and armpit for breast surgery, the thorax for sternotomy, the abdomen for endometriosis, and the leg for TKA.

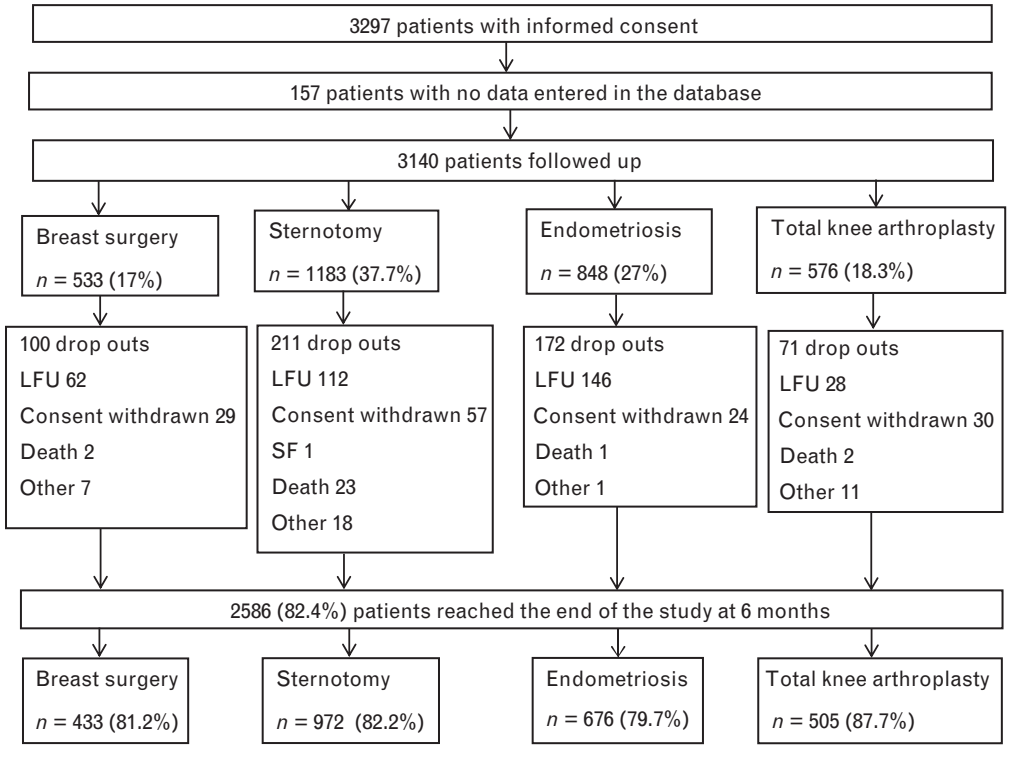
Evolution of pain intensity in case of pre-operative pain

The frequency of pre-operative pain was different for the four types of surgery: 24.3% for breast surgery, 65.6% for endometriosis, 16% for sternotomy, and 73.7% for TKA. For patients with pre-operative pain, the intensity of pain described 6 months after surgery was significantly decreased compared to the pre-operative pain as assessed by the BPI item 'describe your pain on the average'. Compared to the baseline pre-operative pain, there was a 61.4 $\pm$ 47.3% ($n = 349$) reduction in the pain score at 6 months for endometriosis, and 63.6 $\pm$ 38.4% ($n = 331$) for TKA.

Neuropathic characteristics

According to the positivity of the DN4 interviews, a neuropathic component to the CPSP was frequently observed in all surgical groups at M1, and it was stable over time (Table 6).

Fig. 1 Flow chart.



LFU, lost to follow up; SF, screening failure; other, other causes of drop out.

Table 3 Demographics and pain, functional, psychological assessments at baseline

	Breast surgery ($n = 655$)	Sternotomy ($n = 1183$)	Endometriosis ($n = 862$)	Total knee arthroplasty ($n = 597$)
Sex (female)	650 (99.7)	287 (24.3)	862 (100)	365 (61.1)
Age (year)	55.1 ± 11.9	66.4 ± 10.8	32.6 ± 8.1	68.3 ± 9
Height (cm)	165 ± 7	174 ± 9	167 ± 7	167 ± 10
Weight (kg)	70.9 ± 14.7	86.4 ± 16	69.1 ± 14.1	83.4 ± 17.4
Educational level				
- Primary school	120 (18.6)	180 (15.2)	17 (2)	167 (28.1)
- Secondary school	195 (30.2)	551 (46.7)	229 (26.8)	172 (28.9)
- Hich school completed	136 (21.4)	222 (18.8)	360 (42.2)	162 (27.2)
- University or higher	193 (29.9)	228 (19.3)	248 (29)	94 (15.8)
BPI short: preOP pain (yes)	111 (24.3)	152 (16.0)	494 (65.6)	420 (73.7)
HADS – anxiety score	6.5 ± 4.2	4.4 ± 3.4	8 ± 3.9	5.7 ± 3.9
HADS – depression score	3.9 ± 3.5	3.1 ± 3.0	5.1 ± 3.7	5.6 ± 3.7
HADS – total score	10.4 ± 7.2	7.5 ± 5.8	13.2 ± 6.9	11.3 ± 7.0
PSQ minor	3.2 ± 1.9	2.4 ± 1.6	2.5 ± 1.3	4.1 ± 1.9
PCS	12.7 ± 10.0	11.4 ± 9.9	21.6 ± 11.2	17.5 ± 12.4
EQ5D VAS	69.2 ± 20.0	66.7 ± 19.7	68.1 ± 20.6	63.1 ± 18.9
PITS	2.5 ± 2.2	3.4 ± 2.2	3.8 ± 2.3	4.6 ± 2.2
Pain expectation – anxiety	50.4 ± 30.1	44.1 ± 27.7	56.5 ± 28.8	36.0 ± 29.6
DN4 (yes/no)	45 (17.0)	47 (10.3)	235 (38.0)	175 (31.7)

Values are presented as mean ± SD or number (%). BPI, Brief Pain Inventory with specific question on pre-operative pain frequency; DN4, Douleur Neuropathique 4 questions questionnaire; EQ5D VAS, visual analogue scale of the quality of life EQ5D questionnaire; HADS, Hospital Anxiety and Depression scale with three subcores on anxiety, depression and total score; Pain expectation, questionnaire on pain expectation; PCS, pain catastrophising scale; PITs, pain interference total score extracted from BPI; PSQ minor, pain sensitivity questionnaire.

Table 4 Missing data

Variable	Total	Missing	Missing %
Asthma	3297	0	0.0%
IPO location	2987	310	9.4%
IPO intensity	2984	313	9.5%
DN4	1892	1405	42.6%
Fibromyalgia	3297	0	0.0%
Osteoarthritis	3297	0	0.0%
Out of bed POD 1	2581	716	21.7%
Out of bed POD 3	2627	670	20.3%
PITS	1156	2141	64.9%
Pre-operative opioid	3259	38	1.2%
PCS	3151	146	4.4%
PSQ	3203	94	2.9%
Pain Physio POD1	2580	717	21.7%
Pain Physio POD3	2633	664	20.1%
Pain Physio POD7	2669	628	19.0%
Pain move POD1	2562	735	22.3%
Pain move POD3	2637	660	20.0%
Pain move POD7	2670	627	19.0%
Pain rest POD1	2583	714	21.7%
Pain rest POD3	2640	657	19.9%
Pain rest POD7	2672	625	19.0%
Worst pain POD1	2562	735	22.3%
Worst pain POD3	2631	666	20.2%
Worst pain POD7	2672	625	19.0%
Average pain POD1	2539	758	23.0%
Average pain POD3	2628	669	20.3%
Average pain POD7	2656	641	19.4%
Pre-operative opioid	3222	75	2.3%
Number of sites	3295	2	0.1%
Pain relief POD 1	2499	798	24.2%
Pain relief POD 3	2581	716	21.7%
Pain relief POD 7	2596	701	21.3%
HADS Depression	3171	126	3.8%
HADS Anxiety	3166	131	4.0%
Anxiety scale (0 to 10)	3201	96	2.9%

Data are presented as number or percentage. DN4, Douleur Neuropathique quatre question questionnaire; HADS, Hospital Anxiety and Depression Scale; IPO, International Pain Outcome questionnaire; PCS, Pain Catastrophizing scale score before surgery; PITS, functional Pain Interference Total Score on Brief Pain Inventory questionnaire before surgery; POD, postoperative day; PSQ, Pain Sensitivity Questionnaire.

The association of positive DN4 with the incidence of CPSP and its intensity is shown in Fig. 3. The frequency of CPSP was always higher in case of patients with a positive DN4. Severe CPSP was more frequent than moderate CPSP in patients who had a positive DN4. This was observed at M1, M3 and M6 for the four types of surgery.

Consequences of chronic postsurgical pain

Functional impairment was evaluated on the PITS based on the BPI questionnaire. The psychological impact was evaluated by the HADS total score. The quality-of-life impact was measured by the EQ-5D-5L questionnaire. Figure 4 describes the association of CPSP with these three outcomes. CPSP intensity (i.e., moderate versus severe CPSP) and neuropathic pain component were associated with a significantly greater impact on the three outcomes ($P < 0.001$).

Predictive factors of chronic postsurgical pain (the primary outcome)

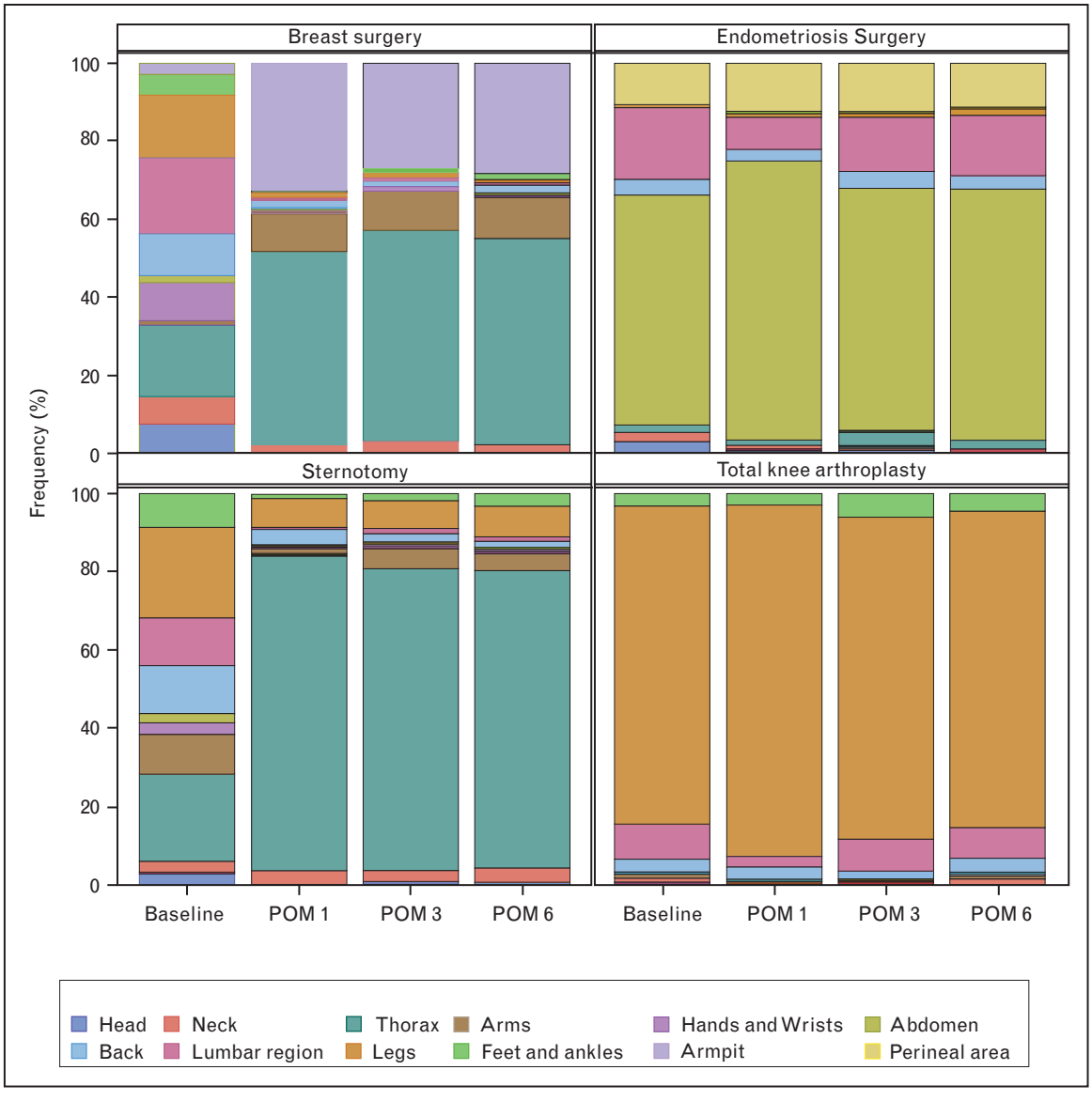
The Lasso regression was unable to define a significant and robust association of any of the peri-operative factors and the development of CPSP. Table 7 describes the results obtained for the four types of surgery. For breast cancer surgery, worst pain at POD 3 [odds ratio (OR) 0.70, 95% confidence interval (CI) 0.54 to 0.90], and the number of sites of pre-operative pain (OR 1.43, 95% CI 1.07 to 1.89) were significantly associated with modification of CPSP incidence. For endometriosis surgery, pre-operative depression score in the HADS questionnaire (OR 1.14, 95% CI 1.03 to 1.26) and average pain at POD7 (OR 1.51, 95% CI 1.08 to 2.09) were associated with increased CPSP incidence. For sternotomy, pre-operative anxiety score in the HADS questionnaire (OR 1.13, 95% CI 1.01 to 1.26) was associated with an

Table 5 Incidence of persistent pain at 1, 3 and 6 months

	Breast surgery ($n = 655$)	Sternotomy ($n = 1183$)	Endometriosis ($n = 862$)	TKA ($n = 597$)	Total population ($n = 3297$)
CPSP at 1 month					
- Missing data	175	289	173	121	758
- No	430 (89.6)	773 (86.5)	580 (84.2)	328 (68.9)	2111 (83.1)
- Yes	50 (10.4)	121 (13.5)	109 (15.8)	148 (31.1)	428 (16.9)
CPSP at 3 months					
- Missing data	200	281	225	137	843
- No	412 (90.5)	835 (92.6)	555 (87.1)	393 (85.4)	2195 (89.4)
- Yes	43 (9.5)	67 (7.4)	82 (12.9)	67 (14.6)	259 (10.6)
CPSP at 6 months					
- Missing data	194	317	251	140	902
- No	427 (92.6)	806 (93.1)	512 (83.8)	398 (87.1)	2143 (89.5)
- Yes	34 (7.4)	60 (6.9)	99 (16.2)	59 (12.9)	252 (10.5)

Value are presented as number and number (%). CPSP, chronic postsurgical pain; TKA, total knee arthroplasty. The small differences between Tables 5 and 6 in the total numbers of patients with CPSP is due to missing DN4 questionnaire responses.

Fig. 2 Locations of pain in the four types of surgery before and after the operation.



Locations of pain are extracted from the BPI diagram on the question 'the area that hurts the most'. The number of patients who filled in the information is mentioned under each time point for each surgery

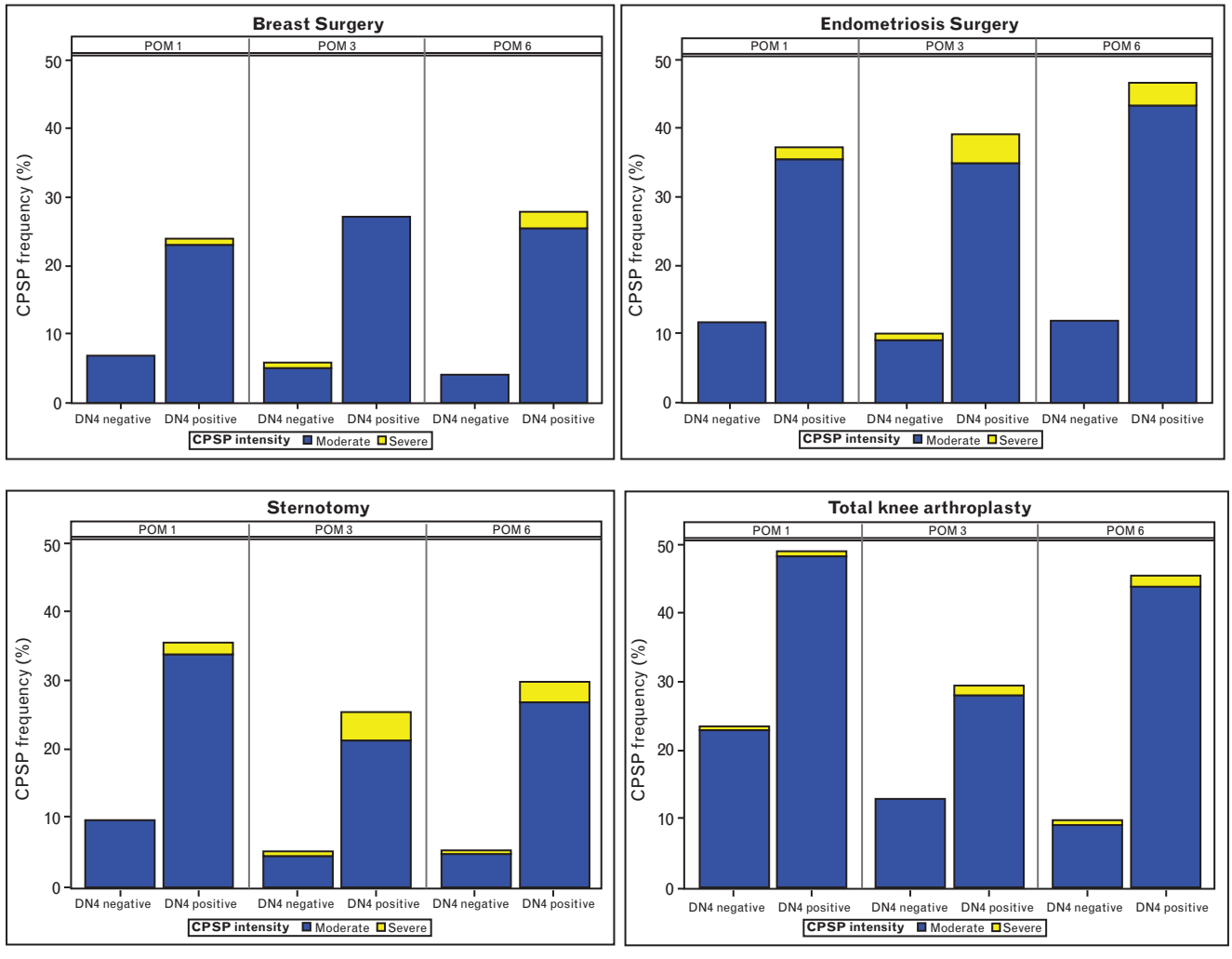
Table 6 Neuropathic component for patient with CPSP

	Breast surgery	Sternotomy	Endometriosis	TKA	Total population
CPSP at 1 month					
- Negative DN4	22 (44.9)	74 (61.2)	65 (60.7)	77 (52)	238 (56)
- Positive DN4	27 (55.1)	47 (38.8)	42 (39.3)	71 (48)	187 (44)
CPSP at 3 months					
- Negative DN4	17 (40.5)	40 (61.5)	50 (61.7)	47 (70.1)	154 (60.4)
- Positive DN4	25 (59.5)	25 (38.5)	31 (38.3)	20 (29.9)	101 (39.6)
CPSP at 6 months					
- Negative DN4	11 (32.4)	40 (66.7)	58 (58.6)	34 (57.6)	143 (56.7)
- Positive DN4	23 (67.6)	20 (33.3)	41 (41.4)	25 (42.4)	109 (43.3)

Values are presented as number (%). CPSP, chronic postsurgical pain; DN4, Douleur Neuropathique 4 questions questionnaire; TKA, total knee arthroplasty. The small differences between Tables 5 and 6 in the total numbers of patients with CPSP is due to missing DN4 questionnaire responses.

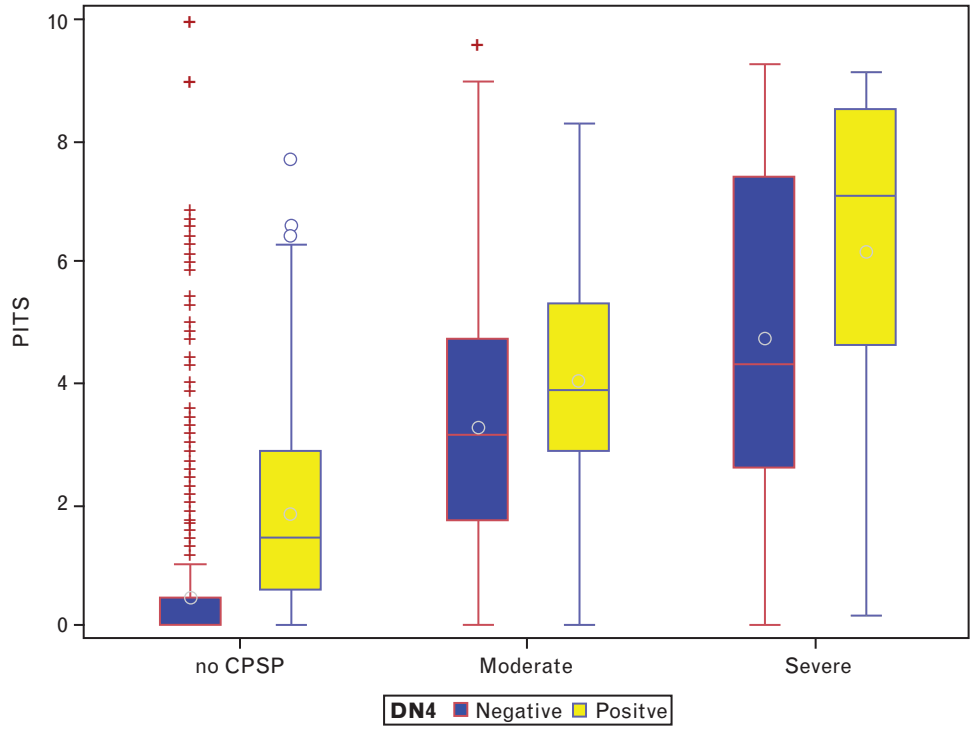
increased CPSP incidence. For TKA, no PROMs associated with CPSP development were identified. Since no transversal or type of surgery-specific predictive model was identified, the construction of a 'Predictor of Chronic Pain' was not possible. In a post-hoc analysis, we investigated the CPSP predictive factors in two sub populations, prolonged CPSP (i.e. patients with CPSP at 3 and 6 months versus only at one time point) and neuropathic CPSP (i.e. patients with CPSP at 6 months and positive DN4 at 6 months. Table 1, Supplemental

Fig. 3 Association of positive DN4 with CPSP incidence and CPSP intensity.



Positivity of DN4 is considered at each time point contemporary to CPSP incidence and intensity. CPSP, chronic postsurgical pain.

Fig. 4 CPSP impact on function, psychology and quality of life.



Functional impairment was evaluated on the PITS, based on BPI questionnaire. The psychological impact was evaluated by the HADS total score. The quality-of-life impact was measured by the EQ-5D-5L questionnaire. Differences between groups are visualised by boxplots, the following summaries are shown in a boxplot: Median, horizontal line in the box; mean, large circle in the box; upper quartile (75th percentile), upper end of the box; lower quartile (25th percentile), lower end of the box; minimum and maximum (excluding outliers and extreme values), end of whiskers; outliers (defined as 1.5 × interquartile range higher/lower than the upper/lower quartile), red crosses; extreme cases (defined as 3 × interquartile range higher/lower than the upper/lower quartile), small circles. CPSP, chronic postsurgical pain.

Digital Content, http://links.lww.com/EJA/A928 and Table 2, Supplemental Digital Content, http://links.lww.com/EJA/A929 list the result of the Lasso analysis; results were similar to the main analysis of the whole population and no clear predictive factors were identified in these two sub-populations

Discussion

We investigated the development of CPSP in a large prospective observational European study. The CPSP incidence was lower than expected and its prediction was not possible with the data obtained. The CPSP characteristics were different depending on the type of surgery. The interference of CPSP with daily activities was associated with pain intensity and neuropathic components.

Large European observational study on chronic postsurgical pain

This observational European survey on CPSP was developed in the IMI Pain Care project. The complex organisation of such a large international survey profited from the PAIN OUT network experience, the largest international registry on acute postoperative pain. The eighteen hospitals involved recruited 3297 patients with a very high follow up rate at M6 (70 to 80%). The use of validated and translated questionnaires allowed reliable data collection.

Incidence and characteristics of chronic postsurgical pain

The mean incidence of CPSP at M6 after surgery was 10.6%; this is lower than the expected incidence in the initial sample size calculation. The tendency towards a lower CPSP incidence is especially clear for breast cancer surgery (7.4%) and sternotomy (6.9%). Interestingly, for breast cancer surgery, despite important variations in the literature, the median CPSP incidence was previously estimated to be 37%, which is much higher than in our prospective study.[23] A previous prospective study[24] described a 13.5% incidence of moderate to severe CPSP at 12 months, which is still twice the incidence of the current study. Less data are available for CPSP after sternotomy but, before our study commenced the estimated mean incidence of CPSP, at 11% to 56%,[25] was also higher than that observed in our current survey. On the other hand, for TKA, the CPSP incidence in the current study appears to be in the range of what has previously been reported for TKA.[26,27] Endometriosis

Table 7 CPSP risk factors: predictive model using LASSO regression

A. Breast surgery Predictor	OR (95% CI)	*P* value
Anxiety scale (0–10)	1.00 (0.98 to 1.02)	0.82
HADS anxiety	1.07 (0.94 to 1.21)	0.31
PCS before surgery	1.02 (0.98 to 1.06)	0.36
Pain on movement POD1	0.88 (0.88 to 1.20)	0.44
Pain on movement POD3	1.18 (0.79 to 1.74)	0.43
Pain on movement POD7	1.01 (0.73 to 1.41)	0.94
Pain at rest POD3	1.32 (0.88 to 1.97)	0.20
Pain at rest POD7	1.39 (0.88 to 2.20)	0.17
Worst pain POD3	0.70 (0.55 to 0.90)	0.006
Average pain POD7	1.48 (0.85 to 2.56)	0.18
Pre-operative opioid	0.71 (0.00 to > 1000)	0.97
Number of sites	1.43 (1.08 to 1.89)	0.02
Pain relief POD1	1.01 (0.99 to 1.03)	0.54
Pain relief POD3	0.99 (0.98 to 1.02)	0.87
Pain relief POD7	0.99 (0.98 to 1.01)	0.45
B. Endometriosis **Predictor**	**OR (95% CI)**	***P* value**
Anxiety scale (0–10)	0.99 (0.99 to 1.01)	0.77
HADS anxiety	0.96 (0.87 to 1.06)	0.45
HADS depression	1.14 (1.03 to 1.26)	0.02
IPO pain intensity before surgery	1.09 (0.99 to 1.21)	0.09
PCS before surgery	0.99 (0.96 to 1.03)	0.72
Pain on movement POD3	1.08 (0.87 to 1.35)	0.49
Pain at rest POD3	1.16 (0.93 to 1.44)	0.19
Pain at rest POD7	1.01 (0.80 to 1.26)	0.96
Worst pain POD7	0.94 (0.75 to 1.16)	0.56
Average pain POD3	1.08 (0.89 to 1.30)	0.44
Average pain POD7	1.51 (1.09 to 2.09)	0.02
Pre-operative opioid	1.00 (0.99 to 1.00)	0.95
Number of sites	1.07 (0.95 to 1.21)	0.28
Pain relief POD1	0.99 (0.97 to 1.00)	0.14
Pain relief POD3	1.00 (0.98 to 1.02)	0.70
Pain relief POD7	1.01 (0.99 to 1.02)	0.50
C. Sternotomy **Predictor**	**OR (95% CI)**	***P* value**
Anxiety scale	0.99 (0.98 to 1.01)	0.23
HADS anxiety	1.13 (1.01 to 1.26)	0.04
HADS depression	1.00 (0.89 to 1.13)	0.93
IPO pain intensity before surgery	1.08 (0.97 to 1.21)	0.18
PCS before surgery	1.01 (0.98 to 1.04)	0.49
Pain during Physio POD1	0.91 (0.78 to 1.06)	0.25
Pain during Physio POD7	1.15 (0.99 to 1.32)	0.06
Pain at rest POD7	1.18 (0.92 to 1.49)	0.21
Average pain POD3	1.05 (0.85 to 1.30)	0.67
Average pain POD7	1.07 (0.77 to 1.49)	0.69
Pain relief POD1	1.00 (0.98 to 1.01)	0.93
Pain relief POD3	0.99 (0.97 to 1.01)	0.29
Pain relief POD7	0.99 (0.97 to 1.00)	0.18
D. Total knee arthroplasty **Predictor**	**OR (95% CI)**	***P* value**
Anxiety scale (0–10)	1.00 (0.99 to 1.01)	0.81
HADS anxiety	1.07 (0.97 to 1.18)	0.21
PCS before surgery	0.99 (0.96 to 1.02)	0.45
Pain at rest POD1	1.13 (0.94 to 1.35)	0.19
Average pain POD1	1.01 (0.76 to 1.34)	0.93
Average pain POD3	1.18 (0.98 to 1.42)	0.09
Average pain POD7	1.26 (1.01 to 1.56)	0.05
Pre-operative opioid	0.99 (0.97 to 1.01)	0.34
Pain relief POD3	1.02 (0.99 to 1.04)	0.10
Pain relief POD7	0.99 (0.97 to 1.01)	0.28

Data are presented as odds ratio (95% confidence interval). The LASSO regression technique selects only relevant predictors for each type of surgery and thus there are different variables in the final models for each type of surgery.

HADS, Hospital Anxiety and Depression Score; IPO, International Pain Outcome questionnaire; PCS, Pain Catastrophising scale score before surgery; POD, postoperative day. Anxiety scale: anxiety before surgery on measured on a scale from 0 (not anxious at all) to 100 (extremely anxious). Average pain POD1, POD3, POD7: average pain intensity on postoperative day 1, day3, and day 7 from BPI questionnaire question 'How intense was your pain on average during the last 24 h'. HADS anxiety: anxiety score on HADS questionnaire before surgery. HADS depression: depression score on HADS questionnaire before surgery. IPO intensity: pain intensity before surgery International Pain Outcome questionnaire. Number of sites: number of sites of pre-operative pain on BPI. Pain on movement POD1, POD3, POD7: pain on movement on postoperative day 1, day3, and day 7 with specific to the surgery; e.g. 'How intense is your pain currently while bending your operated knee?' for total knee arthroplasty. Pain Physio POD1, POD7: pain during physiotherapy on postoperative day 1 and day 7. Pain relief POD1, POD3, POD7: pain relief on BPI questionnaire on postoperative day 1, day3, and day 7. Pain at rest POD1, POD3, POD7: pain at rest on postoperative day 1, day3, and day 7. PCS: Pain Catastrophising scale score before surgery. Preoperative opioid: the preoperative opioid use with equivalent in mg of morphine. Worst pain PO3, POD7: worst pain on postoperative day 3 and day 7.

surgery has been rarely investigated to evaluate the incidence of CPSP. The high CPSP incidence we observed (16.2%) is a first description of this phenomenon in women having surgery for endometriosis.

The discrepancies in CPSP incidence can first be related to difference in methodology. We defined CPSP as moderate to severe pain at M3 to target clinical significance since a more liberal definition (e.g., any pain intensity) risks overestimation of the CPSP incidence.[26] The low CPSP incidence (3.3% of any pain at 12 months) described in a recent large international survey may also be related to less invasive surgical techniques[28] and more efficient perioperative pain management.[29] A connected hypothesis may be that our participating centres had all been involved in peri-operative pain control quality programmes for a long time with potentially higher standards of care reducing CPSP incidence.[30,31] However, reliable data supporting these hypotheses are missing. The most frequent CPSP locations were as expected: the leg for TKA, the thorax and axilla for sternotomy, the thorax for breast surgery,[23,25,27] and the abdomen for endometriosis.

A neuropathic pain component was frequent in all four types of surgery at M6: breast surgery (67.6%), TKA (42.4%), endometriosis (41.4%), and sternotomy (33.3%). This neuropathic pain component appeared early (M1) and then remained stable or even increased after breast surgery. After breast cancer surgery additional treatment (i.e., chemotherapy, radiotherapy) may be responsible for delayed neuropathic pain. However, we did not observe a specific trajectory for CPSP after breast surgery that would suggest a higher frequency of delayed CPSP at M6. Although our methodology, using only the questionnaire part of the DN4 without the physical examination, does not confirm a diagnosis of neuropathic pain,[32] these results suggest a high incidence of a neuropathic pain component, especially in surgical procedures not frequently associated with this neuropathic mechanism (i.e. TKA and endometriosis).[26] In fact, the frequency of a neuropathic pain component is reported to be much lower for TKA, around 5%.[26] CPSP after endometriosis surgery has so far been considered as

mostly nociceptive. However, recent data have found a high (40%) incidence of neuropathic pain, which is supported by our results.[33] These results suggest that the complex mechanisms involved in chronic pelvic pain clearly involve a neuropathic component.[34] A general hypothesis on this high frequency of a neuropathic pain component would be that when the general CPSP incidence decreases the residual CPSP is largely neuropathic.

Our survey offers an interesting insight to the time course of CPSP. I. In fact, of all the 317 patients who developed CPSP, approximately one third had no CPSP at M3 but developed CPSP by M6, approximately one third were 'stable' with CPSP at both M3 and M6 and in approximately one third of symptoms of CPSP at M3 resolved before M6. This delayed appearance of CPSP supports the importance of a prolonged survey of CPSP symptoms in order to have a full picture of CPSP development after surgery.[29] This delay has been described previously,[19] but the frequency of this phenomenon is especially high in our data. It may be related to the frequency of neuropathic pain component in our population with delayed development of neuropathic CPSP.

Reduction of pain after surgery for pre-operatively painful conditions, knee arthrosis and endometriosis

The patients with TKA and endometriosis had a high incidence of pre-operative pain especially in the leg for TKA, and abdomen for endometriosis. The stability of the location for the area where it hurts the most on the BPI questionnaire between pre-operative and postoperative period for these two models offers a reliable evaluation of the evolution of pain intensity overtime. Interestingly, the intensity of CPSP, as measured by the BPI, supports an important reduction, estimated to be more than 60%. These data indicate that surgery for these two painful conditions (TKA and endometriosis) is associated with a reduction in pain intensity at M6 for a high number of patients.

Consequences of chronic postsurgical pain

As discussed previously, the present findings underline that up to a 43% of patients with CPSP had some signs of neuropathic pain at M6 after surgery. This neuropathic pain component was more frequent in patients reporting severe than moderate CPSP. This is in line with previous studies enrolling patients suffering from chronic pain and specifically from CPSP[16,20,26,35,36]

The assessment of functional, psychological, and quality of life impairment caused by CPSP is described as a further important aspect that has been repeatedly recommended for capturing the full picture of disability caused by CPSP.[37] Our results support that these three outcomes are significantly associated with both CPSP severity and the neuropathic pain component. This is in line with previous publications describing the specific burden of severe CPSP[19] and of neuropathic pain in a population of patients with chronic pain.[16,36]

Predictive model of chronic postsurgical pain

Our primary goal was to propose a prediction score for CPSP. A review of literature has recently analysed nineteen published CPSP predictive scores.[7] Using a Lasso regression,[21] we did not find transversal risk factors covering CPSP prediction through all types of surgery. In addition, the few associations between some items and the CPSP incidence in each surgical category do not offer a new reliable prediction tool for a single surgical type. Our study used an adequate methodology to collect data pre-operatively, several days around surgery, and at repeated time points after surgery. We used validated questionnaires and additional questions to investigate the full scope of potential CPSP risk factors related to patient, surgery, and peri-operative pain management. Despite the number of patients followed up in this survey and the high rate of follow up at M6, one explanation for this negative result is that the incidence of CPSP was lower than expected with related lack of power, and in addition, missing data further weakened our results. An alternative hypothesis may be that we were unable to measure real CPSP risk factors such as inflammatory biomarkers, genetics, or brain networks potentially implicated in the pain chronification process.[38,39]

Methodological limitations

Our investigation might not be representative for all European hospitals. The centres enrolled varying numbers of patients and the significant amount of incomplete data sets might be related to the large number of web-based questionnaires, which patients had to complete without support from the research team. Some important data had high percentage of missing values, such as 42.6% for the DN4 questionnaires and 64.9% for the PIT scores. Thus, bias due to this rate of non-responders cannot be excluded and may have resulted in either overestimation or underestimation of the risks. The restrictive definition of CPSP to only pain intensity and the heterogeneity of surgical procedures included in the study may have favoured the negative result on CPSP prediction. The absence of a clinical examination to fully evaluate the characteristics of CPSP might also be a point of discussion especially as the definitive diagnosis of neuropathic pain should be based on physical examination and confirmatory tests.[32,40] However, the validated DN4 questionnaire we used has already been used in large nationwide surveys to estimate the prevalence of CPSP and the neuropathic component of the pain in patients suffering from chronic pain as well as CPSP.[15,19,41]

Conclusion

Our findings do not offer a new CPSP predictive score. However, we present reliable new data on the incidence, characteristics, and consequences of CPSP from a large

European survey. Interesting new data on the time course of CPSP, its neuropathic pain component, and CPSP after endometriosis surgery generate new hypotheses but need to be confirmed by further research.

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