

Re-thinking the definition of CPSP: composites of patient-reported pain-related outcomes versus pain intensities alone

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ABSTRACT

Chronic postsurgical pain (CPSP) is defined by pain intensity and pain-related functional interference. This study included measures of function in a composite score of patient-reported outcomes (PROs) to investigate the incidence of CPSP. Registry data were analyzed

for PROs one day and 12 months postoperatively. Based on pain intensity and pain-related interference with **function**, patients were allocated to the groups “*CPSPF*” (at least moderate pain with interference), “*Mixed*” (milder symptoms) and “*No CPSPF*”. The incidence of CPSPF was compared to CPSP rates referring to published data. Variables associated with the PRO-12 score (composite PROs at 12 months; NRS 0-10) were analyzed by linear regression analysis. Of 2319 patients, 8.6%, 32.5% and 58.9% were allocated to the groups *CPSPF*, *Mixed* and *No CPSPF*. Exclusion of patients whose pain scores did not increase compared to the preoperative status, resulted in a 3.3% incidence. Of the patients without pre-existing pain, 4.1% had CPSPF. Previously published pain cut-offs of NRS >0 , ≥ 3 or ≥ 4 , used to define CPSP, produced rates of 37.5%, 9.7% and 5.7%. Pre-existing chronic pain, pre-operative opioid medication and type of surgery were associated with the PRO-12 score (all $p < 0.05$). Opioid doses and PROs 24 hours postoperatively improved the fit of the regression model. A more comprehensive assessment of pain and interference resulted in lower CPSP rates than previously reported. Although inclusion of CPSP in the ICD-11 is a welcome step, evaluation of pain characteristics would be helpful in differentiation between CPSPF and continuation of pre-existing chronic pain.

Keywords: chronic postsurgical pain (CPSP); ICD-11 code; pain-related affective interference; pain-related functional interference; pre-existing chronic pain; risk factors.

INTRODUCTION

Chronic postsurgical pain (CPSP) is a common and serious clinical problem resulting in impaired postoperative long-term outcome and reduced quality of life [29]. This pain is localized, in the surgical field or a referred area, develops or increases in intensity and persists the normal healing period [25,32,42]. After mixed surgical procedures 3% to 85% of patients de-

velop CPSP, with 2% to 25% suffering from severe CPSP [31]. Pain should be of at least 3 months' duration and other possible causes for the pain should be ruled out [25,31,32]. However, diagnosis should not be based entirely on pain intensity—as was the case in the majority of investigations published in the past—but requires pain that negatively affects quality of life [25,32].

To contribute to identification, diagnosis and therapy, CPSP is now included in the International Classification of Diseases, ICD-11 [32]. Pain severity is one of the newly defined chronic pain specifiers, and encompasses three dimensions: pain intensity, pain-related distress, and pain-related interference with activities of daily living [24]. Thus, the updated definition provides a more global measure of the impact of the complex phenomenon pain on health-related quality of life [25,42].

In this analysis, we assessed CPSP using both pain scores and pain-related functional interference in the activities of daily living, which were combined in a composite score of patient-reported outcomes. This more comprehensively reflects how much a subject is impaired by pain in his function (ability to work, to perform leisure activities or housework as well as in his mood, enjoyment of life etc.) compared to a single measure which may not adequately describe the patients' pain experience [16]. The new term “*CPSPF*” was used to underline the additional consideration of *pain-related impaired function*. We assumed that CPSPF rates would differ from rates previously described for CPSP. Using data from a European cohort retrieved from the registry PAIN OUT, CPSPF rates were compared to CPSP rates, which were calculated by applying pain intensity scores with various cut-offs, as reported in previous publications.

Predictive factors for CPSP have been studied before, but no data are available for variables associated with a composite patient-reported outcome measure encompassing pain intensity as well as pain-related physical and affective interference 12 months after surgery. Thus, as a

second aim, we investigated factors associated with a composite of patient-reported outcomes at 12 months.

METHODS

Data source

The data for this analysis were retrieved from the PAIN OUT registry, a multinational, multicenter project originally funded by the European Commission's 7th Framework program, designed to improve perioperative pain management (ClinicalTrials.gov: NCT02083835). Participating hospitals obtained ethics approval and patient consent according to their local requirements. Details of the PAIN OUT registry have been published previously (www.pain-out.eu) [44]. In brief, patient characteristics, medical history, anesthesia-related and surgery-related data, and analgesics administered perioperatively, were collected by trained surveyors not involved in patient care, to avoid bias. They entered the data into a password secured web-based registry.

Patient-reported outcomes (PROs) were evaluated using the validated International Pain Outcome Questionnaire on the first postoperative day (www.pain-out.eu) [30]. Pain, as well as pain-related physical and affective interference, was quantified by the patients using a numeric rating scale (NRS 0-10; 0: no pain/no interference; 10: pain as bad as you can imagine/interferes completely). Patients' perception of care was assessed with yes/no answers or percentage scales.

Twelve months after surgery, existence of pain, pain-related interference in daily activities, and analgesic treatment were assessed using the questions originating from the Brief Pain Inventory short form (BPI), either filled in electronically by the patient or filled out by a surveyor during a telephone interview [6,12].

Cohort analyzed in this study

A proposal for data analysis with the endpoints CPSPF and patient-reported pain-related outcomes was submitted to the PAIN OUT publication board. Approval from the ethics committee of Bern University Hospital was obtained for analysis of registry data (KEK 2020-02699). Anonymized data of patients who had participated in the 12-month follow-up between 2012 and September 2020 after general surgery, orthopedic surgery/traumatology, gynecological/obstetric surgery and neurosurgery (spine surgery only) were made available by the PAIN OUT consortium. The manuscript adheres to the applicable STROBE/RECORD guidelines.

Patient-reported outcomes and composite scores

For the first day after surgery, the following PROs retrieved from the patient questionnaires were analyzed and summarized as composite scores (Supplemental Digital Content Table S1, available at <http://links.lww.com/PAIN/B623>): Pain Composite Score (**PCS-1**: worst pain, least pain, % time in severe pain) and Pain Interference Total Score at day 1 (**PITS-1**: pain-related interference with activities in bed, taking a deep breath/ coughing, and with sleep, pain-related anxiety and helplessness). The **PRO-1** score is the mean of PCS-1 and PITS-1, thus summarizing pain intensities and pain-related PROs.

For the time point **12 months after surgery**, composite scores were calculated from measures of the BPI as outlined in Supplemental Digital Contents Figure S1 (available at <http://links.lww.com/PAIN/B623>). The four questions on pain intensity (least, worst, average and current pain) were averaged to create the *Pain Composite Score* (**PCS-12**). On the basis of this score, patients were allocated to the groups *pain free* (PCS-12; NRS=0), *mild pain* (NRS <3), *moderate pain* (NRS 3 to <6), and *severe pain* (NRS ≥6). In the same manner, pain-

related functional interference was calculated from the 7 questions of the BPI addressing physical and affective interference as well as pain-related interference with sleep, thus summarizing the reactive dimensions of pain [6,20]. These measures were combined in the *Pain Interference Total Score (PITS-12)*. Patients were allocated to *no, mild, moderate* and *severe functional interference* according to the optimal cut-points described by Shi and coauthors (moderate interference NRS 2-5) and previously used to evaluate functional interference in patients with CPSP [33,35]. Finally, the eleven measures of pain intensity and pain-related interference were averaged to create a composite patient-reported outcome score, **PRO-12**.

Definitions of CPSPF: Taking into account pain intensity (PCS-12) and pain-related functional interference in daily activities (PITS-12), patients were allocated to three CPSPF groups.

- *No CPSPF* group: Patients with neither pain nor pain-related functional interference.
- *Mixed* group: Patients with only mild symptoms (PCS-12 and/or PITS-12 >0) not meeting the criteria for the CPSPF group, and patients reporting functional interference without any pain.
- *CPSPF* group: Patients with a PRO-12 ≥ 3 with at least moderate and at least mild pain-related interference.

Using these three criteria, CPSPF rates were calculated for the whole cohort, as well as for patients with and without any pre-existing chronic pain. Furthermore, we applied the ICD-11 requirement of an increase in pain intensity at 12 months compared to the pre-operative situation.

Aim of the study

The aim of this study was first to calculate PRO-12 scores (primary endpoint) encompassing pain and pain-related interference after surgery. On the basis of PRO-12 scores, the incidence

of CPSPF was generated and then compared to CPSP-rates based on previously published definitions of CPSP. The cut-offs used in the past were pain NRS >0 (*group CPSP-0*), ≥ 3 (*group CPSP-3*) or ≥ 4 (*group CPSP-4*). Because in previous trials these cut-offs referred either to pain at rest, pain with movement, average pain, or type of pain was not specified, we employed the PCS-12 to define CPSP for this comparison.

The second aim of the study was to investigate variables already assessable preoperatively which are associated with PRO-12 / CPSPF group. In a further step, we additionally entered perioperative variables to evaluate whether the regression model could be improved.

Analysis of data

During the process of data cleaning, only hospitals providing at least 50 cases with complete perioperative process data and filled-in patient questionnaires were included in the analysis. Part of the anonymized data set made available for this statistical analysis has been used in the past for other projects derived from this registry [12,35]. As time of enrollment was long, we introduced a variable considering an early study period (2012-2015) and a more recent period (2016-2020) as an additional variable.

Statistics

The definition of CPSPF was more stringent than those used in the past, which referred to pain scores only. Based on a previous investigation [35], we estimated the CPSPF rate at about 10%. Thus, a cohort of roughly 2000 patients would result in a representative cohort of 200 patients reporting CPSPF.

Categorical data were presented as absolute numbers and percentage of patients, continuous data by mean and 95% confidence intervals (CI) of the mean or mean \pm SD (standard deviation), NRS scores by median with interquartile range (IQR). The χ^2 test was applied to test re-

relationships between categorical variables. Two-sided independent samples t test or analysis of variance (ANOVA) was used to compare the mean values of normally distributed data between two or more than two groups, respectively. Ordinal data were compared by the two-sided Mann-Whitney U test or Kruskal-Wallis test.

A multivariable linear regression model was fitted for the PRO-12 score as a dependent variable with risk factors for CPSP known before surgery (patients' demographics and history, type of surgery). Estimated regression coefficients b with 95% confidence intervals (CI) were reported to assess the influence of the independent variables. The results were compared to a model with risk factors known before surgery and additional perioperative data (anesthesia-related variables and PROs retrieved from the first postoperative day). The coefficient of determination R^2 as well as the Bayesian information criterion (BIC) is provided for both models (BIC_{pre} , BIC_{peri}) and the likelihood-ratio test was performed for model selection.

In a sensitivity analysis an ordinal regression model was fitted, with CPSPF as a dependent three-stage variable (no CPSPF, mixed group, CPSPF) and the pre-operative and perioperative risk factors as independent variables. Estimated odds ratios with 95% confidence intervals (OR (95% CI)) were reported, and goodness of fit of the regression model was assessed by Nagelkerkes R^2 .

Additional sub-analyses were performed separately for patients undergoing general, orthopedic, gynecological/obstetric surgery and neurosurgery (spine surgery only), as well as for patients from one single hospital, using the model including pre- and perioperative variables. Statistical analyses were performed using IBM SPSS Statistics 25.0 (Corp., Armonk, NY).

RESULTS

Study cohort and incidence of CPSPF

Data of 5237 patients were obtained from PAIN OUT. After exclusion of patients not responding to the 12-month questionnaire and patients with incomplete data sets, 2319 cases were analyzed (Figure 1). Considering pain and pain-related interference 12 months after surgery, 8.6% of patients were allocated to the *CPSPF* group, 32.5% to the *Mixed* group and 58.9% to the *No CPSPF* group. In the heterogeneous *Mixed* group, 61.3% of the patients reported pain as the leading symptom ($PCS-12 > PITS-12$), and 37.5% reported higher scores for functional interference than for pain ($PITS-12 > PCS-12$). Composite PRO-12 scores amounted to 4.8 (4.6;5.0), 1.2 (1.1;1.2) and 0.0 (0;0) for the groups *CPSPF*, *Mixed* and *No CPSPF*.

Pre-existing chronic pain for at least three months before surgery was frequently reported in patients undergoing orthopedic surgery (69.6%) and neurosurgery (spine surgery): 76.0%). It was more common in group *CPSPF* compared to the other two groups ($p < 0.001$, Figure 1). With regard to location, 15.9% of the patients suffered from pre-existing pain at the surgical site, 54.6% reported pain elsewhere, and 29.4% had pain at both locations (Supplemental Figure S2, available at <http://links.lww.com/PAIN/B623>). Patients' characteristics and clinical data are presented in Table 1. The incidence of CPSPF was highest after neurosurgical (31.9%) and orthopedic back/spine surgery (19.4%) and total knee arthroplasty (19.1%).

CPSPF rates did not vary between the early and the more recent study phase (8.5% versus 8.8%; $p=0.06$). The proportion of patients in the *Mixed* group was higher in the early period (38.2% versus 24.3%; $p < 0.001$). However, different hospitals contributed data to the two study periods, and the types of surgery were not always comparable.

CPSP rates using different definitions of CPSP

Considering the ICD-11 requirement that pain intensity should have increased after surgery compared to the preoperative status, only 3.3% of the patients could be categorized as having CPSPF (indicated in Fig. 2 as CPSPF-ICD-11). Applying previously published cut-offs to the present cohort, incidence rates for CPSP amounted to 37.5% using a PCS-12 cut-off of NRS >0. With a cut-off of NRS ≥ 3 or ≥ 4 , CPSP rates declined (Fig. 2). A comparison of the present results to CPSP-rates reported by other working groups is also displayed in Figure 2. Distribution of patients according to their CPSPF group versus different cut-offs to define CPSP is shown in Supplemental Figure S3 (available at <http://links.lww.com/PAIN/B623>).

Of the patients **without** any pre-existing chronic pain, 322 reported pain at 12 months; 55 of those had CPSPF (4.1% of the whole cohort). In patients with pre-existing pain, CPSPF rates were significantly higher, with the incidence amounting to 22.2% in patients with pain at the surgical site and elsewhere (Supplemental Figure S2, available at <http://links.lww.com/PAIN/B623>). In the majority of patients with pre-existing chronic pain, pain intensity had declined at 12 months, with 50.5% being completely pain-free.

Opioids

A small percentage of the patients (5.6%) took opioids before hospital admission, with the highest rates in patients undergoing orthopedic surgery (10.6%) or spine surgery in the neurosurgical department (19.5%). Of the *CPSPF* groups, the highest proportion of patients were those having CPSPF at 12 months (Table 1; $p < 0.001$). At the end of surgery, 570 patients (27.0%) received opioids to prevent pain immediately after emergence from anesthesia. These opioids were more frequently administered to patients developing CPSPF later on (40.2%) than to patients in the *Mixed* group (33.7%) or the *No CPSPF* group (21.3%; $p < 0.001$).

During their stay in the PACU and on the ward, more patients in the *CPSPF* group received opioids (91.0%) than patients in the *Mixed* (77.5%) and *No CPSPF* groups (70.8%; $p < 0.001$). Twelve months after surgery, opioids were taken more frequently by the *CPSPF* group (23.4%; *Mixed*: 2.9%, *No CPSPF*: 1.1%; $p < 0.001$).

Patient-reported outcome on the first postoperative day

PRO measures evaluated on the first postoperative day differed between *CPSPF* groups (Fig. 3). Greater pain intensity in group *CPSPF* was accompanied by increased pain-related interference with activities as well as increased affective interference. Pain-related interference with sleep was more pronounced for the *CPSPF* group compared to the other groups. Overall, the PRO-1 score was significantly higher in the *Mixed* group than the *No CPSPF* group, and in the *CPSPF* group compared to the *Mixed* group (both $p < 0.001$). Further details are summarized in Supplemental Table S1 (available at <http://links.lww.com/PAIN/B623>). Patients with *CPSPF* spent significantly more time in severe pain during the first 24 hours after surgery ($p < 0.001$), more often expressed the desire for more pain treatment (answered “yes” to the question: “Would you have liked more pain treatment than you received?” *CPSPF*: 18.3%; *Mixed*: 10.4%; *No CPSPF*: 7.6%; $p < 0.001$) and reported less pain relief from the analgesics administered ($p < 0.001$).

Variables associated with *CPSPF*

The multivariable linear regression model, including variables assessable preoperatively, revealed that pre-existing opioid medication increased PRO-12 score on average by nearly 1 point ($\beta = 1.04$ (95% CI: 0.77;1.30), and scheduled spine surgery by 0.63 (0.26;0.99) points (Table 2). Pre-existing chronic pain for at least three months before admission, orthopedic surgery and younger age were also associated with increasing PRO-12.

The second model—which also included perioperative variables—contains some additional explanatory factors (Fig. 4): If opioids were given for postoperative pain management, this was associated with a marginal increase in PRO-12 (for PACU: 0.16 (0.03;0.30)), the administration of nonopioid analgesics with a decrease of PRO-12 (-0.24 (-0.39;-0.09)). Further variables associated with an increase of PRO-12 were “desire for more pain treatment” and an increase in PRO-1 score. Proportion of variance explained by the most relevant variables PRO-1 and opioid medication before admission were 6.3% and 5.4%. Goodness of fit of this model was judged as moderate ($R^2=0.16$) with lower BIC ($BIC_{\text{peri}}=7657$) than the model using only information available preoperatively ($BIC_{\text{pre}}=7965$), indicating strong evidence for the model with perioperative data. The likelihood ratio test also confirmed the better fit of the perioperative model (chi square=73.5, degrees of freedom=9, $p < 0.001$).

Sensitivity analysis using an ordinal regression model with *CPSPF* group as dependent variable confirmed the results of the linear regression model (Supplemental Table S2, available at <http://links.lww.com/PAIN/B623>). The sub-analyses performed for the four different surgical disciplines and data of one single institution underline the relevance of pre-existing chronic pain and/or opioid medication before admission as well as PRO-1 (Supplemental Tables S3 A-E, available at <http://links.lww.com/PAIN/B623>). Receiving regional analgesia was a protective factor in gynecological and obstetric patients, resulting in a decrease of -0.4 (-0.6;-0.1) in PRO-12 at 12 months.

Discussion

In a European cohort of 2319 patients, chronic postsurgical pain was studied using the new ICD-11 definition [24,25,32]. Results showed lower rates than published before, in part due to

inclusion of pain-related functional interference, in part due to restrictions on cases presenting with an increase of pain intensity compared to the preoperative status.

In the 1990's, Kehlet and co-workers underlined that low pain intensity could no longer be the only goal of pain management; thus they promoted the early return to functional recovery [23,26]. This fundamental change in approach gained additional proponents when it became clear that striving for pain intensities below a distinct cut-off was in part the reason for increased prescription of opioids, resulting in the opioid crisis. To the best of our knowledge, this is the first large-scale study assessing CPSPF rates in a mixed surgical cohort by employing measures to capture the multidimensional pain characteristics.

Defining CPSP using pain scores alone

Evaluation of CPSP in the past clearly relied on pain scores and focused on unidimensional measures. Pain was often assessed at rest or as average pain, reflecting a defined period of time (one day up to three months) [1,12]. Sometimes, details of pain assessment were not even specified [9,19,22]. Applying published cut-offs in the present cohort and adding results of other working groups uncovers striking differences in CPSP rates (Fig. 2).

However, even if more extensive questionnaires were to be used taking into account pain-severity as a combination of pain intensity, pain-related distress and functional interference [32], we still have to question whether we need cut-offs to define CPSP, and if yes, which cut-off is clinically meaningful from the patients' point of view. Development of standardized, validated assessment tools is a further crucial step to identify meaningful PROs reflecting pain severity and pain-related functional interference at long-term after surgery. The present study suggests an approach that could serve as a basis for further discussion.

Alternative tools for assessment of CPSP

Enhanced restoration of function after abdominal surgery—helping the patient to breath, cough and move easily— has been described as one central aspect of pain relief [23]. More sophisticated, complementary measures have been proposed [16,42], but evaluating them requires additional resources and tools. The Initiative of Methods, Measurement, and Pain Assessment in Clinical Trials recommended measurement of the outcome domains of physical and emotional functioning, side effects and satisfaction [7]. The BPI has been suggested as one option; however, other questionnaires on quality of life can be employed [4,10,21]. Certainly, introducing some surgery-specific items is advisable, as interference after joint replacement differs from interference after hernia repair or thoracotomy [11,21,43].

Time as a factor

CPSP develops or increases in intensity after a surgical procedure and persists more than 3 months after the surgery [31]. Previous investigations were aimed at periods ranging from two months after the surgery up to several years [13,17]. After most types of surgery, rates of moderate to severe CPSP decreased over time. In a European study, rates declined from 16.0% at 6 months to 11.8% at 12 months [12]. In breast cancer patients, the incidence of any permanent pain one and two years after surgery decreased from 67% to 45% [13]. However, as indicated by the ICD-11, some patients may suffer from pain after an asymptomatic time interval [13,25,27,42].

Continuing pre-existing pain versus CPSP

Another challenge is distinguishing CPSP from continuing pre-existing pain [22]. This issue has rarely been addressed [11,21,22,40], and might have contributed to higher CPSP rates re-

ported previously. In the present trial, only 3.3% of the cohort remained in the CPSPF group when an increase of pain intensity compared to the preoperative status was required. This decline is certainly due to the high proportion of patients with long-term pre-surgical pain, a lot of them presenting for e.g., joint replacement and spine surgery.

In a population-based study, 18% of patients reported moderate to severe pain at the surgical site 3 to 36 months after surgery [22]. If all patients who had the same kind of pain before surgery were excluded, 10.5% were allocated to CPSP. If patients with any pain before surgery were excluded, 6.2% were left with CPSP. Apart from pain intensity, CPSP was frequently not a continuum of pre-existing pain for other reasons. Of the CPSP patients with preoperative pain at the surgical site, 74.1% reported a change of “kind of pain” compared to preoperative pain [22]. A change in characteristics of pain and/or sensory disturbance, the location or spatial distribution compared to pre-surgery are further diagnostic criteria [11,27,39,42]. However, these are not considered in the ICD-11. Thus, there is potential for a misclassification of patients, an issue to be addressed by the ICD-12. As the questionnaires do not consider characteristics and temporal patterns of pain, we could not further classify subjects. For the future, a more detailed evaluation of patients’ history including physical examinations before and after surgery would be helpful [11,21,27].

Incidence of CPSP and CPSPF

The results—including a large variance in the incidence of CPSP depending on different definitions—confirm previous findings [12,31]. It is likely that a considerable number of patients who were categorized in the past as having CPSP would not meet the current definition, as their chronic pain did not increase in intensity compared to preoperative pain or was not related to surgery, since questionnaires did not capture this information and thorough pre- and postoperative evaluation was not performed.

The *Mixed* group comprised patients with milder symptoms, with some pain but no or marginal interference, or with (nearly) no pain and at least moderate interference. Based on these results, it is not possible to determine which of these patients are in need of or would benefit from a multimodal therapeutic approach. However, regardless of whether their pain is categorized as CPSPF, Mixed, or a continuation of pre-existing chronic pain, patients should be offered treatment.

It seems appropriate to provide some information before discharge to patients at risk, such as whom to consult if pain-related problems associated with surgery continue or arise. Patients with pain as the leading symptom need other therapeutic strategies than patients suffering from impaired function in whom pain plays a minor role. Reasonable options could be consultation of a multidisciplinary team of pain experts, e.g., within the setting of a transitional acute pain service, offering a multidimensional assessment and providing an interdisciplinary treatment approach [14,19]. Composite outcomes can reflect a more comprehensive assessment of CPSP, however, treatment approaches have to consider both pain and functional interference, to provide individualized care [16].

CPSP versus CPSPF: What is the difference?

Orthopedic surgery, spine surgery and a positive DN4 (possible neuropathic pain) are associated with pain and the most interference [35]. These patients are frequently categorized as having CPSPF; however, some of them do not qualify for CPSP due to only mild pain. The same is true for patients with high affective interference. Subjects' individual perception might vary considerably depending also on the preoperative status, type of surgery and the patient's preoperative expectations for surgical outcome.

The use of cut-offs results in precisely separated groups of patients with CPSP/CPSPF or no CPSP/CPSPF. However, reality is different, with no arbitrary lines between the groups, but a

smooth transition from one group to the other. Thus, calculating incidences of CPSP/CPSPF can give an impression of the proportion of patients suffering from CPSP, but does not meet the needs of an individual subject. It is well accepted that the multidimensional phenomenon pain should be best considered by a biopsychosocial model [3]. The WHO specifiers with additional extension codes for pain intensity, pain-related interference and pain-related distress provide clinically useful categories giving a more detailed picture that will improve patient management and research [3,38].

Variables associated with CPSPF

This analysis confirmed previously described risk factors, such as pre-existing chronic pain and opioid medication. Sex was not associated with PRO-12, probably due to the very mixed types of surgery, ranging from younger females undergoing laparoscopic surgery to old patients undergoing extensive orthopedic surgery.

Interestingly, not only acute postoperative pain but also pain-related physical and affective interference and administration of analgesics during the first 24-hour period after surgery were associated with PRO-12 and CPSPF and improved the regression model. This points to the usefulness of evaluating additional physical and emotional measures of acute pain, as recommended [4,16] and provided by PAIN OUT. Specifically, the time in severe pain is important from the patients' perspective [12,35,36]. Hence, this also implies a change in patient education: acute pain management should no longer focus on pain scores only, but on rapid recovery of function.

It should be underlined that the administration of opioids was associated with increased, nonopioid analgesics with decreased PRO-12. This does not imply that opioids are the reason

for CPSP, but rather, that those patients suffering from severe acute pain were given more opioids.

Limitations and strengths

Limitations of this analysis include the general shortcomings of registry data (data quality, electronic questionnaires). There is no preoperative patient assessment of functional impairment, psychological and psychosocial variables, although these provide valuable information [1,8]. Electronic questionnaires, specifically when applied within a registry project, cannot capture all aspects of CPSP and have to be considered as a screening tool, not as a final diagnosis.

The strengths of this investigation are the large European cohort from clinical routine settings, a standardized documentation of process and outcome variables with validated questionnaires addressing pain as well as pain-related functional physical and affective impairment. The results do not reflect artificial study settings, in which patient selection is rigorous, excluding “problematic cases”, and more staff is involved.

Conclusions

CPSPF was identified in 8.6% of the patients using PRO measures encompassing pain and functional interference. Using a more stringent definition, including only patients with increased pain scores at 12 months, 3.3% would be diagnosed with CPSPF.

Introducing CPSP into the ICD-11 and the inclusion of pain-related functional interference are welcome steps for clinicians, patients, and the scientific community. However, patients with pre-existing pain should be evaluated more extensively, both before and after surgery. Pain characteristics and a change in pain localization could be valuable information. We should continue to discuss and re-think the definition of CPSP for ICD-12.

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Figure Legends

Figure 1: Flow chart with number (%) of patients.

Definition of CPSPF considers not only pain but also pain-related functional interference assessed with a questionnaire 12 months (12M) after surgery. CPSPF: CPSP defined by chronic postsurgical pain and pain-related interference of function.

Figure 2: Percent of patients with CPSPF and CPSP in the present cohort applying different definitions of CPSP. For comparison some results of previous studies are displayed [1,2,5,9,11,12,14,15,18,22,28,34,35,37,39,40,41,43].

CPSPF ICD-11: Patients meeting the ICD-11 requirement that pain intensity at the site of surgery had increased compared to the pre-operative situation. CPSP-0, CPSP-3 and CPSP-4 (orange bars): application of the cut-off NRS >0 , NRS ≥ 3 or NRS ≥ 4 to the present cohort.

Time after surgery is indicated after the author's name (i.g. 3M: 3 months). a: mixed surgical group; b: trauma/orthopedic surgery; c: breast cancer surgery; d: gynecological surgery; e: thoracic/cardiac surgery; f: outpatient surgery.

Figure 3: Patient-reported outcomes of the three CPSPF groups 24 hours after surgery.

PCS-1: Pain composite score at the first day after surgery; PRO-1: composite score for patient-reported outcomes at the first day after surgery; side effects: composite score corresponding to the mean of the variables dizziness, drowsiness, nausea, and itching.

Box and whisker plots with median, IQR, 10-90% percentiles; +: mean; *** $p < 0.001$.

Figure 4: Multivariable linear regression analysis with PRO-12 score as dependent variable.

Reference for analysis of the surgical groups is general surgery. Boxes represent regression coefficients, whiskers are 95% CI. Exact measures are shown in the right column. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

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Table 1: Patient characteristics and clinical data according to the CPSPF groups

		All patients	No CPSPF	Mixed	CPSPF	p^d
All patients		2319	1365 (58.9)	754 (32.5)	200 (8.6)	
Females	n (%)	1457 (62.9)	895 (61.4)	452 (31.0)	110 (7.5)	0.002
Males	n (%)	862 (37.1)	470 (54.5)	302 (35.0)	90 (10.4)	
Age	years	51.5±15.2	51.6±15.3	51.1±15.2	52.9±14.1	0.300
BMI	kg/m ²	28.9±7.9	29.8±8.5	27.4±6.4	28.7±6.9	<0.001
Patients with comorbidities ^a	n (%)	1514 (65.9)	916 (67.4)	448 (60.5)	150 (75.8)	<0.001
Number of comorbidities		1.2±1.2	1.2±1.2	1.0±1.2	1.4±1.3	<0.001
Pre-existing pain ^b	n (%)	959 (41.4)	453 (33.2)	361 (48.1)	145 (72.5)	<0.001
Pain scores all patients ^b	NRS	0.0 (0.0/4.0)	0.0 (0.0/4.0)	0 (0.0/6.0)	6.0 (0.0/8.0)	<0.001
Patients with pain only		6.0 (4.0/8.0)	6.0 (4.0/8.0)	6.0 (4.0/7.0)	7.0 (5.0/8.0)	<0.001
Opioids before surgery	n (%)	129 (5.6)	48 (3.5)	40 (5.3)	41 (20.5)	<0.001
Duration of surgery	min	147.7±90.8	142.0±91.7	153.9±91.3	164.5±79.7	0.002
Surgical group						

		All patients	No CPSPF	Mixed	CPSPF	p^d
General surgery		837	603 (72.0)	200 (23.9)	34 (4.1)	
Orthopedic surgery		651	257 (39.5)	290 (44.5)	104 (16.0)	
Gynecology		629	397 (63.1)	198 (31.5)	34 (5.4)	<0.001
Neurosurgery (spine surgery)		129	57 (44.2)	47 (36.4)	25 (19.4)	
Others		73	51 (69.9)	19 (26.0)	3 (4.1)	
Regional analgesia ^c	n (%)	632 (27.5)	359 (26.4)	223 (30.2)	50 (25.0%)	0.127

Data presented as n (%), mean±SD or median (IQR). a: Patients with at least one comorbidity, refers to 2298 patients; b: refers to 2316 patients (3 missing data in Group Mixed) with data regarding pre-existing pain before surgery for at least 3 months; c: regional analgesia includes neuraxial anesthesia and peripheral nerve blocks either performed intraoperatively only, postoperatively or during both time intervals (n=2296); d: χ^2 test, ANOVA or Kruskal-Wallis test. BMI: body mass index.

Table 2: Results of multivariable linear regression analysis including only variables assessable preoperatively. Dependent variable is patient-reported pain-related outcome 12 months after surgery (PRO-12 score).

Variables	Regression coefficient	95% CI	P
Sex: female vs. male (reference)	0.018	-0.125; 0.160	0.808
Age	-0.006	-0.010; -0.001	0.009
Weight	-0.001	-0.004; 0.001	0.312
Pre-existing chronic pain: yes vs. no (reference)	0.455	0.322; 0.589	<0.001
Opioids before admission: yes vs. no (reference)	1.035	0.768; 1.302	<0.001
Type of surgery: General surgery (reference)			
Orthopedic surgery	0.551	0.384; 0.719	<0.001
Gynecology	0.194	0.025; 0.362	0.024
Neurosurgery (spine surgery)	0.031	-0.417; 0.479	0.891
Others	-0.090	-0.446; 0.266	0.619
Spine surgery ^a : yes vs. no (reference)	0.625	0.264; 0.986	0.001
Number of comorbidities	0.046	-0.021; 0.114	0.180
Cancer: yes vs. no (reference)	0.028	-0.154; 0.210	0.765
Smoking: yes vs. no (reference)	0.116	-0.057; 0.289	0.190
Alcohol: yes vs. no (reference)	0.063	-0.303; 0.428	0.737

Variables	Regression coefficient	95% CI	P
Substance abuse: yes vs. no (reference)	-0.208	-0.690; 0.275	0.399

n=2236; R²: 0.128. a: spine surgery either performed in the neurosurgical or orthopedic department

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