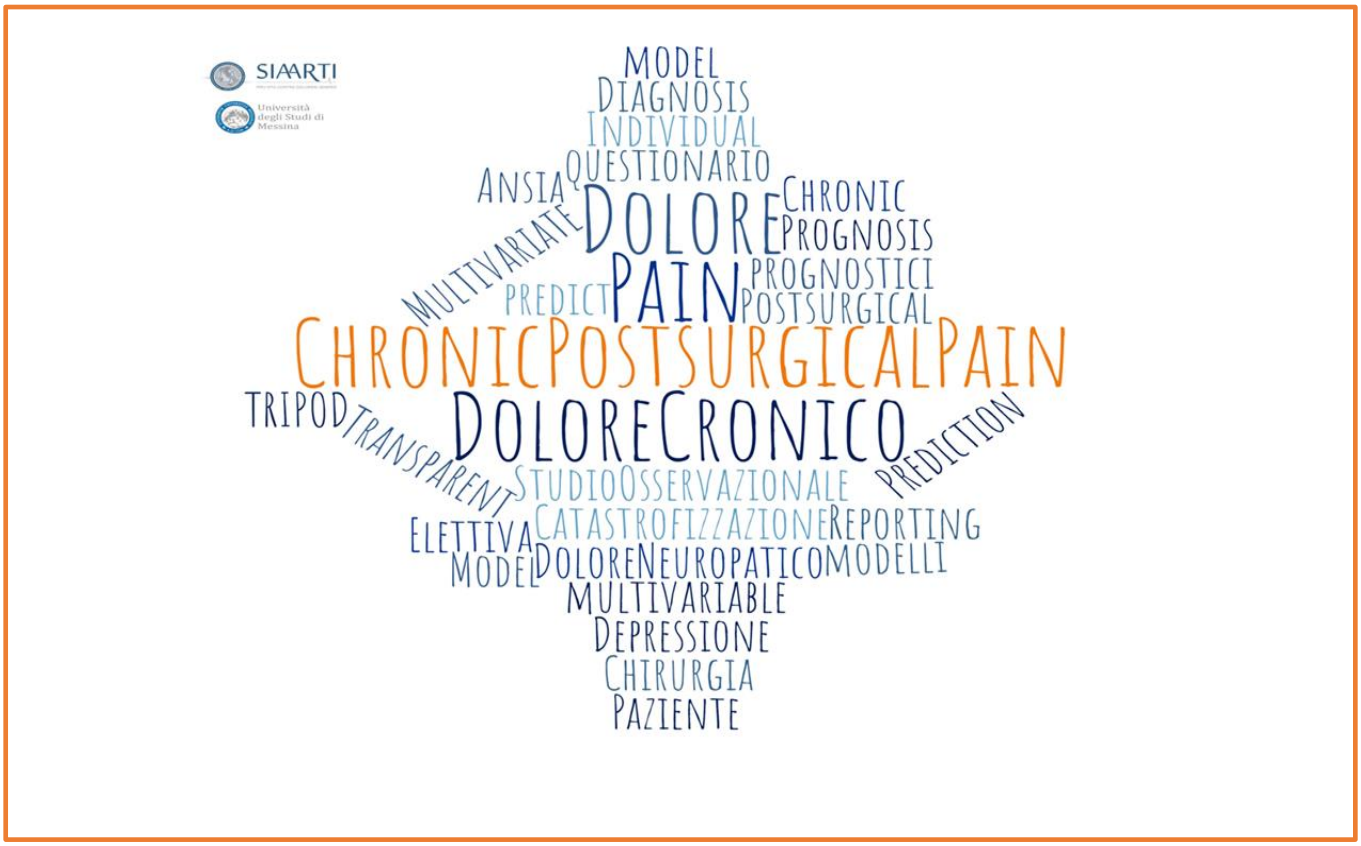

OBSERVATIONAL STUDY PROTOCOL

Version 1.2 of 02.11.23

TITLE OF THE STUDY

Chronic Postsurgical Pain: Multivariate Prediction Model

ACRONYM OF THE STUDY:

CPoP

Promoter

SIAARTI-Società Italiana di Anestesia Analgesia Rianimazione e Terapia Intensiva

(Italian Society of Anesthesia, Analgesia, Intensive Care and Resuscitation)

Coordinating Center

Azienda Ospedaliera Universitaria “Gaetano Martino”, Messina

Abstract

Chronic post-surgical pain (CPSP) is a common and disabling postoperative complication; it is defined as pain that develops or increases in intensity after surgery and persists for at least 3 months after surgery.

CPSP syndrome affects millions of people around the world, with an incidence between 10 and 50%. Furthermore, it is considered a serious health but also social and economic problem and represents a significant part of medical prescriptions and healthcare costs. Furthermore, in combination with psychological consequences, chronic pain significantly impairs quality of life and productivity, placing patients at risk of drug addiction.

Several risk factors for CPSP have been established, but the relationship with the characteristics of surgery is unclear, although it is widely associated with iatrogenic nerve damage, and chronicity is linked to remodeling of the central nervous system linked to central sensitization phenomena; a wide inter-individual range characterizes the sensation of pain, furthermore, psychological factors such as depression, pain catastrophism, mood, and, stress, could influence pain perception itself. Although surgery is a determining factor in the onset of chronic pain, certain patient characteristics also appear predictive of an increased risk of persistent pain.

Identifying risk factors for CPSP before surgery could help recognize patients at higher risk, using risk prediction models and enabling preventative strategies.

The present study aims to identify the risk factors of CPSP three months after surgery, and, subsequently, develop a risk index to identify high-risk patients considering the multifactorial etiology of CPSP.

A comprehensive item pool was derived from a systematic literature search. Data collection will record parameters at four different times: preoperative assessment (60 to 1 day before the scheduled procedure); evaluation of the perioperative period; and postoperative period (from the third month following surgery).

The outcome variable is the presence of CPSP assessed 3 months after surgery and defined as an average pain intensity of at least 3 on the NRS scale (11-point one-dimensional pain scale) in the last three days, and pain localized to the surgical field (or in the lesion area) projected into the innervation territory of a nerve located in this area or referred to a dermatome.

Separate prediction models will be developed using data derived from surveys conducted at the relevant time points for the development of the risk index.

The sample size of the development dataset must be large enough to develop a prediction model equation that is reliable when applied to new individuals in the target population. The Authors estimate to include approximately 1500 patients to develop a clinical prediction model of CPSP three months after surgery.

The Authors estimate that at least 10 Centers are needed to enroll the intended study population.

The total expected time, from the date of project approval to the production of the draft manuscript, is 24 months.

Background

Chronic post-surgical pain (CPSP) is a common and disabling postoperative complication; it is defined as pain that develops or increases in intensity after surgery and persists at least 3 months after surgery. It can

be localized in the surgical field, projected into the innervation territory of a nerve located in this area, or referred to a dermatome [1].

CPSP affects millions of individuals worldwide, with an estimated incidence between 10 and 50%, depending on the surgery performed [2]. It is rated serious by 2-10% of patients [2;3]. Furthermore, CPSP is considered a serious medical but also social and economic problem [4;5] and represents a significant portion of medical prescriptions and healthcare costs [6]. Furthermore, in combination with psychological consequences, chronic pain significantly impairs the quality of life [7] and productivity, exposing patients to the risk of drug addiction [8].

Several risk factors for CPSP have been established [9;10;11]. A wide interindividual range characterizes the sensation of pain; multiple factors influence the perception of pain, such as genetic determinants, neurological diseases affecting the central or peripheral nervous system, inflammatory modulation of tissues, and the presence of inflammatory mediators, as well as the experience of pain [12;13;14;15; 16]. CPSP is widely associated with iatrogenic nerve lesions and chronicity is also linked to the remodeling of the central nervous system which determines central sensitization phenomena [17;18]. Furthermore, psychological factors such as depression, pain catastrophizing, mood, and stress could influence the perception of pain [19;20;21;22].

Although surgery is a determining factor in the onset of chronic pain, some patient characteristics also appear to be predictive of an increased risk of persistent pain: young age [23], female sex [24], preoperative pain [25], high levels of acute postoperative pain [25] and psychosocial factors [26;27]. The most significant limitations of current awareness in this field are the heterogeneity of study methodology, including assessment of pain timing, different definitions of pain, and the small sample size of most of the previous studies.

Identifying risk factors for CPSP before surgery could help identify high-risk patients using risk prediction models and allocate preventative strategies [28;10]. Identification of risk groups in the patient population is critical to providing individualized pain treatment [29] and may help reduce long-term opioid use.

The present study aims to identify the risk factors of CPSP three months after surgery and, to develop a valid risk index to detect high-risk patients that considers the multifactorial etiology of CPSP.

Aim

The main objective of this multicenter observational study is to estimate the occurrence of CPSP three months after any type of surgery and identify risk factors for the development of a multivariate clinical prediction model of CPSP at three months.

Methods

This is a multicenter, prospective, observational study on adult patients requiring any type of surgical procedure. This study is designed and will be reported according to the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement. Ethics Committee approval is mandatory to begin registration at all recruitment centers.

The treatments will be performed according to the rules and ethical standards on human experimentation and the Helsinki Declaration of 1964 (further revised in 2013). All study participants will provide written informed consent (including all the information about possible risks and side effects) for participation in the study. Every precaution will be taken to protect patient privacy.

For the development and validation of the prognostic models, the guidelines on prognostic modeling studies of individual participant data and the recommendations of the Transparent Reporting of a multivariable predict model for Individual Prognosis or Diagnosis (TRIPOD) will be followed.

- Population

Inclusion criteria:

Age ≥18 years

Patients scheduled for elective surgery

Exclusion criteria:

Patients with perceptive (or sensorial) alterations of pain

Patients unable to communicate

Cognitive impairment

Insufficient knowledge of the Italian language.

- Data collection

Recruitment is competitive. Each participating Center undertakes to include at least 20 patients in the study. Patients will participate in the study voluntarily and will not receive compensation of any kind from anyone, either directly or indirectly. Competitive enrollment means that being a multicentric research project, the number of patients included by each participating Center may vary depending on the inclusion capacity of each. There is therefore no maximum limit to the number of patients that each Center can include. The inclusion of patients in the study will end as soon as the total number of subjects described by the protocol is reached.

Web-based electronic case report forms (CRFs) will be used to collect data. All data will be anonymous and only the local principal investigator could match patients and reference numbers.

A comprehensive item pool was derived from a systematic literature search.

Data collection will record parameters at four different times:

• preoperative evaluation

• evaluation of the perioperative period (before surgery)

• evaluation of the perioperative period (after surgery)

• postoperative period

As regards the post-operative follow-up (three months after surgery), a telephone or outpatient evaluation is foreseen at the discretion of each center.

Preoperative evaluation (60 to 1 day before the scheduled procedure)

• Age

18-35

36-55

≥55

• Sex

Female

Male

• BMI

≤18.5 - 24.9

25 - 29.9

≥30

• Alcohol or substances of abuse (Y/N) (specify the substance)

• Previous experience of pain NRS ≥5 for 7 days (Y/N)

• Presence of chronic pathologies (Y/N) (if yes, provide the list of medications)

• Pharmacological treatments including supplements or nutraceuticals (continuous in the last 3 months) (Y/N) (if yes, provide the list of drugs)

• Chronic pain (NRS ≥3 for ≥3 months) (Y/N)

• Neuropathic pain (Y/N) (assessment via questionnaire)*

• Pain catastrophizing (Y/N) (assessment via questionnaire)*

• Anxiety (Y/N) (assessment via questionnaire)*

• Depression (Y/N) (assessment via questionnaire)*

• Presence of pain in the last three days (NRS ≥3 mean pain intensity in the 24 hours) (Y/N)

**Questionnaires*

• Evaluation of neuropathic pain: Douleur Neuropathique en 4 questions (DN-4)

• Pain Catastrophizing: Pain Catastrophizing Scale (PCS)

• Anxiety: General Anxiety Disorder-7 (GAD-7)

• Depression: Beck Depression Inventory (BDI)-II

Evaluation of the perioperative period

Evaluation before surgery

• Site of surgery

Head

Vertebral column

Arms/legs

Chest

Abdomen

Genitourinary system

• Surgical technique

Open surgery

Minimally invasive surgery

Robotic surgery

• ERAS (enhanced recovery after surgery) protocol (Y/N)

• Anesthesiologic technique

General Anesthesia

Spinal Anesthesia

Epidural Anesthesia

Peripheral nerve block

• Preventive/protective analgesia (Y/N)

• Premedication (Y/N)

• OFA opioid-free anesthesia protocol (Y/N)

• Postoperative analgesic prescription (Y/N)

Evaluation after surgery

• Pain NRS score ≥3 at the end of the surgery (Y/N)

• Presence of pain (NRS ≥5 - average value in the 24 hours) in the region of the operation at rest or during movement after surgery (Y/N)

• Analgesic prescription after surgery

≤12 hours of coverage

13-24 hours of coverage

≥ 24 hours of coverage

• Postoperative surgical complications (Y/N)

• Postoperative infectious complications (Y/N)

• Mobilization after surgery ≤6 hours? (Y/N)

Postoperative period (third month after surgery)

• Pain assessment: average pain intensity assessed using a standard NRS scale (the cutoff score will be set at ≥3 mean pain intensity over the last three days) (Y/N).

• Diagnosis of CPSP (the pain is localized in the surgical field or in the area of the lesion, projected into the innervation territory of a nerve located in this area, or referred to a dermatome) (Y/N)

• Surgical complications (Y/N)

• Infectious complications related to surgery (Y/N)

• Malignancy (Y/N)

Questionnaires:

• Douleur Neuropathique in 4 questions (DN-4)

- Outcome variable

The outcome variable is the presence of CPSP assessed 3 months after surgery and defined as an average pain intensity of at least 3 points on the NRS scale (one-dimensional pain scale - from 0 to 10 points) in the last three days and pain localized to the surgical field (or in the lesion area) projected into the innervation territory of a nerve located in this area, or referred to a dermatome [30;31].

- Development of the risk index

Separate prediction models will be developed using data derived from investigations conducted at the relevant time points.

(1) Primary version of the risk index, made up of items derived from a systematic bibliographic search (compilation of the item pool).

(2) In a second phase, the Authors will analyze the associations between each of these indices and the probability of CPSP 3 months after surgery (dichotomous variable), evaluated using logistic regression models.

(3) Items that were found to be significant in the bivariate analyses will then be analyzed multivariately (logistic regression models).

(4) In a fourth step, the Authors will safeguard the results of the multivariate analyses by calculating the area under the ROC curve of the model, and then, the cut-off score for a high risk of developing CPSP will be identified with an optimal compromise between sensitivity and specificity.

(5) Finally, the items that will generate significant predictive factors in the logistic regression analyses will be collected into an index. For each value of this index, the Authors will calculate the proportion of patients who reported CPSP at 3 months after surgery.

- Statistical analysis of results

The study population will be described by summarizing the variables collected in each period of evaluation of the subject (preoperative, perioperative before surgery, perioperative after surgery, three months post-operatively after surgery). In particular, the discrete variables will be reported in terms of absolute and relative frequency, and the continuous variables will be summarized via mean and standard deviation or via median and interquartile range, based on the symmetry of each distribution.

The study population will be stratified based on the presence/absence of CPSP three months after surgery, and a comparison will be made between the two groups. In detail, the Student's T test for independent samples will be used in the case of normally distributed variables (normality assessed using the Kolmogorov-Smirnov test), the non-parametric Wilcoxon-Mann-Whitney test in the case of non-normally distributed variables, the Pearson Chi-Square in case of discrete variables or Fisher's exact test if the expected frequency is low.

Univariate and multivariate logistic regression models will be used to study the association between the probability of CPSP three months after surgery (dependent variable) and the collected variables (independent variables). The results of each model will be reported in terms of model parameters and odds ratios and their 95% confidence intervals. For each logistic model, the discriminated ability will be evaluated via the C-statistic of the area under the ROC curve and calibration via the Hosmer-Lemeshow test. To identify significant (preoperative and intraoperative) predictors of CPRS three months after surgery, backward elimination will be used with the threshold of 0.05 as the level to remain in the model. The parameters of the multivariate logistic regression model resulting from this process will be used to assign a score to each predictor. Internal validation will be conducted using bootstrapping to correct for optimism.

Given the observational nature of the study, as well as the large sample size and multicenter nature, any variable reporting a high proportion of missing values (>25%) will be eliminated from the analyses. Subjects in which more than half of the variables are missing will be excluded from the analysis. Lower proportions will lead to the use of the statistical technique of multiple imputations of missing data, assuming that the missing data are random (independent of the missing value, but dependent on other variables). Based on the total proportion of missing data, if this is relatively low (less than 5%) the possibility of analyzing only those subjects with all available data may also be taken into consideration.

For all statistical analyses, the significance level is set at $p < 0.05$ and the tests used are two-tailed.

- Power analysis

The sample size of the development dataset must be large enough to develop a prediction model equation that is reliable when applied to new individuals in the target population.

The authors estimate that approximately 1500 patients are necessary to develop a logistic model for clinical prediction of CPSP (presence/absence) three months after surgery.

The estimate of the sample size was performed following the methodological recommendations of Riley [33] and hypothesizing two scenarios with a cumulative incidence of CPSP 3 months after the intervention of 10% and 50%. It was necessary to hypothesize two scenarios since the aggregate incidence of CPSP in the

target population is not known in the literature. The information is available only based on the type of surgery and the estimate varies between 10% and 50%.

Assuming an incidence of 50% and that the final predictive model can explain more than 15% of the variability with 15 candidate parameters (risk of overfitting), a sample size of 1124 subjects is estimated for the development of a logistic predictive model, corresponding to 37 subjects with CPSP per parameter.

Assuming an incidence of 10% and that the final predictive model can explain more than 15% of the variability with 15 parameters, a sample size of 1799 subjects is estimated for the development of a logistic predictive model, corresponding to 12 subjects with CPSP by parameter. The sample size is reduced to 1440 individuals for the development of a final predictive model with 12 parameters.

Given the uncertainty on the estimated incidence of CPSP three months after surgery, a sample size of, at least, 1500 individuals is therefore sufficient to meet the main objective of the study.

Expected number of centers to enroll

Authors estimate that, at least, 10 centers are needed to enroll the study population.

Schedule

The calendar will be organized into three-time windows:

• First phase - Authorization from the Local Ethics Committee of the participating Center, patient enrollment, and first evaluations: from the 1st to the 12th month from the date of project approval.

• Second phase - completion of follow-up and sending of complete clinical documentation from the registered Centers: from the 12th month to the 18th month from the date of project approval.

• Third phase – conducting the synthesis and statistical analysis of the data and producing the manuscript draft: from the 18th month to the 24th month from the date of project approval.

Cost analysis

There is no cost or funding for this study.

List of centers

The updated list of Centers currently enrolled is attached to this document.

Administrative aspects

Confidentiality

Subject confidentiality is strictly entrusted to the participating investigators, research personnel, and the sponsoring institution. The study protocol, documentation, data, and all other information generated will be kept in strict confidentiality. All data reported in eCRF are anonymized (patient number center number). No information relating to the study or data will be released to unauthorized third parties without the prior written approval of the study management committee.

This study will use SIAARTI Research Electronic Data Capture (REDCap) for data collection, transmission, and storage. REDCap is a secure web platform for creating and managing online databases and surveys. All study data will be entered via a unique, password-protected REDCap database website. REDCap servers are hosted within the European Union and all web-based information transmission is encrypted.

Ethical considerations

Each investigator will have to evaluate whether the study protocol requires formal approval by the relevant Ethics Committee. This is a low/minimal-risk study. Only deidentified data will be recorded and patient data in the database cannot be linked to patients. No data present in the medical/outpatient record will be removed, altered, or modified. Regarding the protection of privacy, it should be considered that clinicians are bound by professional secrecy. The study does not involve the collection and analysis of genetic data.

Sponsor/Promoter

The Italian Society of Anesthesiology, Analgesia, Resuscitation, and Intensive Care (SIAARTI) is the promoter, data custodian, and responsible for data security and management. Where requested, SIAARTI will provide for the recruitment of participating centers, the data transfer agreements, and the management of the Local Ethics Committee of the involved Centers. The study is spontaneous, and not financed by any external body. There are no external charges or supports for those held by the proponents of the study.

Closing of data collection, Collaboration criteria for publication purposes

The study data manager will evaluate the quality of the data. At the end of the enrollment period, specific questions will be sent to each center by the study data manager, in agreement with the members of the Steering Committee. The principal investigators must have completed the appropriate data collection start and end forms for their center to consider the data collection complete and be included in the final count of participating centers.

The Steering Committee will conduct the synthesis and statistical analysis of the data and produce the draft manuscript.

The authorship group ("SIAARTI Study Group") will be created, which will include all researchers from the participating Centers according to these rules:

• 20 patients recruited: 1 collaborator

• For every 50 patients recruited: 1 author and unlimited collaborators

The final publication of the data, in the form of an article published in a peer-reviewed journal, will consider the participation of all the members of the SIAARTI Study Group whose names will be traceable through scientific databases (PubMed, Scopus).

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