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Masterthesis / Original study

Incidence of chronic postsurgical pain in high risk patients. A prospective observational study and statistical analysis of risk factors

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Abstract

Background and Objectives: **Chronic postsurgical pain (CPSP) is a common complication of surgery with significant consequences. Identifying and addressing risk factors for CPSP can enhance shared decision-making between clinicians and patients. It can significantly improve patient outcomes and overall quality of care. The aim of this study was to evaluate the predictive value of the preoperative modified risk index for CPSP (RICP-4) score along with independent risk factors for CPSP. These independent risk factors include early postoperative pain, sex, age, and type of surgery.**

Design and Setting: **This prospective observational cohort study included 200 adult patients, who underwent either elective total hip arthroplasty or total knee arthroplasty or mastectomy at our hospital group (GZA Hospitals, campus Sint-Augustinus and Sint-Vincentius, Antwerp), from February 2022 until December 2022.**

Methods: **The combination of descriptive analysis and longitudinal analysis of repeated pain measurements using general estimating equations contributes to a more thorough understanding of postoperative pain dynamics. Multivariable statistical models were used to identify potential characteristics associated with (a) postoperative Numeric Rating Scale (NRS) scores and (b) the incidence of CPSP. As a final step, a prediction model for the occurrence of CPSP was developed using receiver operating characteristic analysis.**

Main Outcome Measures: **The primary outcome was the incidence of CPSP. As cut-off, we define a NRS score ≥3 at three months postoperatively as CPSP. As a secondary outcome, we used the results of the 15-item quality of recovery questionnaire within 48 hours and at three months postoperatively. And as a tertiary outcome, we evaluated the RICP-4 and Althaus' scores for each surgical group.**

Results: **The overall incidence of CPSP during movement and at rest was 35.50% and 16,50%, respectively. An increased incidence of CPSP and lower quality of recovery scores at three months were associated with (a) higher NRS scores in the immediate postoperative period (≤48 hours) and with (b) TKA patients who received loco-regional anaesthesia. The modified RICP-4 score demonstrates poor predictive ability and should not be used as a tool for predicting CPSP. Using the median postoperative (≤48 hours) NRS score with a threshold of a NRS score ≥5 provides a correct prediction of CPSP in 61% of cases. Using Althaus' composite Risk Index for CPSP (RICP-5) with a threshold of ≥3, a correct prediction of CPSP could be made in 59.50% of cases.**

Conclusions: **In conclusion, while the RICP-4 score currently in use in our hospital shows more promise for predicting severe acute postoperative pain, its use for predicting CPSP remains limited. Further research and additional studies are needed to improve its predictive capabilities and overall usefulness in clinical settings.**

Trial Registration: **This study is in accordance with the latest version of the Helsinki Declaration and GDPR guidelines, unfortunately the research protocol was not registered at clinicaltrial.gov before the study began.**

Keywords: **Chronic postsurgical pain, anaesthesia.**

The research protocol received approval from the ethics committee of GZA (Dr. H. Debois, Oosterveldlaan 22 Wilrijk, Belgium) on January 11, 2022 (number: 211205ACADEM). Patient inclusion happened between February and December 2022. We obtained written informed consent from the study participants.

Introduction

Nociception is an adaptive response to noxious stimuli, allowing the central nervous system to detect and prevent further injury or damage[1]. Pain, usually coinciding with tissue damage, results from activation or sensitization of nociceptors (peripheral sensory neurons). Some postsurgical pain is to be expected; but when this pain remains ever-present, it loses its usefulness[2]. Persisting pain, beyond the expected postsurgical course, is presumably either the consequence of ongoing inflammation or a form of neuropathic pain[3]. Pain negatively affects recovery and rehabilitation and could consequently lead to a prolonged hospital stay. In some patients, pain persists beyond the expected postsurgical course and becomes chronic[4]. The transition from acute to chronic pain is related to both peripheral and central sensitization.

Chronic postsurgical pain (CPSP) is defined as persisting pain for at least three months after surgery, after exclusion of other causes, and results in a loss of quality of life. This pain may remain localized to the surgical field, but it can also be projected to the innervation territory or a dermatome of nerves situated in this area[5]. Studies show that the risk for CPSP is higher after certain types of surgery (thoracotomy 41%, knee and hip arthroplasty 18-28%, open inguinal hernia repair 30%, mastectomy 43-56%, lower limb amputations 75% and gynaecological procedures 15%)[6]. In 35-57% of patients with CPSP, a neuropathic component is present, which increases pain intensity and shows a loss of quality of life[7]. The degree of tissue damage or nerve injury can nevertheless not be the sole explanation for the development of CPSP[8]. Several other risk factors have been identified: severe acute postoperative pain, pre-existing pain at the site of surgery or elsewhere, age, sex, genetic factors and mental status (e.g. depression, psychological vulnerability, catastrophizing,…)[8,9]. Still, objective assessment is complicated by varying interpretations regarding type and severity of the pain.

Studies suggest mainly three pillars in the prevention of CPSP: identification of at-risk individuals preoperatively, reduction of acute postoperative pain, and avoidance of opioid-induced hyperalgesia[10,11]. Different screening tools for predicting CPSP are developed, but they differ in the number of risk factors included and their complexity in use. For example, the model developed by Montes et al. has the strongest evidence (sensitivity of 58.9% and specificity of 68.4%), but because of the complexity it is less practical to use[12].

At our hospital, a modified screening tool based on Althaus' methodology was implemented[13]. The 4 preoperative factors proposed by Althaus are included in the preoperative electronic questionnaire: (1) preoperative pain in the surgical field and (2) elsewhere, (3) capacity overload, and (4) the presence of two or more co-morbid stress symptoms (i.e. sleeping disorder, exhaustibility/exhaustion, intake of sleeping/sedation pills, frightening thoughts, dizziness, tachycardia, feeling of being misunderstood, and trembling hands). Patients with a preoperative RICP-4 score of three or four, are automatically followed up by our postoperative pain team.

The aim of this study was to evaluate the predictive value of the preoperative modified RICP-4 score along with independent risk factors for CPSP. These independent risk factors include early postoperative pain, sex, age, and type of surgery. Additionally, the study seeks to analyse the quality of recovery and the incidence of CPSP after high-risk surgeries performed at our hospital.

Methods

Study Design, Setting and Participants

We performed a prospective observational cohort study, adhering to the guidelines outlined in the STROBE statement and in accordance with the latest version of the Helsinki Declaration and GDPR guidelines[14]. The research protocol received approval from the ethics committee of GZA Hospitals (Dr. H. Debois, Oosterveldlaan 22 Wilrijk, Belgium) on January 11, 2022 (number: 211205ACADEM). We ensured that all ethical guidelines and standards were met to protect the rights and well-being of the participants. Unfortunately, the research protocol was not registered at clinicaltrial.gov before the study began.

Patients were recruited between February 2022 and December 2022, in both campuses of our hospital group (GZA Hospitals, campus Sint-Augustinus and Sint-Vincentius). Adult patients who underwent elective mastectomy, thoracotomy, open inguinal repair, amputation, total hip arthroplasty (THA), or total knee arthroplasty (TKA), were eligible for inclusion. These procedures are known to have a higher risk of developing CPSP. Unfortunately, during the recruitment period thoracotomy, open inguinal repair and amputation procedures were not performed at the hospital study location. The evaluation of postoperative pain was limited to 48 hours, because of the average hospital stay (patients were on average discharged after two

days). Re-evaluation of postoperative pain was performed after three months.

All patients provided written informed consent prior to participation. Exclusion criteria were patient refusal, cognitive impairment and insufficient knowledge of the Dutch language. For each patient, details of the anaesthesia technique (i.e. multimodal general anaesthesia or loco-regional anaesthesia) were reported. The focus of this local study was to evaluate our current clinical practice. Further subgroup analysis for different comorbidities was not performed, because it was outside the scope of our local study.

Primary, secondary and other outcomes

A. The primary outcome of interest was the incidence of CPSP (Numeric Rating Scale (NRS) score ≥3 at three months postoperatively).13 This outcome was measured by determining the proportion of patients (expressed as both a number and a percentage) who developed chronic pain following specific surgical procedures, namely either THA or TKA or mastectomy. The incidence of CPSP was assessed both, at rest, and during movement.

B. As a secondary outcome, we used the results of the Quality of Recovery questionnaire (QoR-15) within 48 hours and at three months postoperatively.

C. Further outcomes were:
(a) The incidence of preoperative risk factors (number/%) in patients of the three surgical groups. These risk factors included capacity overload, preoperative pain in the operated body part, other chronic preoperative pain, and the presence of two or more stress symptoms.
(b) The four-point preoperative risk index (RICP-4) and Althaus' five point risk index (RICP-5) for each surgical group.
(c) Repetitive NRS scores at successive times within the first 48 hours and at three months postoperatively. Perceived pain in the first 48 hours postoperatively was rated three times daily, i.e. in the morning, at noon, and in the evening. This was assessed both, at rest, and during movement.

Data acquisition

Patients were asked to rate their pain by choosing a number from the scale between zero and ten, in which zero indicates "no pain at all" and ten represents "the worst pain imaginable, and write it down in a pain diary. The study involved a telephonic re-evaluation of patients after three months, assessing their pain levels and quality of recovery. To get a more accurate representation of the perceived pain, patients were asked to make use of the "Provoking, Quality, Radiation, Severity, Timing" (PQRST) principle, to better describe and differentiate their pain.

Addressing potential sources of bias

1. Selection bias was addressed by random inclusion of participants from the population undergoing the specific type of surgery to ensure a representative sample.

2. Confounding bias. For a variable to be a confounder, it should meet three conditions: (a) be associated with the exposure being investigated; (b) be associated with the outcome being investigated; and (c) not be a step in the process that leads from the exposure to the outcome. Confounding was addressed by (a) the collection of detailed information on potential confounders such as demographics; and (b) by the use of multivariable regression analysis to adjust for confounders.

3. Observer bias was addressed by (a) the use of a centralized team of outcome assessors who were not involved in the recruitment or baseline assessment of the participants and (b) blinded data-analysis, i.e. conducting the statistical analysis of the collected data without knowledge of the participants.

4. Bias due to loss to follow-up was addressed by the use of statistical techniques such as general estimating equations (GEE) and multiple imputation.

Sample size calculation

We calculated the sample size needed to demonstrate a clinical meaningful difference in CPSP prevalence among postoperative patients having either (1) a higher preoperative RICP score, or (2) a higher early postoperative NRS score. As we have no background info, we assume that there is a small effect size, e.g. Cohen h=0.20. The R code for calculation of the sample size, assuming a significance level = 0.05 and power = 80%:
n<-pwr.p.test(h=0.2, sig.level=0.05, power=0.80, alternative="two.sided").

The number of patients required for our observational cohort study (n) is 196.

Explorative data analysis

A descriptive analysis of the quantitative data was carried out. Normality of data was tested using the Kolmogorov-Smirnov, Shapiro-Wilk, or the Q-Q plot. Common descriptive statistics, including the mean, median, standard deviation, range, and interquartile range (IQR) were used to summarize the data. CPSP and NRS scores are measured on an ordinal scale and analysed using nonparametric

statistics. For qualitative data, we used frequencies (percentages). A significance level of 5% was assumed. Statistical analysis was performed using Stata 16.1 and R version 4.0.5.

Analysis of longitudinal NRS data

Based on their advantages over RM-ANOVA, GEE were considered for the analysis of longitudinal NRS data[15]. GEE is an extension of Generalized Linear Models (GLM). The advantages of GEE are (a) its greater flexibility in handling different types of outcomes (e.g. non-continuous ordinal data), (b) its ability to model a wide variety of correlation patterns between repeated measures, and (c) the possibility of handling missing data, mainly under the assumption of completely random missing data.

In the GEE analysis we also included covariates that might influence pain perception, such as (a) the type of surgery, (b) demographic variables such as age and sex, (c) the activity status of the patient at the time of the pain score (at rest, or while moving), (d) on which part of the day (morning, afternoon, evening), and (e) on which postoperative day (first or second day) the assessments were done. Including covariates in a GEE analysis helps to control for confounding variables and allows for a more accurate estimation of the relationship between the primary predictors and the outcome.

Multivariate analyses

Multivariable statistical models were used for identifying potential characteristics associated with (a) postoperative NRS scores and (b) the incidence of CPSP. Linear regression was applied to explore the association between a dependent continuous (QoR-15 within 48 hours or at three months postoperatively) or ordinal (i.e. postoperative NRS values) variable and one or more co-variables. Logistic regression was applied to estimate the probability of a CPSP occurring (yes/no or 1/0), based on a set of independent co-variables. Possible co-variables for inclusion were based on existing knowledge and clinical judgment. Following co-variables were explored for their association with the dependent variable: sex, age, preoperative RICP, type of surgery, anaesthesia technique, and postoperative pain intensity. Backward elimination was performed to remove co-variables one at a time as they were no longer significant ($p<0.05$) in the multivariate model.

Development of a prediction model for CPSP

In the first step, we explored the association between the incidence of CPSP and our institutional RICP (RICP-4). In the second step, we examined the relationship of CPSP with the early postsurgical pain. In the third step we tested the performance of the Althaus' RICP-5 for the prediction of CPSP in our population[13].

Receiver-Operating Characteristic (ROC) analysis for evaluating diagnostic tests and predictive models

A prediction model was developed for the occurrence of CPSP using ROC analysis. The aim was to find a screening test (a binary classifier) that indicates whether the patient is likely to be non-diseased (not suffering from CPSP) or diseased (suffering from CPSP).

The criterion value refers to the standard that is set to classify patients into the non-diseased (not having CPSP or NRS<3 at three months) or diseased (having CPSP or NRS ≥3 at three months) categories. The classification variables (RICP-4, NRS, or Althaus' RICP-5) are used in the model to make predictions. The binary classifier categorizes the outcome of the classification variables as "positive" (high probability that CPSP is present) or "negative" (low probability that CPSP is present).

The fundamental measures of diagnostic accuracy are sensitivity (i.e., true positive rate) and specificity (i.e., true negative rate), with the area under the curve (ROC AUC) as a measure of test performance[16].

In our ROC analysis, NRS ≥ 3 at three months postoperatively (yes/no or 1/0) is the criterion value. Either (1) the preoperative RICP-4, (2) the median NRS value within the first 48 hours, or (3) the Althaus' RICP-5 are the classification variables.

Results

Cohort analysed in this study

Between 01/02/2022 and 31/12/2022, 236 patients were eligible for inclusion. We obtained data sets from 200 eligible participants who underwent either THA [n=98], TKA [n=75], or mastectomy [n=27]. In total, 36 patients were lost due to follow-up. Pre-intervention demographics and quantifiable characteristics are represented in Table I. The average age of patients included was 65.1 (63.5-66.7) years. Exploratory data analysis showed that more women than men were included in the current survey (129 females versus 71 males).

Primary and secondary outcomes

The overall incidence of CPSP [NRS ≥3 at three months postoperatively] (1) during movement; and (2) at rest was 71/200 (35.50%); and 33/200 (16,50%), respectively. More specifically, the incidence of CPSP after THA, TKA and

Table I. — Exploratory data analysis.

Item	THA	TKA	Mastectomy	Total
Number (n)	98 (48.51%)	75 (37.13%)	27 (13.37%)	200
Age (yr) (mean [95CI])	64.95 [63.94-68.91]	65.35 [63.85-67.90]	57.26 [51.83-62.69]	65.09 [63.46-66.73]
Sex (F/M)	59/39	44/31	26/1	129/71
Preoperative pain (n(%))	90 [91.84]	69 [92.00]	7 [25.93]	166 [83.00]
Preoperative pain elsewhere in the body (n(%))	37 [37.76]	35 [46.67]	9 [33.33]	81 [40.50]
Capacity overload (n(%))	25 [25.51]	22 [29.33]	7 [25.93]	54 [27.00]
Stress symptoms (n(%))	18 [18.37]	18 [24.00]	8 [29.63]	44 [22.00]
Institutional pre-operative RICP-4 score (median [iqr])	2 [1-2]	2 [1-3]	1 [0-2]	2 [1-2]
Althaus' 5 item RICP score (RICP-5) (median [iqr])	2 [2-3]	3 [2-4]	1 [0-2]	2 [2-3]
QOR-15 PO score (mean [95CI])	114.61 [111.71-117.51]	109.19 [104.71-113.29]	110.78 [103.76-117.79]	111.72 [109.34-114.09]
QOR-15 3M score (mean [95CI])	135.59 [132.38-138.80]	130.93 [126.72-135.15]	143.11 [138.97-147.25]	134.77 [132.44-137.11]
NRS in the morning of the 2nd PO day in motion (median [iqr])	4 [3-6]	6 [5-8]	4 [2-6]	5 [3-7]
NRS at noon of the 2nd PO day in motion (median [iqr])	4 [3-6]	6 [5-8]	3 [2-5]	5 [3-6]
NRS in the evening of the 2nd PO day in motion (median [iqr])	4 [2-5]	5 [4-7]	4 [2-5]	5 [3-6]
NRS in the morning of the 2nd PO day at rest (median [iqr])	3 [2-4]	4 [3-6]	2 [1-4]	3 [2-5]
NRS at noon of the 2nd PO day at rest (median [iqr])	2 [1-4]	4 [3-6]	2 [0-4]	5 [2-4]
NRS in the evening of the 2nd PO day at rest (median [iqr])	2 [1-3]	4 [2-5]	2 [0-4]	3 [1-4]
Median NRS during the first 48h after surgery	3 [2,5]	5 [4,6]	3 [1,5]	4 [2,5]
NRS 3M during movement (median [iqr])	1 [0-3]	2 [0-5]	0 [0-3]	0 [0-4]
NRS 3M at rest (mean (median [iqr])	0 [0-2]	0 [0-2]	0 [0-0]	0 [0-2]
NRS 3M ≥ 3 during movement (n(%))	29 (29.59)	32 (42.67)	9 (33.33)	71 (35.50)
NRS 3M ≥ 3 at rest (n(%))	14 (14.29)	15 (20.00)	4 (14.81)	33 (16.50)

Values are numbers or (n); mean (standard deviation) [95% confidence interval] or (mean (sd)[95CI]); median [25-75% interquartile range]) or (median [iqr]). F/M: Female/Male ratio; THA: total hip arthroplasty; TKA: total knee arthroplasty; NRS: numeric rating scale value; RICP-4 score: 4-item pre-operative risk index for chronic post-surgical pain; RICP-5: 5-item pre- and postoperative risk index for chronic post-surgical pain; QoR-15 PO: postoperative 15 item-Quality of Recovery score; QoR-15 3M: 15 item-Quality of Recovery score after 3 months of surgery.

mastectomy was 29/89 (29.59%), 32/75 (42.67%), and 9/27 (33.33%), respectively, during movement; and 14/89 (14.29%), 15/75 (20.00%), and 4/27 (14.81%), respectively, at rest.

The QOR-15 scores for the whole population, immediately after the operation, and at the months were: 111.72 [109.34,114.09], and 134.77 [132.44,137.11], respectively. The QoR-15 scores for THA, TKA, and mastectomy immediately after the operation were 114.61 [111.71,117.51], 109.61 [104.71,113.29], and 110.78 [103.76,117.79], respectively; and at three months were: 135.59 [132.83,138.80], 130.93 [126.72,135.15], and 143.11 [138.97,147.25], respectively.

Further outcomes

Outcomes for the institutional RICP-4, Althaus' RICP-5, and the postoperative NRS values are represented in Table I.

Evolution of NRS scores in the first 48 hours postoperatively

Analysis of consecutive NRS data using GEE shows that perceived pain (a) depended on the

type of surgical procedure, specifically TKA (p<0.0001), and (b) was higher during the first postoperative day (p<0.0001), and (c) exacerbated with movement (p<0.0001). Additionally, higher preoperative RICP-4 scores and female sex are significant predictors of increased pain levels in the early postoperative period [Table II].

Multivariate analyses

An increased incidence of CPSP (yes/no or 1/0) was associated with (a) higher NRS scores within the first 48 hours postoperatively (p=0.021), (b) with movement (p<0.001), and (c) post-TKA for those who received loco-regional anaesthesia (p=0.016) [Table III].

We could demonstrate that lower post-operative QOR-15 scores could be observed post-TKA (p=0.014). Additionally, higher preoperative RICP-4 scores (p<0.0001) and female sex (p=0.006) were significant predictors of lower QoR-15 scores postoperatively [Table IV].

QoR-15 scores at three months postoperatively were lower with (a) higher average NRS scores in the immediate (≤48 hours) post-operative period (p=0.049) and (b) post-TKA for those who received loco-regional anaesthesia (p=0.001) [Table V].

Prediction of CPSP using ROC analysis

(1) When using the preoperative RICP-4 to predict the likelihood of CPSP (NRS after 3 months in motion ≥3: yes/no), the ROC analysis yielded an AUC=0.53 (0.04) [0.45-0.62], which was not different from random chance (AUC=0.5). An AUC of 0.5 indicates no discriminative ability.

Table II. — Analysis of the consecutive Numeric Rating Scale (NRS) scores, obtained during the immediate post-operative episode (≤48h) using Generalized Estimating Equations (GEE).

Co-variable / Predictor	Coefficient mean [95% CI]	z	p
Activity status: moving (yes/no or 1/0)	1.46 [1.35,1.58]	25.83	<0.0001*
Activity status: at rest (yes/no or 1/0)	-0.15 [-0.26,-0.04]	-2.61	0.009 *
Post TKA	1.52 [1.04,1.99]	6.26	<0.0001*
First postoperative day	0.32 [0.23,0.41]	6.94	<0.0001*
Female (yes/no or 1/0)	1.00 [0.53,1.48]	4.13	<0.0001*
RICP-4	0.42 [0.20,0.63]	3.82	<0.0001*
Constant term	1.33 [0.79, 1.87]	4.81	<0.0001*

Post-TKA: status after total knee arthroplasty; RICP-4: 4-item risk index for assessing the risk of chronic postoperative pain. p values assess the statistical significance of each predictor. P values assess the statistical significance of each predictor. *: statistically significant.

Table III. — Multivariable logistic regression model to explore candidate predictors for their association with the incidence of chronic post-surgical pain (CPSP) (yes/no or 1/0).

Co-variable / Predictor for CPSP incidence	Odds Ratio: mean [95%CI]	z	p
Activity status: moving (yes/no or 1/0)	0.99 [0.44,2.23]	4.25	<0.0001*
Average NRS during first 48h postoperatively	1.16 [1.02,1,32]	2.31	0.021*
Post TKA (yes/no or 1/0)	0.50 [0.15,1.62]	-1.16	0.246
Post TKA*LRA	3.84 [1.28,11.55]	2.40	0.016*
Constant term	1.89 [0.12, 0.31]	-6.67	<0.0001*

Odds ratios (ORs) are used to quantify the relationship between predictors (independent variables) and the binary outcome (dependent variable, CPSP). "Post-TKA": status after total knee arthroplasty; "LRA": loco-regional anaesthesia; "Post TKA*LRA": cross term representing TKA patients that received loco-regional anaesthesia; p values assess the statistical significance of each predictor. *: statistically significant.

Table IV. — Multivariable linear regression to explore candidate predictors for their association with the postoperative 15-item Quality of Recovery score.

Co-variable / Predictor for PO QoR-15	Coefficient mean [95%CI]	z	p
Post TKA (yes/no or 1/0)	-4.23 [-7.60, -0.87]	-2.47	0.014*
Female (yes/no or 1/0)	-4.72 [-8.10, -1.35]	-2.75	0.006*
RICP-4	-3.05 [-4.57, -1.54]	-3.96	<0.0001*
Constant term	121.91 [118.11,125.71]	3.10	<0.0001*

"Post-TKA": status after total knee arthroplasty; RICP-4: 4-item preoperative risk index for assessing the risk of chronic postoperative pain; p values assess the statistical significance of each predictor. *: statistically significant.

Table V. — Multivariable linear regression to explore candidate predictors for their association with the 15-item Quality of Recovery score at 3 months postoperatively.

Co-variable / Predictor for QoR-15 3M	Odds Ratio: mean [95%CI]	z	p
Average NRS during first 48h postoperatively	-0.77 [-1.53, -0.01]	-1.97	0.049*
Post TKA (yes/no or 1/0)	-1.01 [-6.17, 4.15]	-0.39	0.70
Post TKA*LRA	-6.82 [-10.74, -2.90]	-3.42	0.001*
Constant term	139 [136.25, 142.56]	6.90	<0.0001*
"Post-TKA": status after total knee arthroplasty; "LRA": loco-regional anaesthesia; "Post TKA*LRA": cross term representing TKA patients that received loco-regional anaesthesia; p values assess the statistical significance of each predictor. *: statistically significant.			

Table VI. — ROC analysis of the diagnostic tests with NRS ≥ 3 during movement at 3M postoperatively (yes/no or 1/0) as criterion.

Classification variable	Cut-off	Accuracy (%)	Sensitivity (%)	Specificity (%)	ROC AUC
1. Preoperative screening for risk of CPSP Preoperative GZA 4 points CPSP risk index	Risk index ≥2	54.29	47.89	60.31	0.53 (0.04) [0.45-0.62]
2. Efficiency of postoperative analgesia Average NRS during the first 48h after surgery	Average NRS ≥5	60.50	50.00	66.15	0.60 (0.04) [0.52-0.68]
3. Postoperative screening for risk of CPSP Althaus' composite 5 points CPSP risk index	Risk index ≥3	59.30	51.52	59.17	0.56 (0.04) [0.51-0.62]
Cut-off: binary classifier; Accuracy: correctly classified (%); Sensitivity: true positive for CPSP (%); Specificity: true negative for CPSP (%); ROC AUC represents the area under the ROC curve. It has a value between 0 and 1 and measures the overall performance of the binary classification model. A greater value of AUC denotes better model performance. A perfect model would have an AUC of 1, while a random model would have an AUC of 0.5.					

Therefore, the RICP index cannot be a reliable predictor of CPSP [Table V].

(2) Using the median value of the NRS scores within the first 48 hours postoperatively with NRS ≥5 as a binary classifier, we were able to correctly classify 61% of patients regarding their risk for CPSP (AUC=0.60 (0.04) [0.51-0.68]) [Figure 1]. This means that patients with a median NRS ≥5 in the first 48 hours postoperatively are classified as being at higher risk of developing CPSP [Table VI].

(3) We also developed a composite RICP index by combining preoperative risk assessment (RICP-4) with the occurrence of significant pain (NRS ≥5) within the first 48 hours after the operation [Table 5]. This concept was inspired by Althaus' methodology.13 We calculated an Althaus' RICP-5 ≥3 as a binary classifier; this cut-off allowed us to

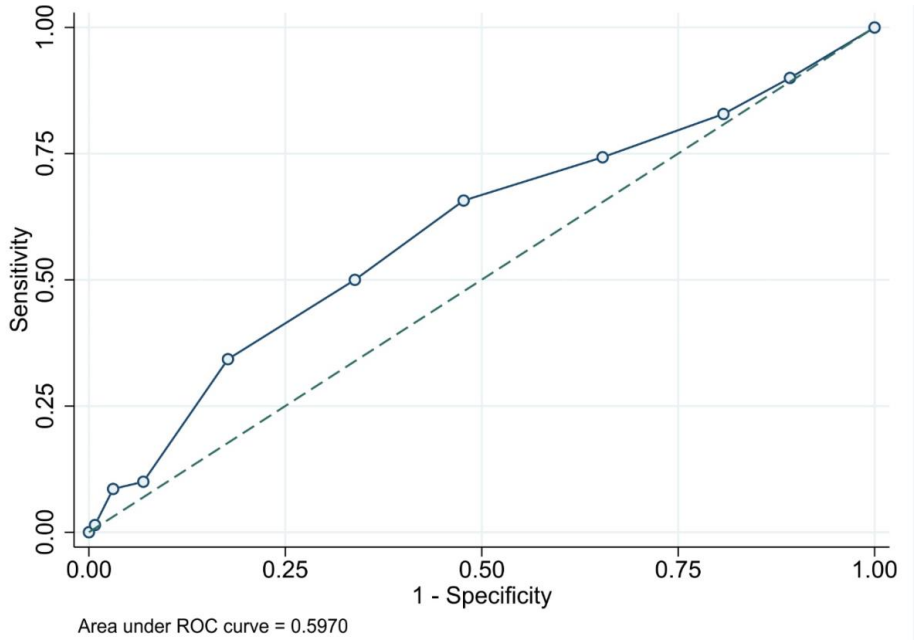

Fig. 3 — The area under the Receiver Operating Characteristic (ROC) curve of a CPSP model using NRS ≥3 at three months as a criterion value and average NRS during the first 48h after surgery as a classification value.

correctly classify 59.50% of patients with respect to their risk of CPSP. (0.56 (0.04) [0.50-0.62].

Discussion

In current prospective cohort study, the overall incidence of CPSP during exercise and at rest was 35.50% and 16.50%, respectively, which is consistent with previously published results. The incidence of CPSP is associated with the average pain score in the immediate postoperative period (≤48 hours), and as far as TKA is concerned, with the type of anaesthesia. Moreover, these patients suffering from CPSP often have lower QoR-15 scores at three months postoperatively, indicating poorer long-term recovery. Acute pain in the immediate postoperative period (≤48h) is more common in patients with (a) high RICP-4 score, (b) in those who underwent TKA, or (c) in females. Additionally, these patients tend to have lower QoR-15 scores, indicating poorer short-term recovery outcomes. The results of this prospective study indicate that the modified screening tool demonstrates only moderate predictive value (59%) for chronic post-surgical pain, but was significantly associated with acute postoperative pain. In contrast, Althaus' based RICP-5 score showed moderate accuracy (59%) for predicting CPSP in our population.

For current prospective cohort study we included patients scheduled for THA, TKA and mastectomy. TKA and THA are major orthopaedic procedures with a focus on restoring mobility and function through significant surgical intervention and rehabilitation. Mastectomy, on the other hand, is major both in terms of the physical and psychological impacts, especially related to cancer treatment and prevention.

Preoperative risk index for CPSP

Our institutional RICP-4 is based on capacity overload, preoperative pain in the operated body part, other chronic preoperative pain, and the presence of two or more stress symptoms. However, using this measure, we could not reliably predict CPSP in our patients. Using the median value of the NRS scores within the first 48 hours postoperatively with NRS ≥5 as a binary classifier, a correct prediction of CPSP could be made in 61.5% of cases. Using the modified Althaus' composite risk index with RICP-5 ≥3 as a binary classifier, a correct classification could be achieved in 59% of patients [Table 6]. Althaus' original evaluation found a sensitivity of 60% and an accuracy of 68% at 6 months postoperatively. In the current investigation, moderate-to-severe pain (NRS ≥3/10) at three months postoperatively is considered as CPSP[13].

Prediction of CPSP guided by perceived pain and Quality of Recovery

The median NRS score within the first 48 hours postoperatively as the only predictor highlights the strong predictive value of moderate to severe acute postoperative pain. This should alert us to the importance of aggressive analgesic treatment to prevent the transition from acute to chronic postoperative pain.

Local anaesthetic infiltration (LIA) to the surgical site is a simple and widely used analgesic technique and is recommended for perioperative analgesia in TKA by the PROSPECT guidelines[17]. Due to institutional policy, no preoperative adductor canal block was performed.

However, pain scores on the first postoperative day were low but within 24 hours pain scores increased as the effect of the local anaesthetic wears off, despite prescription of multimodal analgetics. This indicates that we, as anaesthesiologists, should look beyond our usual scope of the operation and recovery room. Maybe we should extend our acute pain service to a more 'transitional pain service' to include follow-up of high-risk patients on the surgical ward.

The correlation of RICP-4 with clinically significant pain in the first two days postoperatively could indicate its potential utility in preventing chronic postoperative pain (CPSP). In practical terms, a score of three or higher means that closer postoperative follow-up is required. This RICP-4 is analogous to e.g. the Kalkman score published in 2003, as a predictor for immediate postoperative surgical pain (in the first postoperative hour)[18].This preoperative score is a 10-point scale and also includes type and duration of surgery, sex, age, obesity, and use of antidepressants besides the factors included in the RICP[19].

CPSP after TKA

We compared two groups of TKA patients subjected to different anaesthesia techniques. Patients included in these groups were similar regarding demographic characteristics and other measurable parameters. However, after TKA, the incidence and severity of CPSP depended on the anaesthesia technique and was significantly higher in the loco-regional anaesthesia (LRA) + LIA group compared to the general anaesthesia (GA) + LIA group, both during exercise and at rest.

These results may seem surprising, since loco-regional anaesthesia pre-emptively impairs nociceptive input during surgery. Our observations,

however, are in agreement with previous studies that found no significant evidence supporting the impact of perioperative loco-regional anaesthesia on the incidence and severity of CPSP after total TKA[20,21]. Furthermore, there was no significant difference between the two anaesthesia methods in terms of perceived pain within the first 48 hours after TKA.

Furthermore, these results question the association between acute pain and CPSP and the long-term benefits of early pain control in a procedure where severe preoperative pain is generally present. Currently, the optimal treatment for acute pain after TKA is still under debate, particularly peripheral nerve blocks, which may interfere with early mobilization in protocols for enhanced recovery. Patients scheduled for TKA suffer from preoperative pain at the knee and/or elsewhere in the body[22]. Prolonged preoperative pain and analgesic intake sensitize the central nervous system, which make postoperative analgesic management more challenging. In addition, the postoperative analgesia provided by LRA + LIA might have contributed to the perception that multimodal pain management might not be necessary in the first hours after surgery[23]. Examining the impact of pre-emptive interruption of pain transmission after a period of preoperative nociceptive stimulation, is beyond the scope of this study. Nonetheless, further investigation seems necessary.

Limitations and future projections

The primary aim of the current study was twofold: first, to assess the incidence of CPSP among patients in our hospital group, and second, to develop a predictive screening tool that can be easily utilized by anaesthesiologists during preoperative visits. Although using NRS scores ≥3 at three months postoperatively as a cut-off value has its limitations, the current study can still provide valuable insights into the incidence of CPSP. The neuropathic pain component has been shown to be associated with development of severe CPSP and higher functional impairment. We agree that including assessments such as the Brief Pain Inventory (BPI) short form, evaluating for neuropathic pain components, would have provided a more holistic understanding of the impact of chronic pain. Future studies should include these approaches to provide a more complete understanding of the risk factors for chronic pain.

To improve the accuracy of predicting CPSP, it is essential to extend postoperative pain assessments beyond the initial 48 hours and include follow-ups at later stages, such as two weeks postoperatively[24]. The lack of pain follow up at two weeks may explain the weakness of a screening tool only based on preoperative factors.

Differences between men and women have been identified in pain perception, response to pain and pain management. It is not unreasonable to suppose that women undergoing mastectomy surgery may have different pain outcomes than men.

Widespread evidence supports the role of early postoperative pain in the development of CPSP. The PAIN-OUT study shows that the number of hours spent in severe acute postoperative pain is a stronger risk factor for CPSP than the single worst pain score itself[25]. Control of the pain trajectory of an at-risk patient implies optimal multimodal analgesia, prevention of rebound pain after loco-regional anaesthesia and bedside visits or phone evaluation after discharge for several consecutive postoperative days, with attention for specific needs of the individual patient.

The use of predictive scores for CPSP aims to identify patients at risk and implement preventative measures. Despite their potential, the clinical impact and predictive accuracy of these scores remain controversial. Future research in this domain should focus on two key objectives: (a) validation of clinical impact, and (b) large-scale, high-quality research to demonstrate the reliability and clinical benefit of chronic postoperative pain prediction and intervention[26].

Conclusion

The modified preoperative RICP-4 score, which we currently use in our hospital, seems to be more effective in predicting acute postoperative pain than CPSP. However, due to the nature and design of this study, along with certain limitations, we were unable to explore the contribution of additional co-variables. Consequently, additional studies are necessary to further investigate these findings and validate the predictive accuracy of the score.

References

1. Julius D, Basbaum AI. Molecular mechanisms of nociception. Nature. 2001;413:203-10.
2. Chen YYK, Boden KA, Schreiber KL. The role of regional anaesthesia and multimodal analgesia in the prevention of chronic postoperative pain: a narrative review. Anaesthesia. 2021;76(S1):8-17.
3. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. The Lancet. 2006; 367(9522):1618-25.
4. Kinloch Cromble I, Oackley Davis HT, Macrae WA. Cut and Thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. Pain. 1998;76(1-2):167-71.
5. International Classification of Diseases 11th Revision. The global standard for diagnostic health information.

6. Lopes A, Seligman Menezes M, Antonio Moreira de Barros G. Chronic postoperative pain: ubiquitous and scarcely appraised: narrative review. Brazilian Journal of anesthesiology. 2021;71(6): 649-655.
7. Richebé P, Capdevila X, Rivat C. Persistent Postsurgical Pain: Pathophysiology and Preventative Pharmacologic Considerations. Anesthesiology. 2018;129(3):590-607.
8. Rosenberger DC, Pogatzki-Zahn EM. Chronic post-surgical pain - update on incidence, risk factors and preventive treatment options. BJA Education. 2022;22(5):190-196.
9. Ashraf S Habib AS, Kertai MD, Cooter M, Greenup RA, Hwang S. Risk factors for severe acute pain and persistent pain after surgery for breast cancer: a prospective observational study. Regional Anesthesia and Pain Medicine. 2019;44(2):192-199.
10. Althaus A, Arranz Becker O, Neugebauer E. Distinguishing between pain intensity and pain resolution: using acute post-surgical pain trajectories to predict chronic post-surgical pain. Eur J Pain. 2014;18:513–21.
11. Fletcher D, Stamer UM, Pogatzki-Zahn E, Zaslansky R et al. Chronic postsurgical pain in Europe: An observational study. Eur J Anaesthesiol. 2015;32(10):725-34.
12. Montes A, Roca G, Cantillo J, Sabate S; GENDOLCAT Study Group. Presurgical risk model for chronic postsurgical pain based on 6 clinical predictors: a prospective external validation. Pain. 2020;161(11):2611-2618.
13. Althaus A, Hinrichs-Rocker A, Chapman R et al. Development of a risk index for the prediction of chronic post-surgical pain. Eur J Pain. 2012;16:901–10.
14. Vandenbroucke JP, von Elm E, Altman DG et al. STROBE initiative. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med. 2007;147(8):163-94.
15. Ma Y, Mazumdar M, Memtsoudis SG. Beyond repeated-measures analysis of variance: advanced statistical methods for the analysis of longitudinal data in anesthesia research. Reg Anesth Pain Med. 2012;37(1):99-105.
16. Zou KH, O'Malley AJ, Mauri L. Receiver-operating characteristic analysis for evaluating diagnostic tests and predictive models. Circulation. 2007;115(5):654-7.
17. S. Pissens, L. Cavens, G. P. Joshi, M.P. Bonnet, A. Sauter, J. Raeder, M. Van de Velde, on behalf of the PROSPECT Working Group of the European Society of Regional Anaesthesia and Pain Therapy (ESRA). Pain management after hip fracture repair surgery: a systematic review and procedure-specific postoperative pain management (PROSPECT) recommendations. Acta Anaesth Bel. 2024;75:15–31.
18. Kalkman CJ, Visser K, Moen J, Bonsel GJ, Grobbee DE, Moons KG. Preoperative prediction of severe postoperative pain. Pain. 2003;105(3):415-23.
19. Geradon P, Lavand'homme P. Use of regional analgesia to prevent the conversion from acute to chronic pain. Curr Opin Anaesthesiol. 2022;35(5):641-646.
20. Bugada D, Allegri M, Gemma M et al. Effects of anaesthesia and analgesia on long-term outcome after total knee replacement: A prospective, observational, multicentre study. Eur J Anaesthesiol. 2017;34(10):665-672.
21. Wylde V, Beswick A, Bruce J, Blom A, Howells N, Gooberman-Hill R. Chronic pain after total knee arthroplasty. EFORT Open Rev. 2018;3(8):461-470.
22. Shin SK, Lee DK, Shin DW, Yum TH, Kim JH. Local Infiltration Analgesia Versus Femoral Nerve Block for Pain Control in Anterior Cruciate Ligament Reconstruction: A Systematic Review With Meta-analysis. Orthop J Sports Med. 2021;9(11).
23. van Driel MEC, van Dijk JFM, Baart SJ, Meissner W, Huygen FJPM, Rijsdijk M. Development and validation of a multivariable prediction model for early prediction of chronic postsurgical pain in adults: a prospective cohort study. Br J Anaesth. 2022;129(3):407-415.
24. R. Zaslansky et al. PAIN OUT: an international acute pain registry supporting clinicians in decision making and in quality improvement activities. J Eval Clin Pract. 2014;20(6).
25. Fletcher D, Lavand'homme P. Towards better predictive models of chronic post-surgical pain: fitting to the dynamic nature of the pain itself. Br J Anaesth. 2022;129(3):281-284.

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