Finding the vulnerable postoperative population: A two-step cluster analysis of the PAIN-OUT registry

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Abstract

Background: Identifying predictors of poor postoperative outcomes is crucial for planning personalized pain treatments. The aim of this study was to examine pain outcomes using cluster analysis in N=2,678 patients from the PAIN-OUT registry at first postoperative day.
Methods: Indicator variables of the clustering analysis assessed multiple domains, such as clinical and surgical conditions, analgesic-anesthetic variables, desire for more pain treatment and outcome variables of the International Pain Outcome Questionnaire (IPO) summarized as factor scores.
Results: Two-step cluster identified the three-cluster solution as the optimal. Two empirical groups (C1 and C2) included patients with good postoperative outcomes based on peripheral nerve block use, while the other cluster (C3) grouped patients with the worst outcomes, where all patients desired more pain treatment. C3 comprised about 20% of the participants, mostly lower limb, abdominal and spine procedures. The best predictors of belonging to C3 included younger age, being male, preoperative opioid use, bone and fracture reduction procedures, number of comorbidities and use of morphine equivalents in the recovery room.
Conclusions: IPO factor scores can be used to select pain outcomes phenotypes in large clinical databases. Most of the predictors were presented before the recovery period so perioperative planning should focus in the preoperative and intraoperative periods.

Trial registration

Data analyzed in this study was registered in the PAIN OUT project (NCT02083835 at ClinicalTrials.gov)

Keywords

Postoperative pain outcomes, PAIN-OUT registry, IPO factor scores, preoperative opioids

Significance

Improvement in postoperative pain requires assessment methods that goes beyond pain intensity scores. We present a novel analytical approach of postoperative patients using the factor scores of the International Pain Outcome Questionnaire, a composite measure of postoperative pain outcomes and explore the phenotypes of vulnerable patients of the PAIN-OUT registry using cluster analysis. Procedures that require urgent quality improvements and risk factors are identified.

Introduction

Composite measures of patient reported outcomes (PROMs), that better capture the broad picture of benefits and harms of postoperative pain and its treatments, are recommended in the new surgery's paradigms such enhanced recovery pathways. (Chou et al., 2016; Kehlet, 2018) There is a low correlation between different pain outcomes. Van Boekel demonstrated that patients reported good pain acceptability and satisfaction with pain treatment despite having high postoperative pain intensity.(Van Boekel et al., 2017) Additionally, unidimensional outcomes like cutoff pain intensity scores (NRS < 4), have favored the opioids overuse with its associated adverse effects and may not accurately estimate pain interference with function.(Stamer et al., 2020)

The International Pain Outcome Questionnaire (IPO) is a validated postoperative PROM that covers three main factors: Pain intensity and interference (F1), Adverse effects (F2) and Perception of care (F3), plus items on non-pharmacological treatments, chronic pain before surgery and desire of more pain treatment.(Polanco-García et al., 2021a; Rothaug et al., 2013) As a global outcome analysis tool, patients with low scores in F1 and F2; and high scores in F3 will have optimal quality of care, while patients with high scores in F1 and F2 and low scores in F3 will have the worst postoperative outcomes. Characterizing this vulnerable population and finding predictors of poor postoperative outcomes beyond worst pain intensity seem essential for personalized treatment approaches and quality improvement programs.

Hypothesis-free statistical segmentation methods and machine learning algorithms, such as clustering analysis, have been widely used as exploratory data analysis to divide large amounts of data into natural subsets or clusters, where subjects in a cluster are similar to one another, yet different to subjects in another cluster.(Han et al., 2012) The PAIN-OUT Registry offers the possibility of analyzing huge amounts of information from postoperative patients from different parts of the world collected in a homogenized way. A two-stage cluster analysis of PAIN-OUT patients is performed to explore intrinsic phenotypes of vulnerable/protected patients (phenotypic characterization) with different pain outcome profile, using the IPO factors scores.

This study aims (1) to explore the existence of empirical clusters with distinct pain outcome profiles in a large sample of postoperative patients from Spanish hospitals who underwent different types of procedures; (2) to perform comparison between the emerging cluster to identify different variables related to each pain outcome profile.

Methods

Participants

This work examined a subsample from the PAIN OUT project, a multinational observational cohort study (NCT02083835 at ClinicalTrials.gov) aimed to improve the postoperative outcomes by analyzing the process of care and hospital structure. The subsample contained data from 13 hospitals across seven regions of Spain collected for four years. The sampling procedure, including the recruitment plan, is extensively described elsewhere.(Polanco-García et al., 2017) After approval by the local ethics committee at each hospital, surgical patients older than 17 years old who were in the first postoperative day and in the ward for at least 6 hours and gave their consent to participate were included in the study. Exclusion criteria included: refused to participate, were not in the ward, were asleep or sedated, had visual or hearing impairment, were not fluent in Spanish language or were cognitive impaired. Patient with one or more missing data in any of the indicator variables were excluded from the analysis. Cases where anatomic location of the procedure was not specified (four cases) or surgeries with a small number of collected cases (ophthalmology (one case) and ear nose and throat (ENT) procedures (three cases)) were also excluded from the analysis.

Instruments

The PAIN-OUT project collected data from a structure, a process of care and an outcome questionnaire, following the Donabedian principles of quality improvement. The Structure questionnaire, filled out by the principal investigator of each hospital, gathered information about the size and type of hospital as well as the availability of postoperative pain management protocols and an acute pain service. The process of care questionnaire collected demographic information, type and characteristics of the procedure and detailed perioperative pharmacologic and non-pharmacologic information. Finally, the International Pain Outcome Questionnaire (IPO) is a multi-language validated questionnaire that uses mostly a 0 to 10 numerical rating scale, except for some dichotomous (yes/no) questions such as: Would you have liked more pain treatment than you received? The 18 continuous variables of the IPO have a three factors structure(Polanco-García et al., 2021a; Rothaug et al., 2013): a) Pain intensity and interference (F1) that included: worst pain, least pain, how often in severe pain, interference with in-bed activities, interference with breathing and coughing, interference with sleep, interference with out of bed activities, feeling anxious and feeling helpless; b) Adverse effects (F2) that included: nausea, drowsiness, itching and dizziness; and c) Perception of care (F3) that included: pain relief, allowed to participate in treatment decisions and satisfaction with pain treatment. Detailed questionnaires and information about the PAIN-OUT project are available online (http://pain-out.med.uni-jena.de/downloads, retrieved 3 Dec 2021).

Definition of surgical groups

Surgical procedures were categorized using the 4-digit ICD-9-CM hierarchical codification. The first two digits label the organ and anatomical system while the last two digits label specific procedures. From the first two digits of this categorization, we classified surgical procedures by body system and location as: gastrointestinal, hepatobiliary, abdominal wall, non-abdominal general surgery, urologic, gynecological, and obstetrical, cardiothoracic, bone, joint, back and nervous system, fracture, tendon and muscle, and skin.

Analgesic therapies

The preoperative, intraoperative, and postoperative analgesic techniques used in each procedure were obtained from the process of care questionnaire, which collected both non-pharmacologic and pharmacologic therapies, doses, and administration routes. Paracetamol and metamizole were grouped as antipyretics. We converted the analgesic opioid doses administered to oral morphine equivalents using published equianalgesic tables.(Pereira et al., 2001) Oral opioids were converted directly to oral morphine while i.v. opioids were first converted to i.v. morphine and then to oral morphine multiplying by a bioavailability factor of 3.

Procedure

All the participants in the study were treated in Public University Hospitals (with 300 to 800 beds) with an acute pain service. Patients were invited to participate in the study. Those who voluntarily accepted gave written consent and filled in the self-administered IPO questionnaire. The participants were recruited by research assistants (RA), who were not in charge of clinical decisions. They were trained before the beginning of the study and followed a standard operational procedure. The RA also filled out the process of care questionnaire from the patient's medical records. Finally, the dataset of each participant was loaded with an anonymous code in a web-based database, called the PAIN-OUT registry. It is maintained by the Institute of Medical Informatics, Statistics, and Epidemiology at the University of Leipzig in Germany, which ensures confidentiality and data quality.(Zaslansky et al., 2012)

Statistical analysis

Software package SPSS-25 for Windows (IBM Corp, Armonk, NY) was used for the statistical analysis. We used the two-step cluster analysis to identify empirical clusters within the sample. This is a person-centered, free-hypothesis approach for exploring the existence of naturally empirical groups of individuals with similar characteristics. This system uses the log-likelihood distance

measure, which allows the inclusion of both categorical and quantitative indicators, employing the multinomial probability mass function (categorical variables) and the normal density (continuous variables). The Schwarz Bayesian Information Criterion and the large ratio of distance measures are also considered to automatically select the optimal number of clusters. Indicator variables of the two-step clustering were: age, oral morphine equivalents in the recovery room and the ward, duration of surgery, the three-factor scores of the IPO (pain intensity and interference, adverse effects, and perception of care), gender, non-opioids as premedication, sedatives, peripheral nerve block during the perioperative period, desire for more pain treatment (dichotomy answer of the IPO question: Would you have liked more pain treatment than you received?), the surgical procedure, intraoperative epidural nerve block, multimodal or unimodal analgesia ordered as no analgesic, one analgesic, more than one analgesic with similar action and multimodal analgesia, and chronic pain before surgery categorized in quartiles. The final model selected in this study was based on the following criteria:(Nylund et al., 2007) a) adequate goodness-of-fit based on the Silhouette-coefficient, a cohesion and separation index which ranges from -1 to +1 and measures how similar individuals are to their cluster compared to other clusters (values higher than 0.50 are interpreted as good fitting, between 0.30 and 0.50 as fair, and lower than 0.30 as poor)(Rousseeuw, 1987); b) adequate clinical interpretability (based on clear distinction between clusters in outcome variables); and c) groups with adequate frequency to guarantee statistical power.

After selecting the optimal solution for the clustering, the comparison between the groups for categorical variables was performed with Chi-square tests ($\chi 2$). For quantitative variables, T-test procedures for independent groups were used. Effect sizes for the proportion and mean differences were based respectively on Cohen-h and Cohen-d coefficients, considering poor-low effect size for $|d|>0.20$, moderate-medium for $|d|>0.5$, and large-high for $|d|>0.80$.(Kelley and Preacher, 2012) Type-I errors due to multiple statistical tests were controlled with Finner's method (Finner, 1993)(a stepwise familywise error rate procedure that offers a more powerful test than the classical Bonferroni correction).

Multivariate logistic regression was used to identify the best predictors of being in the most dysfunctional empirical cluster. First, univariate analysis was performed, and multicollinearity was examined among predictors through the examination of bivariate correlations (Kendall tau-b). Second, partial step-wise procedures introducing variables grouped by clinical coherence (clinical, preoperative, intraoperative, postoperative) were performed and predictors with $p \leq 0.10$ were selected. Third, a regression analysis was performed with the preselected predictors using stepwise procedure, with the aim of automatically choose those predictors that significantly contribute to differentiate between clusters. The Hosmer-Lemeshow test was used to assess the goodness-of-fit, the increase in Nagelkerke's pseudo-R^2 was used to assess the overall predictive capacity, and the area under the Receiver Operating Characteristic (ROC) curve (AUC) to assess the overall discriminative capacity.

Results

Patients

The sample considered for the clustering procedure included n=2,678 participants, with complete data for all the variables considered in the study (Figure 1). There was no difference in the IPO factor scores and desire for more pain treatment between included and excluded patients. However, patients excluded were older (M=62 vs M=59, $p<0.001$, $|d| = 0.13$) and received multimodal analgesia less frequently (74.4% vs 96.1%, p=0.01, $|d|=0.66$). Table 1 summarizes the patient characteristics and description of the sample.

- Insert Figure 1 -

- Insert Table 1 -

Clustering procedure

Table S1 (Appendix 1) shows the results of clustering procedure. The three-cluster model was selected as the optimal solution because it had the largest ratio of distance measure (1.50) and the highest cohesion/separation measure (Silhouette = 0.3, within the fair range). This solution also had clinical interpretability as it clearly differentiated between two functional clusters and one dysfunctional cluster with the worst postoperative outcomes. Figure 2 shows the weight of each indicator in the clustering procedure (with values into the range 0 to 1, interpreted as the relevance of the variable for the identification of the empirical groups). Higher values associated to a variable indicate greater discriminative capacity for the indicator. Both peripheral nerve block and patient´s desire for more pain treatment had a value of 1, indicating that these variables were the most important in the clustering. Procedure categorization, pain intensity and interference, perception of care, and chronic pain before surgery were also relevant for the identification of the empirical groups. Multimodal analgesia and gender were the variables with the lowest discriminative capacity.

- Insert Figure 2 -

Comparison between three empirical clusters

Table S2 (Appendix 2) shows the bivariate comparison between the empirical clusters for the variables of the study. Cluster 1 (C1) grouped n=522 patients (20% of the sample), characterized by peripheral nerve block use, and by not desiring of more pain treatment. This cluster presented low values of both pain intensity-interference (F1) and adverse effects (F2), and high scores in perception of care (F3). The patients in C1 had the oldest mean age (mean ± SD, 65±14) compared to C2 (58±16, d=0.49) and C3 (56±17, d=0.61). The frequency of use of non-pharmacological methods to relieve pain was similar between the different clusters, except for cold packs, which were used more frequently in C1 (C1 55.6%, C2 17.3%, C3 21.3%). The most frequent procedures in C1 were joint surgery and fracture.

Cluster 2 achieved the largest sample size, with n=1,644 patients (61% of the sample). Most of the patients in Cluster 2 did not receive a peripheral nerve block and did not desire more pain treatment. The postoperative outcomes in C2 were comparable to those in C1, except that C2 patients had more interference with breathing and coughing (2.5±2.9 vs 0.7±1.7, |d|=0.73). The most frequent procedures were gastrointestinal, joint, abdominal, and hepatobiliary surgery.

Cluster 3 consisted of n= 512 patients (19%). All patients in Cluster 3 desired more pain treatment. They had the worst results in pain intensity and interference, adverse effects, and perception of care. They were the youngest and received more morphine equivalents in the recovery room and in the ward than the other clusters. The most frequent procedures in C3 were joint, gastrointestinal surgery, non-abdominal procedures, and fractures.

Figure 3 displays two radar-charts with the distribution of the IPO measures (IPO triangle with the total factor scores and a radar-chart with each item score) within the empirical clusters, which provides a visual representation of the pain measures in the empirical groups.

- Insert Figure 3 -

The frequency of patients grouped into C3 varied according to the type of procedure, as shown in Figure 4. The procedures with the highest percentage of patients within the cluster characterized by the worst pain outcomes (C3) were foot, ankle and toe procedures, intervertebral disc repair and open fracture reduction. On the other hand, the procedures that yielded less than 10% of the patients within C3 were mainly thyroid, breast and hernia repair procedures.

- Insert Figure 4 -

Comparison between C3 versus C1+C2

A bivariate analysis was performed to compare C3 with the aggregate of C1+C2 (this aggregate is justified in the common postoperative outcomes among patients within these both groups compared to C3). Outcome scores in intensity and interference score (F1) obtained a mean difference in the T-test procedure of 18.1 points (M=38.8 vs M=20.7, p< 0.001), in adverse events (F2) the mean difference was 3.0 points (M= 8.9 vs M=5.9, p<0.001) and in perception of care (F3) the mean difference was -4.5 (M=10.5 vs M=15.0, p < 0.001).

Table 2 shows the comparisons between C3 compared to C1+C2. These results indicate that C3 grouped patients with younger age, lower proportion of women, higher prevalence of patients with persistent pain before surgery, psychiatric affective disorders, substance abuse of drugs and opioid use before surgery. They received less frequently paracetamol and metamizole in the intraoperative period and less NSAIDs in the ward, while in the recovery room, they required more opioids and in higher doses.

- Insert Table 2 -

Figure 5 displays a radar chart (z-standardized means for quantitative variables and proportion for categorical) as a summary of the results of the comparisons between C3 versus C1+C2.

- Insert Figure 5 -

In the final stepwise multivariate regression model, younger age, male gender, morphine equivalents in recovery, number of comorbidities, type of procedures (fracture reduction and bone compared to non-abdominal wall procedures) and the institution where the patient where treated, significantly increased the risk of belonging to C3 and were retained in the model. The model explained 14.8% of the variability of the regression line with an area under the curve of 68.9% (Table 3).

- Insert Table 3 -

Discussion

This exploratory study on postoperative outcome profiles yields a model with three cluster groups: two clusters with good postoperative outcomes (C1 and C2) and one cluster (C3) with bad postoperative outcomes. We found that 19% of the patients belonged to C3 and had undergone a wide range of procedures that include lower limb, back surgery, bariatric surgery, and abdominal hysterectomy. When C3 was compared with C1 and C2 using the univariate analysis, the variables with the largest size effect were age (being younger), drug dependence or substance abuse, preoperative opioid use, institution, and morphine equivalents in the recovery room. Finally, the multivariate analysis showed risk variation by institution and procedures, retained age, opioid use before surgery, morphine equivalents in the recovery and added male gender and number of comorbidities as risk factor of being in the worst postoperative outcome group.

There are a few studies that quantify pain variation among procedures.(Gerbershagen et al., 2013; Sommer et al., 2008) Gerbershagen et al. analyzed the results of the QUIPS study and proved that “minor” procedures were associated with high pain intensity, with the same frequency as “major” procedures like thoracic surgery. They found that foot arthrodesis, spinal fusion, fracture reduction, and gynecologic surgery were among the top ten most painful surgeries as we did.(Gerbershagen et al., 2013) The other procedures did not follow the same order exactly, which indicates differences in the structure and process of care between the two studies. The procedures that require urgent quality improvement stand out most clearly using the global images provided by the IPO factor scores, compared with previous studies that were focused on pain intensity. For example, appendectomy and cholecystectomy were among the 25 most painful surgeries in the QUIPS study but are not among the surgeries with more patients in C3 in our study.

The comparison of quality of care among different healthcare systems is important for determining the difference between the structural, cultural, and individual factors that influence pain outcomes. For example, Chapman at al (Chapman et al., 2013) and Zaslansky et al (Zaslansky et al., 2018) showed that US patients compared to European patients, perceived a greater extent of participation in pain treatment decisions and information about pain treatment options but reported worse pain intensity and more adverse effects, despite that there were no differences in risk factors. Widespread use of opioids and lower assessment of pain in the ward were more frequently seen in US patients. Our study found that opioid use before surgery and high opioid doses in the recovery room were the most important predictors of the worst postoperative outcomes (High scores in F1 and F2 and low scores in F3 as shown in figure 3). On the other hand, the number of intraoperative analgesics,(Baca et al., 2021) the use of preoperative NSAIDs,(Khan et al., 2016) and the use of NSAIDs in the ward (Andrew Moore et al., 2018; Helander et al., 2017; Martinez et al., 2017) were found to be protective factors against postoperative pain. These findings support the need of early intense non-opioids treatments to prevent the onset of severe pain and the around-the-clock prescription of NSAIDs if there is no contraindication.

By changing the focus from severe pain intensity to the worst postoperative pain outcomes, novel risk factors appeared. Substance addiction, which is not commonly described as a risk factor in severe postoperative pain studies, was more frequent in C3 patients. Substance abuse is known to complicate perioperative management as addicts require an individually adjusted analgesic plan and adequate management of expectations due to their behavioral and emotional alterations. Additionally, several substance addict patients have an enhanced expression of dopamine D2 receptor (DRD2) that has been associated in genetic polymorphisms studies with development of chronic postsurgical pain(Harbaugh and Suwanabol; Montes et al., 2015; Sen et al., 2016)

Male gender was found to be a risk factor of the worst postoperative outcomes. It seems contradictory as female gender has generally been considered a risk factor of severe postoperative pain. However, Komann et al. recently demonstrated that men desire more pain treatment than women despite having less pain.(Komann et al., 2021) As C3 included patients that not only had high scores in pain intensity and interference, but also high scores in adverse effects and low scores in perception of care, it suggests that men with high intensity pain perceived, more frequently than women, that their pain treatment were inadequate; men have less tolerance to pain or higher expectations with pain treatment.

Morphine equivalents in the recovery room had a stronger association with worse postoperative outcomes than total, intraoperative, and ward morphine equivalents. This is an interesting finding as it suggests that risk factors of poor pain control and bad postoperative pain outcomes are already present before the recovery period and that patients with intense pain in the recovery room will report bad outcomes, despite the ward analgesic treatment received.(Montes et al., 2020) The use of high doses of morphine in the recovery could favor the appearance of opioid tolerance and opioid induced hyperalgesia, which hinders subsequent analgesic management.(Fletcher and Martinez, 2014; Sanfilippo et al., 2016; Shanthanna et al., 2021) Other intraoperative variables such incision type, surgeon's experience, surgical material, and intraoperative complications can worsen pain and increase inflammation after surgery.(van Boekel et al., 2021) Therefore, efforts to control pain should focus on identifying key factors during the preoperative and intraoperative periods.

Number of comorbidities also appeared as a risk factor of belonging to C3 suggesting that healthier patients tend to have good postoperative outcomes. Finally, given the differences between institutions, other structural factors such as the team's experience, the adherence and effectiveness of written protocols; and acute pain service structure could have influenced the outcomes of our results.(Ramsay, 2019)

This study has some limitations. The shortcomings of the PAIN-OUT methodology are inherited by this study (Zaslansky et al., 2018). For example, as only public university hospitals were involved and participation was voluntary, the sample is representative only of patients attending public university hospitals. The multivariate analysis identified predictive variables of poor postoperative outcomes; however, the results are difficult to validate and replicate as IPO factor scores is a novel analytical approach and clustering procedures have not previously been used. Outcomes scores of C3 patients (F1 38.8, F2 8.9, and F3 10.5) could be used to select patients with bad outcomes and characterize them. The mean difference of the outcome scores in each of the three-factor scores of the IPO questionnaire between C3 and C1+C2 (F1 18.1, F2 3.0, and F3 -4.5), could be used as a measure of responsiveness and clinically significant change in posterior quality improvement studies. IPO factor scores give more information than isolated questions like the desire of more pain treatment (Polanco-García et al., 2021b). Although the data collected seem dated, recent studies suggest that both the process of care and the outcomes haven't varied in the last few years.(Gan, 2017; Garduño-López et al., 2021; Komann et al., 2021)

Conclusions

This study demonstrates the method's utility to summarize and characterize the postoperative outcomes (Polanco-García et al., 2021b). Efforts to control pain should focus on identifying key factors during the preoperative and intraoperative periods. In subsequent validation studies, both the cut-off points in the factor scores and the question about the desire for more pain treatment can be used to differentiate patients with poor and good outcomes.

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Table 1 *Descriptive of the sample (N=2,678)*

Clinical characteristics		
Age, yr		59 (16.3)
Body mass index, Kg/m^2		29 (6.5)
Gender (Women)		1559 (58.2%)
Previous Chronic Pain		1403 (52%)
Previous Chronic Pain Intensity (NRS 0 to 10)		6.9 (2.3)
Patients with Comorbidities		1921(72%)
Affective disorders [a]		346 (13%)
Addictive disorders [b]		329 (12%)
Preoperative opioid use		158 (6%)
Process of care		
Duration of surgery, hours		1.9 (1.1)
Type of anesthesia	*Regional*	1043 (39%)
	General	1297 (49%)
	Combined	318 (12%)
Wound infiltration		206 (8%)
Epidural block		213 (8%)
Peripheral nerve block		704 (26%)
Intraoperative morphine equivalents, mg		3.9 (9.5)
Morphine equivalents at recovery room, mg		5.2 (11.1)
Morphine equivalents at ward, mg		11 (28.5)
Analgesia type	*No analgesic*	71 (2.7%)
	One analgesic	17 (0,6%)
	>1 analgesic with similar action	16 (0.6%)
	Multimodal analgesia	2574 (96.1%)
Pain outcomes		
Pain intensity and interference (F1)		24 (16)
Adverse effects (F2)		6.5 (7)
Perception of care (F3)		14.2 (6)
Desire of more pain treatment, *n(%)*		482 (18%)

Note. SD standard deviation. Mean (and SD) are used for continuous variables and n (and percentage, %) for categorical variables.

[a] Addictive disorders include the process of care items: alcohol use disorder, current smoker and substance abuse of drugs (Legal and illegal)

[b] Psychiatric disorders include the process of care items: Affective disorders and Schizophrenia.

Table 2 *Comparison between Cluster 1 and 2 versus Cluster 3*

		C1-2 (n=2166)	*C3(n=512)*	*p*	*d*
Age (years)		59.6 (16)	55.8 (17.2%)	**<0.001**[a]	**0.23**[b]
Gender (Female)		1290 (57%)	269 (53%)	**0.004**[a]	0.14
Body Mass Index (kg/m2)		28.7 (6.5)	29 (6.6)	0.637	0.04
Persistent Pain before surgery		1111 (51.3%)	292 (57%)	**0.019**[a]	0.12
Comorbidities		1541 (71.6%)	380 (74.7%)	0.164	0.07
Number of comorbidities		1.03 (1.02)	1.10 (1.1)	0.132	0.07
Cancer		157 (7.2%)	34 (6.6%)	0.570	0.02
Psychiatric affective disorders		233 (10.8%)	74 (14.5%)	**0.031**[a]	0.11
Alcohol use disorder		17 (0.8%)	7 (1.4%)	0.565	0.06
Substance abuse of drugs (Legal and illegal)		18 (0.8%)	18 (3.5%)	**<0.001**[a]	**0.20**[b]
Current smoker		196 (9.0%)	58 (11.3%)	0.166	0.08
Addictive disorders		252 (11.6%)	77 (15.0%)	**0.035**[a]	0.10
Psychiatric disorders		265 (12.2%)	81 (15.8%)	0.089	0.10
Cardiovascular diseases		901 (41.6%)	203 (39.6%)	0.836	0.04
Hypertension [c]		827 (38.2%)	188 (36.7%)	0.836	0.03
Location of chronic pain (Elsewhere-Both vs Site of surgery)		341 (34.3%)	99 (37.2%)	0.413	0.06
Opioids use before surgery		105 (4.9%)	53 (10.5%)	**<0.001**[a]	**0.21**[b]
Sedatives (pre-medication)		1589 (73.4%)	389 (76.1%)	0.370	0.06
Non-opioids (pre-medication)		218 (10.1%)	61 (11.9%)	0.370	0.06
Morphine equivalents preoperative		2.0 (8.4)	2.9 (12.6)	0.115	0.08
Peripheral nerve block (intra-op)		288 (13.3%)	76 (14.8%)	0.413	0.04
Non-opioids (intra-op)		1257 (58.3%)	261 (51.3%)	**0.011**[a]	0.14
Antipyretics (intra-op)		892 (41.4%)	169 (33.2%)	**0.004**[a]	0.17
NSAIDS (intra-op)		485 (22.5%)	94 (18.5%)	0.092	0.10
Number of non-opioids used intraoperative		0.9 (0.8)	0.8 (0.8)	**0.042**[a]	0.12
Wound infiltration (intra-op)		162 (7.6%)	44 (8.8%)	0.488	0.04
Remifentanil (intra-op)		206 (10.9%)	30 (6.8%)	**0.031**[a]	0.14
Tramadol (intra-op)		357 (16.5%)	84 (16.4%)	0.977	0.00
Peripheral nerve block (recovery and ward)		349 (16.1%)	83 (16.2%)	0.977	0.00
Duration of surgery, hours		1.9 (1.1)	1.9 (1)	0.739	0.02
Morphine equivalents in Recovery, mg		4.1 (7.7)	9.9 (19.1)	**<0.001**[a]	**0.40**[b]
Opioid (recovery)		699 (32.3%)	223 (43.6%)	**<0.001**[a]	**0.23**[b]
Number of non-opioids used in the recovery room		1 (0.8)	1 (0.9)	0.739	0.02
Morphine equivalents in the Ward, mg		3.1 (16.3)	18.9 (55.2)	**<0.001**[a]	**0.24**[b]
NSAIDS (ward)		761 (35.2%)	145 (28.3%)	**0.003**[a]	0.15
Perioperative dose of IV metamizole, mg[b]		2253 (3286)	2276 (3101)	0.886	0.01
Perioperative dose of IV paracetamol, mg		2868 (1719)	2783 (1679.4)	0.664	0.05
Perioperative dose of IV dexketoprofen, mg		103 (163)	110 (191)	0.664	0.04
Number of non-opioids used in the ward		1.8 (0.7)	1.9 (0.8)	0.664	0.06
Type of anesthesia [c d]	Regional	823 (38%)	220 (43%)	**<0.001**[a]	0.10
	General	1070 (50%)	227 (45%)		0.11
	Combined	255 (12%)	63 (12%)		0.01
Institution [a b c d]	H1	25 (1.2%)	12 (2.3%)	**<0.001**[a]	0.09
	H2	159 (7.3%)	64 (12.5%)		0.17
	H3	69 (3.2%)	25 (4.9%)		0.09
	H4	6 (0.3%)	2 (0.4%)		0.02
	H5	170 (7.9%)	49 (9.6%)		0.06
	H6	323 (14.9%)	90 (17.6%)		0.07
	H7	143 (6.6%)	38 (7.4%)		0.03
	H8	42 (1.9%)	10 (2%)		0.00
	H9	52 (2.4%)	12 (2.3%)		0.00
	H10	340 (15.7%)	72 (14.1%)		0.05
	H11	747 (34.5%)	128 (25.0%)		**0.21**[b]
	H12	6 (0.3%)	1 (0.2%)		0.02
	H13	84 (3.9%)	9 (1.8%)		0.13
Procedure type	Fracture	139 (6.7%)	50 (10.1%)	**<0.001**[a]	0.12
	Bone	126 (6.0%)	41 (8.3%)		0.09
	Back and Nervous system	122 (5.8%)	39 (7.9%)		0.08
	Joint	664 (31.8%)	178 (35.9%)		0.09
	Gynecological and obstetrical	64 (3.1%)	17 (3.4%)		0.02
	Gastrointestinal	395 (18.9%)	97 (19.6%)		0.02
	Hepatobiliar	207 (9.9%)	39 (7.9%)		0.07
	Adbominal wall	154 (7.4%)	23 (4.6%)		0.12
	Non abdominal	215 (10.3%)	12 (2.4%)		**0.34**[b]
	Urinary system	21 (1.0%)	6 (1.2%)		0.02
	Cardiothorax	15 (0.7%)	3 (0.6%)		0.01
	Tendon and Muscle	28 (1.3%)	6 (1.2%)		0.01
	Skin	16 (0.7%)	1 (0.2%)		0.08

SD standard deviation. Mean (SD) are used for continuous variables and n (%) for categorical variables.
[a] Bold: significant comparison [b] effect size greater or equal than 0.2

Table 3

Predictive multivariate regression analysis

Model for: belonging to cluster 3		*B*	*SE*	*p*	*OR*	*95%CI (OR)*		*H-L*	R^2	*AUC*
Institution	H1			**.001**				.727	0.148	0.689
	H2	.380	.741	.608	1.463	.342	6.250			
	H3	.509	.498	.307	1.664	.627	4.416			
	H4	1.168	.560	**.037**	3.215	1.073	9.633			
	H5	.488	.726	.502	1.629	.392	6.762			
	H6	.011	.478	.982	1.011	.396	2.579			
	H7	.157	.516	.761	1.170	.425	3.217			
	H8	.343	.701	.625	1.409	.356	5.571			
	H9	.869	.731	.235	2.385	.569	10.001			
	H10	.525	.484	.278	1.690	.655	4.363			
	H11	-.396	.468	.398	.673	.269	1.686			
	H12	.089	1.211	.941	1.094	.102	11.736			
Age (Years)		-.012	.005	**.027**	.989	.978	.999			
Gender (0=women; 1=men)		.493	.152	**.001**	1.637	1.216	2.203			
Opioids before surgery (0= no; 1= yes)		.785	.227	**.001**	2.193	1.406	3.422			
Morphine equivalents (Recovery)		.045	.007	**.000**	1.046	1.033	1.060			
Number of comorbidities		.234	.077	**.002**	1.263	1.087	1.468			
Procedure type	Non abdominal			**.023**						
	Fracture	1.513	.678	**.026**	4.541	1.203	17.133			
	Bone	1.385	.587	**.018**	3.994	1.263	12.626			
	Back and Nervous system	.347	.592	.557	1.415	.444	4.514			
	Joint	.899	.551	.103	2.457	.835	7.229			
	Gynecological and obstetrical	.792	.750	.291	2.209	.508	9.602			
	Gastrointestinal	.824	.590	.162	2.279	.718	7.238			
	Hepatobiliar	.313	.610	.608	1.367	.413	4.523			
	Abdominal wall	.566	.626	.366	1.762	.517	6.008			
Constant		-2.406	.746	.001	.090					

H-L: Hosmer-Lemeshow test (*p*). R^2: Nagelkerke's pseudo-R. AUC: Area under ROC curve.

Bold: significant parameter (.05 level).

Figure 1

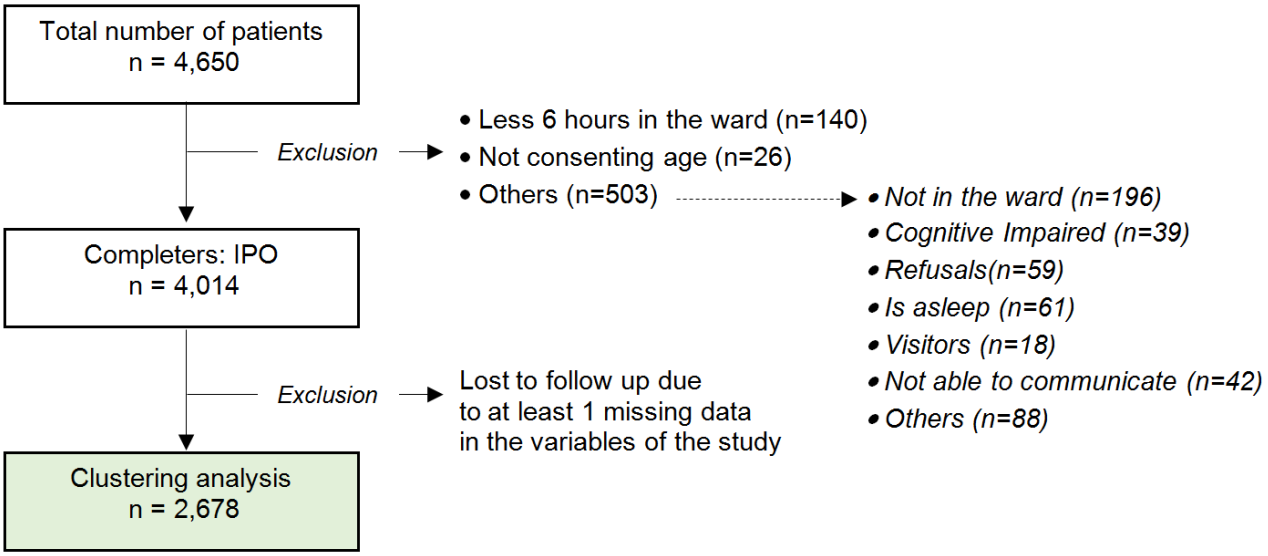


Figure 2

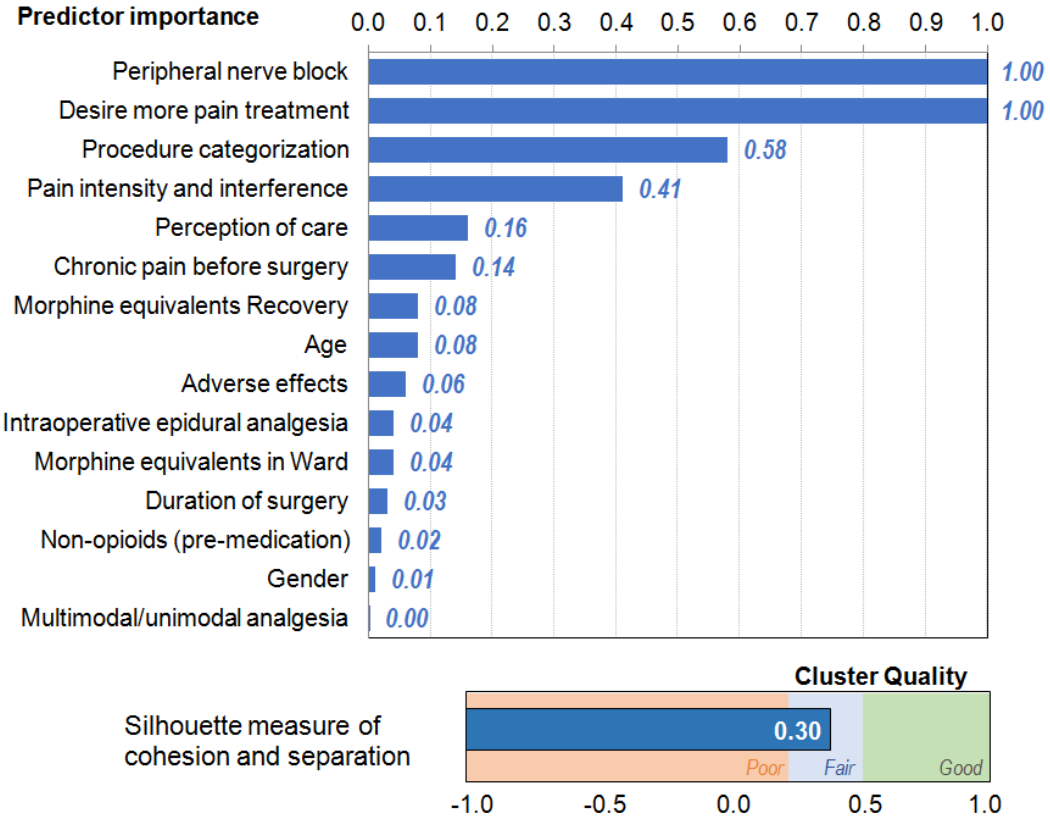


Figure 3

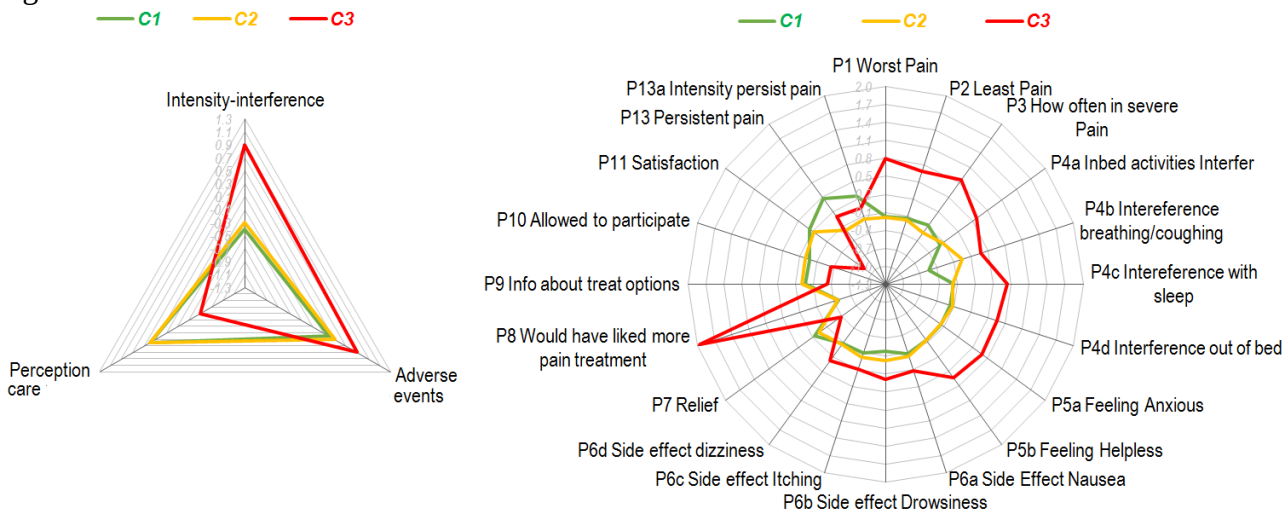
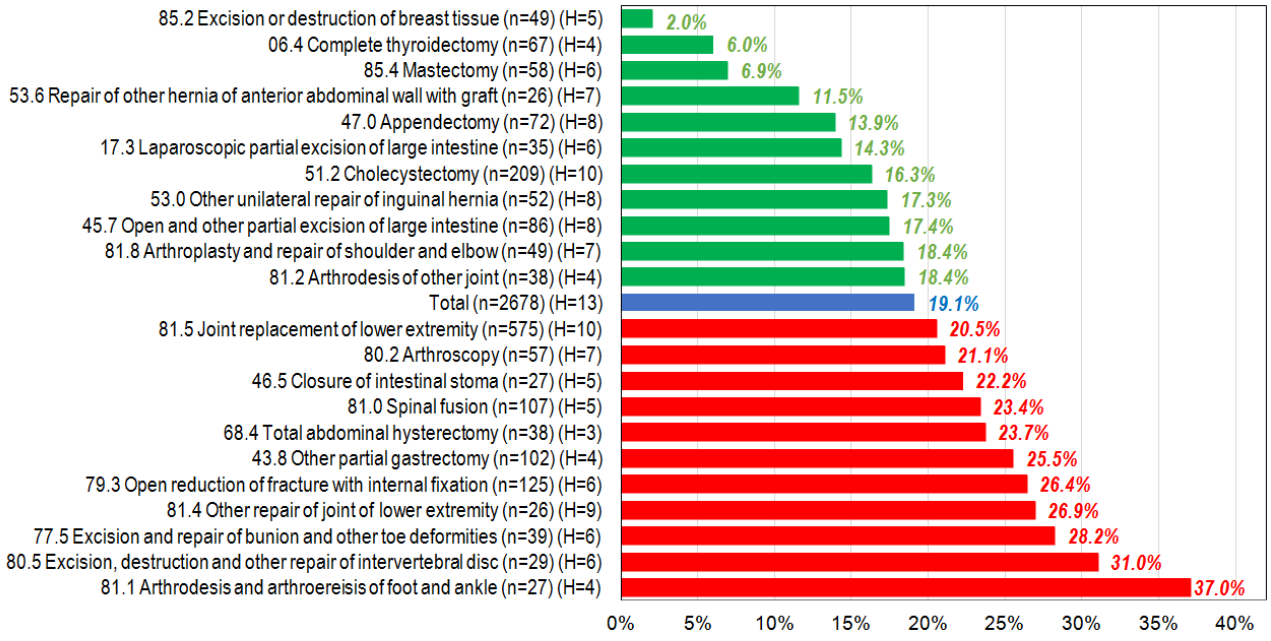


Figure 4



Appendix 1. Supplementary table 1

Results of the clustering

Number of Clusters	Schwarz's Bayesian Criterion (BIC)	BIC Change[a]	Ratio of BIC Changes[b]	Akaike's Information Criterion (AIC)	AIC Change[a]	Ratio of AIC Changes[b]	Ratio of Distance Measures[c]
1	45192.350			44968.423			
2	42458.893	-2733.458	1.000	42011.038	-2957.385	1.000	1.071
3	39926.546	-2532.347	.926	39254.764	-2756.274	.932	1.501
4	38339.350	-1587.196	.581	37443.641	-1811.123	.612	1.188
5	37051.171	-1288.180	.471	35931.534	-1512.107	.511	1.280
6	36110.209	-940.961	.344	34766.645	-1164.889	.394	1.186
7	35363.523	-746.686	.273	33796.031	-970.614	.328	1.042
8	34658.911	-704.612	.258	32867.492	-928.539	.314	1.096
9	34042.279	-616.632	.226	32026.933	-840.559	.284	1.105
10	33512.879	-529.400	.194	31273.605	-753.328	.255	1.299

Statistical indicators of the clustering procedure and the separation and cohesion indexes of each candidate solution.
a. The changes are from the previous number of clusters in the table.
b. The ratios of changes are relative to the change for the two-cluster solution.
c. The ratios of distance measures are based on the current number of clusters against the previous number of clusters.

Appendix 2. Supplementary table 2

Centroids and comparison between the empirical clusters

	Total (n=2678)	*Cluster 1 (n=522)*	*Cluster 2 (n=1644)*	*Cluster 3 (n=512)*	Pairwise comparisons C1-C2		C1-C3		C2-C3	
					p	|*d*|	*p*	|*d*|	*p*	|*d*|
Clinical characteristics										
Age, yr	59 (16.3)	65 (13.8)	58 (16.3)	56 (17.2)	**<0.001**	0.49	**<0.001**	**0.61**	**0.016**	0.12
Body mass index, Kg/m^2	29 (6.5)	29.2 (5)	28.6 (6.9)	29 (6.6)	**0.067**	0.10	0.569	0.04	0.267	0.06
Gender (Women)	1559(58.2%)	344 (65.9%)	946 (57.5%)	269 (52.5%)	**0.001**	0.17	**<0.001**	0.27	**0.055**	0.10
Previous Chronic Pain	1403 (52%)	394 (75.5%)	717 (43.6%)	292 (57%)	**<0.001**	**0.66**	**<0.001**	0.39	**<0.001**	0.27
Previous Chronic Pain Intensity (NRS 0 to 10)	6.9 (2.3)	7.5 (2)	6.6 (2.5)	7 (2.1)	**<0.001**	0.41	**0.002**	0.23	**0.008**	0.19
Patients with Comorbidities	1921(72%)	390 (75%)	1151 (70.5%)	380 (74.7%)	0.134	0.10	0.899	0.01	0.134	0.09
Affective disorders [a]	346 (13%)	85 (16.3%)	180 (11%)	81 (15.9%)	**0.004**	0.16	0.850	0.01	**0.005**	0.14
Addictive disorders [b]	329 (12%)	37 (7.1%)	215 (13.2%)	77 (15.1%)	**<0.001**	0.20	**<0.001**	0.26	0.260	0.06
Preoperative opioid use	158 (6%)	43 (8.4%)	62 (3.8%)	53 (10.5%)	**<0.001**	0.19	0.245	0.07	**<0.001**	0.27
Process of care										
Non-opioids (pre-medication)	279 (10.4%)	22 (4.2%)	196 (11.9%)	61 (11.6%)	**<0.001**	0.29	**<0.001**	0.29	0.999	0.00
Duration of surgery, hours	1.9 (1.1)	1.6 (0.6)	1.9 (1.2)	1.9 (1)	**<0.001**	0.37	**<0.001**	0.35	0.267	0.06
Type of anesthesia *Regional*	1043 (39%)	409 (78.5%)	414 (25.4%)	220 (43.1%)	**<0.001**	**1.12**	**<0.001**	**0.74**	**<0.001**	0.38
General	1297 (49%)	20 (3.8%)	1050 (64.5%)	227 (44.5%)	**<0.001**	**1.47**	**<0.001**	**1.07**	**<0.001**	0.41
Combined	318 (12%)	92 (17.7%)	163 (10%)	63 (12.4%)	**<0.001**	0.22	**0.026**	0.15	0.135	0.07
Wound infiltration	206 (8%)	5 (1%)	157 (9.6%)	44 (8.8%)	**<0.001**	0.43	**<0.001**	0.40	0.578	0.03
Intra-operative epidural block	213 (8%)	1 (0.2%)	172 (10.5%)	40 (7.8%)	**<0.001**	**0.55**	**<0.001**	0.47	0.164	0.08
Peripheral nerve block	704 (26%)	522 (100%)	43 (2.6%)	139 (27.1%)	**<0.001**	**2.82**	**<0.001**	**2.05**	**<0.001***	**0.77**
Intraoperative morphine equivalents, mg	3.9 (9.5)	0.9 (3.9)	4.7 (10.4)	4.3 (9.9)	**<0.001**	0.48	**<0.001**	0.45	0.463	0.04
Morphine equivalents at recovery room, mg	5.2 (11.1)	3.7 (7)	4.2 (7.9)	9.9 (19.1)	0.254	0.06	**<0.001**	0.43	**<0.001**	0.39
Morphine equivalents at ward, mg	11 (28.5)	10 (15.8)	8.8 (16.5)	18.9 (55.2)	0.167	0.07	**<0.001**	0.22	**<0.001**	0.25
Analgesia type *No analgesic*	71 (2.7%)	13 (2.5%)	43 (2.6%)	15 (2.9%)	0.875	0.01	0.868	0.03	0.868	0.02
One analgesic	17 (0.6%)	1 (0.2%)	13 (0.8%)	3 (0.6%)	0.586	0.09	0.667	0.07	0.868	0.02
>1 analgesic with similar action	16 (0.6%)	2 (0.4%)	10 (0.6%)	4 (0.8%)	0.875	0.03	0.875	0.05	0.875	0.02
Multimodal analgesia	2574(96.1%)	506 (96.9%)	1578 (96%)	490 (95.7%)	0.875	0.05	0.875	0.07	0.875	0.01
Outcomes										
Pain intensity and interference (F1)	24 (16)	19.1 (13.9)	21.2 (14.6)	38.8 (14.8)	**0.004**	0.15	**<0.001**	**1.37**	**<0.001**	**1.2**
Adverse effects (F2)	6.5 (7)	5.3 (6.8)	6.1 (6.6)	8.9 (8.1)	**0.024**	0.11	**<0.001**	0.48	**<0.001**	0.38
Perception of care (F3)	14.2 (6)	14.9 (5.8)	15.1 (6.1)	10.5 (5.9)	0.621	0.03	**<0.001**	**0.75**	**<0.001**	**0.75**
Would have liked to receive more pain treatment, *n (%)*	482 (18%)	0 (0%)	3 (0.2%)	479 (93.6%)	0.380	0.09	**<0.001**	**2.63**	**<0.001**	**2.54**
Procedure type										
Gastrointestinal	492 (18.4%)	0 (0%)	395 (24%)	97 (18.9%)	**<0.001**	**1.02**	**<0.001**	**0.90**	**0.017**	0.12
Hepatobiliar	246 (9.2%)	1 (0.2%)	206 (12.5%)	39 (7.6%)	**<0.001**	**0.64**	**<0.001**	0.47	**0.003**	0.16
Abdominal wall	177 (6.6%)	0 (0%)	154 (9.4%)	23 (4.5%)	**<0.001**	**0.62**	**<0.001**	0.43	**0.001**	0.19
Non abdominal	227 (8.5%)	6 (1.1%)	209 (12.7%)	12 (2.3%)	**<0.001**	**0.51**	0.142	0.09	**<0.001**	0.42
Urologic	27 (1%)	0 (0%)	21 (1.3%)	6 (1.2%)	**0.019**	0.23	**0.020**	0.22	0.851	0.01
Gynecological and obstetrical	81 (3%)	0 (0%)	64 (3.9%)	17 (3.3%)	**<0.001**	0.40	**<0.001**	0.37	0.618	0.03
Cardiothoracic	18 (0.7%)	0 (0%)	15 (0.9%)	3 (0.6%)	0.056	0.19	0.117	0.15	0.542	0.04
Bone	167 (6.2%)	44 (8.4%)	82 (5%)	41 (8%)	**0.020**	0.14	0.805	0.02	**0.030**	0.12
Joint	842 (31.4%)	395 (75.7%)	269 (16.4%)	178 (34.8%)	**<0.001**	**1.28**	**<0.001**	**0.85**	**<0.001**	0.43
Back and Nervous	161 (6%)	2 (0.4%)	120 (7.3%)	39 (7.6%)	**<0.001**	0.42	**<0.001**	0.44	0.810	0.01
Fracture	189 (7.1%)	55 (10.5%)	84 (5.1%)	50 (9.8%)	**<0.001**	0.21	0.682	0.03	**<0.001**	0.18
Skin	34 (1.3%)	18 (3.4%)	10 (0.6%)	6 (1.2%)	**<0.001**	0.22	**0.023**	0.16	0.233	0.06
Tendon and Muscle	17 (0.6%)	1 (0.2%)	15 (0.9%)	1 (0.2%)	0.281	0.10	0.989	0.00	0.281	0.10

SD standard deviation. Mean (SD) are used for continuous variables and n (%) for categorical variables.

Note. Bold: significant comparison. Bold: effect size into the range mild-medium (|*d*|>0.50) to large-high (|*d*|>0.80).