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Patient and Procedural Determinants of Postoperative Pain Trajectories

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Abstract

Background: The primary goal of this study was to evaluate patterns in acute postoperative pain in a mixed surgical patient cohort with the hypothesis that there would be heterogeneity in these patterns.

Methods: This study included n = 360 patients from a mixed surgical cohort whose pain was measured across postoperative days 1 through 7. Pain was characterized using the Brief Pain Inventory. Primary analysis used group-based trajectory modeling to estimate trajectories/patterns of postoperative pain. Secondary analysis examined associations between sociodemographic, clinical, and behavioral patient factors and pain trajectories.

Results: Five distinct postoperative pain trajectories were identified. Many patients (167/360, 46%) were in the moderate-high pain group, followed by moderate-low (88/360, 24%), high (58/360, 17%), low (25/360, 7%), and decreasing (21/360, 6%) pain groups. Lower age (OR: 0.94, 95%CI: 0.91–0.99), female sex (OR: 6.5, 95%CI: 1.49–15.6), higher anxiety (OR: 1.08, 95%CI: 1.01–1.14), and more pain behaviors (OR: 1.10, 95%CI: 1.02–1.18) were related to increased likelihood of being in the high pain trajectory in multivariable analysis. Preoperative and intraoperative opioids were not associated with postoperative pain trajectories. Pain trajectory group was, however, associated with postoperative opioid use ($P < 0.001$), with the high pain group (249.5 oral morphine milligram equivalents) requiring four times more opioids than the low pain group (60.0 oral morphine milligram equivalents).

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Conclusions: There are multiple distinct acute postoperative pain intensity trajectories, with 63% of patients reporting stable and sustained high or moderate-high pain over the first 7 days following surgery. These postoperative pain trajectories were predominantly defined by patient factors and not surgical factors.

Summary Statement:

Patient groups assigned using growth-based trajectory models of acute postoperative pain intensity differ by sociodemographic, behavioral, and surgical factors.

Introduction

Of the 100 million patients who undergo surgery worldwide each year, over 60% will experience moderate to severe postoperative pain.[1] Increased acute postoperative pain intensity is associated with the development of persistent postsurgical pain, which is defined by the International Classification of Diseases-11 as pain persisting over 3 months following surgery.[2–4] Depending on the type of surgery, 10% to 56% of surgical patients will develop persistent postsurgical pain.[5–7] Epidemiologic work by Fletcher *et al.* suggests that for every 10% increase in the patient estimate of the percentage of time spent in severe postoperative pain, there is a 24% increase in pain intensity at 6 months after surgery.[8] This suggests that a better understanding of postoperative pain trajectories may influence not just acute postoperative suffering, but also lead to preventative therapies for persistent postsurgical pain.

To personalize postoperative analgesia to these anticipated temporal profiles of acute and persistent postoperative pain, we must first develop better models of postoperative pain trajectories.[9–12] Foundational work by Lavand'homme, Hah, Althaus, and others have characterized heterogeneity in the trajectory of postoperative pain and have linked these trajectories to the risk of persistent postsurgical pain.[13–16] More recently, Althaus applied growth mixture modeling analyses using postoperative day 1 through 5 average pain intensity ratings to assign individual patients into three classes described as high initial pain–high resolution (29.3% of subjects), low initial pain–moderate resolution (56.9%), and high initial pain–flat slope (13.4%).[17]

Although Althaus *et al.*'s growth mixture models established an empirical typology of acute postoperative pain trajectories, such typologies do not include details on sociodemographics, behavioral factors, or surgery type. These details are critical given the role of age, sex, anxiety, catastrophizing, surgical procedure, and myriad additional factors previously shown to relate to both acute and persistent postsurgical pain outcomes.[18] In addition, given the increasingly recognized problem of rebound pain after surgery, exploring growth mixture modeling with non-monotonic functions (e.g., lines that both increase and decrease over time) may unmask late "bumps" in pain intensity that may be otherwise smoothed over in prior trajectory-modeling strategies.[12,19]

The primary goal of this study was to use group-based trajectory modeling to characterize unique groups of postoperative pain trajectories for postoperative days 1 through 7 across a mixed surgical cohort. We hypothesized that we would identify more than two groups

of pain trajectories. The secondary goal of this study was to examine sociodemographic, clinical, and behavioral factors in relation to pain trajectories; we hypothesized that these factors would differ across the identified trajectory groups.

Materials and Methods

This study was a prospective cohort using a mixed surgical sample that aimed to investigate how group-based trajectory modeling were associated with acute postoperative pain trajectories. The study protocol (IRB 201500153) was approved by the University of Florida Institutional Review Board (UF IRB-01) and was registered at ClinicalTrials.gov (NCT02407743; ClinicalTrials.gov; Principal Investigator: Patrick J. Tighe, MD, MS; April 3, 2015) prior to study initiation. All patients provided written informed consent for participation in this study and were generally recruited and enrolled more than 24 hours prior to their surgery to avoid undue time pressure. This manuscript adheres to the STROBE guidelines.

Study Participants

The study included patients undergoing elective, major orthopedic, urologic, colorectal, pancreatic/biliary, thoracic, or spine surgery with anticipated postoperative admission of at least 48 h. Inclusion criteria was age greater than 18 years, anticipated length of stay 72 h or longer, and expected survival of longer than 6 months following surgery. Exclusion criteria included anticipated need for postoperative intubation greater than 24 h, urgent or emergent surgery, or the inability to understand or participate in data collection instruments. All subjects received surgery at UF Health Shands Hospital between November 2015 and September 2018. The convenience sample of patients was screened and recruited by trained research coordinators within the presurgical clinic, generally 1 to 3 weeks prior to surgery. All research participants were compensated for initial enrollment and for study completion. All eligible patients were screened by appropriate clinical staff on all weekdays, at all hours, to minimize the risk for selection bias. Figure 1 depicts the study flow diagram for the analytical sample of the current paper. Given that the cohort consisted of multiple surgical services, it was not possible to consider a universal analgesic strategy. Appendix 1 provides additional details on the perioperative analgesic strategy for surgical patients.

Data Collection

Sociodemographics and Clinical Measures.—Sociodemographic variables, including age, sex, race, ethnicity, and preoperative body mass index, were extracted from the electronic health record using the values listed at the time of the surgical encounter. The use of a preoperative nerve block or intraoperative ketamine was noted and collected from the electronic health record. Type of pain medication was recoded preoperatively as part of the Brief Pain Inventory. Intraoperative opioid administration, calculated as oral morphine milligram equivalents, was also recorded along with use and dosage of intraoperative ketamine and lidocaine. Postoperative oral morphine milligram equivalents were recorded and analyzed as the sum of daily oral morphine milligram equivalents from postoperative days 1 to 7. Patient-controlled analgesia (PCA) use was extremely low due to shortages and updated protocols, which de-emphasized PCA use as a standard treatment. At our

institution, preoperative gabapentin and intraoperative magnesium and dexmedetomidine were not included in a general perioperative multimodal analgesic strategy and were instead used very rarely due to concerns over sedation, safety, and/or cost.

Pain Assessment.—The perioperative pain experience was characterized using the average pain severity item from the Brief Pain Inventory, which asks subjects to indicate the number (0, "*No Pain*" to 10, "*Pain As Bad As You Can Imagine*") that best describes their pain on average, as well as worst and least pain in the last 24 h.[20] Patients were assessed with the Brief Pain Inventory before surgery and then each day following surgery through postoperative day 7. The postoperative Brief Pain Inventory was administered by trained research coordinators in the patient's hospital room; in the event that a patient was discharged before postoperative day 7, the research coordinator contacted the subject via telephone to complete the assessment.

Inpatient and phone (following hospital discharge) Brief Pain Inventory assessments were completed from 9 to 11 a.m., with follow-up at 1 to 3:30 p.m. if the patient was unavailable during the first interview attempt. In the event that a patient preferred to receive follow-up assessments via an emailed link to the REDCap assessment interface for post-discharge timepoints, the email was sent at 7 a.m. each postoperative day and participants completed the surveys at their convenience.

Preoperative Mental Health and Behavioral Factors.—Several assessments related to mental health and behavioral were conducted prior to the patients undergoing surgery. Three measures were developed and validated as a part of the Patient-Reported Outcomes Measurement Information System (PROMIS), including adult measures of PROMIS Anxiety, PROMIS Depression, and PROMIS Pain Behavior (i.e., behaviors that would indicate to others that an individual is experience pain, such as grimacing or sighing).[21] Patients also completed the Pain Catastrophizing Scale.[22,23] The Pain Catastrophizing Scale has three subscales: magnification, rumination, and helplessness. These subscales assess the degree to which a patient views his/her pain experience in extreme terms (e.g., "I become afraid that the pain will get worse"); worries about their pain (e.g., "I keep thinking about how much it hurts"); and feels helpless to control their pain (e.g., "It's terrible and I think it's never going to get better").

Statistical Analysis

Analyses were performed in JMP Pro 14 and SAS 9.3 (SAS Institute Inc, Cary, NC). Continuous measures were summarized with means and standard deviations (or medians and interquartile range), and categorical measures were summarized with percentages. Normality of the primary measurement of average pain was examined graphically, using histogram and normal quantile–quantile plots, stratified by postoperative day. Distributions were normal within each day, with no outliers detected.

In primary analysis to identify clusters or subgroups of patients with similar progressions (i.e., trajectories) of pain following surgery, group-based trajectory modeling, using maximum likelihood estimation, was implemented with PROC TRAJ in SAS® software (SAS Institute).[24] Each individual was clustered into the trajectory group to which they

had the highest posterior probability of membership.[25] Group-based trajectory modeling was used to determine both the number of distinct trajectory groups and the shape of each trajectory (i.e., order of polynomial). Model-fitting followed a two-stage iterative process. First, the number of groups was determined by modeling each trajectory group as a higher-order shape (i.e., cubic), then by comparing models with different numbers of groups, starting with one group (no separate trajectories). After the number of groups was determined, the models were run to determine the shape of each trajectory. Bayesian information criteria (BIC) was used to identify the most parsimonious, best fitting model, i.e., the model that has the best fit using the fewest number of trajectories.[26] To compare fits, Bayes factor was calculated, which is approximately two times the difference in BIC between two models ($2 \times$ [BIC more complex model – BIC simpler model]).[27] Bayes factor >2 suggests positive evidence to support meaningful change in BIC for a more complex model, with Bayes factor ≥10 providing very strong evidence.[27] In addition, it is suggested that any given model should comprise at least 1% of the total sample.[28] Because group-based trajectory modeling uses full information maximum likelihood estimation, patients with missing values were still included in the models.

The relationship between several preoperative factors and these trajectory groups were examined as our secondary analyses. Chi-square test or Fisher's Exact Test analysis was used for categorical preoperative factors, and one-way ANOVA was used for continuous preoperative factors. For parametric tests, normal quantile–quantile plots were used to evaluate normality assumption; if violated, a non-parametric Kruskal-Wallis test was used. Levene's test was used to evaluate equal variance assumptions, with Welch's correction employed if this assumption was violated. Factors were entered into a multivariable multinomial logistic regression with pain trajectory as outcome. Variable selection was based on univariate criteria of $P < 0.25$. Collinearity was assessed using variable inflation factor and univariate analyses between factors. Estimates are reported as odds ratios and 95%CIs. Internal validation was performed for our multivariable multinomial model using the bootstrapping approach (n = 500 samples) with the frequency with which variables were selected to the model estimated.[29] Additionally, bootstrapped CIs for odds ratios were calculated to compare to those from the original sample. $P < 0.05$ (two-tailed) was considered statistically significant; *P*-values for individual univariate analyses (n = 16 tests) were corrected with a false-discovery rate approach.[30]

The sample size was based on available data from patients participating in the current study (see "Study Participants"). No statistical power calculations were performed prior to this analysis.

Results

Patient Characteristics

There were n = 363 patients included in this sample (Figure 1). Table 1 summarizes patient preoperative other clinical measures. The average age of patients was nearly 60 years, with an even representation of men and women. Fourteen percent (51/362, 14%) of the sample was non-white and 4% (14/363) was Hispanic. Colorectal surgery was the most common surgical service, followed by thoracic/cardiovascular surgery and urologic surgery (Table 1).

Daily Pain and Group-Based Trajectory Analysis

For group-based trajectory analysis, n = 3 did not have enough postoperative pain data, with subsequent analyses having n = 360 patients (Figure 1). For this entire sample, average daily pain for the first day following surgery was moderate (5.1 ± 2.6), with a modest decrease across the 7 days following surgery (3.5 ± 2.4, figure 2). Missinginess at each time point (postoperative days 1–7) ranged from 6% to 18%. Ninety-one (91%, n = 326) had complete pain data for at least 5 postoperative days. Table 2 reports model fitting for group-based trajectory analysis. The best-fitting model included five trajectory groups, with a combination of linear and quadratic trajectory groups. Figure 3 graphically represents these trajectory groups with Figure 4 displaying individual plots for patients within each trajectory. Data and SAS code for trajectory analysis is presented in Supplemental Digital Content 1.

Nearly one-half of patients (167/360, 46%) was in the moderate-high pain group. One-quarter of patients (88/360, 24%) was in the moderate-low pain group. Seven percent (25/360) of patients was in the low pain group, while 16.9% (58/360) of patients was in the high pain group. There was also a group comprising 6% (22/360) of patients that had steep decreases in pain across the 7 days following surgery.

Table 3 shows patient characteristics by trajectory group, and Figure 4 depicts a mosaic plot between surgical service and trajectory groups. Below is summary of key demographic and clinical characteristics of each pain trajectory group:

High.—This was the youngest group (54 ± 12 years), and two-thirds of the patients were female. This group also had the largest proportion of Hispanics (4/58, 7%). Patients in this group were distributed relatively evenly across surgical services. These patients had higher opioid use across the 7-day postoperative period and greater opioid requirement intraoperatively.

Moderate-High.—Patients in this group had an average age of 58 ± 12 years, and over 50% (89/167) of the patients were female. Over 10% (20/167) of the patients in this group were Black and 4% (6/167) were Hispanic. Nearly one-third (46/167) of this group was in the colorectal service. This group also had higher need for opioids later in postoperative period.

Moderate-Low.—The average age of this group was 61 ± 13 years, and over one-half of the patients were male. Over 90% (81/88) of the patients in this group were white, and 5% (4/88) reported being Hispanic. Nearly all patients in this group were evenly distributed across four surgical services: colorectal, orthopedics, thoracic/cardiovascular, and urology.

Low.—Patients in this groups were the oldest (66 ± 13 years) compared to other pain trajectory groups. Men comprised three-quarters (19/25) of the patients in this group, and all patients reported that they were non-Hispanic. Nearly 40% (9/25) of the patients in this group were in the colorectal surgical service. The low pain group also had the lowest opioid requirement during the 7-day postoperative period.

Decreasing.—This group was similar to the low pain group, with an average age of 63 ± 10 years. Nearly 70% (15/22) of the patients in this group were male, and no one reported being Hispanic. Nearly one-third (6/22) of the patients in this group was in the urology service.

Trajectory groups were statistically significantly associated with age ($F_{(4,355)} = 6.02$, $P_{raw} < 0.001$; $P_{FDR} < 0.001$), sex ($\chi^2 = 17.6$, df = 4, $P_{raw} = 0.002$; $P_{FDR} = 0.005$), and postoperative opioid requirement ($\chi^2 = 57.8$, df = 4, P_{raw} & $P_{FDR} < 0.001$) (Table 3). After adjustment for multiple comparisons, the trajectory group was not statistically significantly associated with race, ethnicity, body mass index, intraoperative medications, preoperative block, or preoperative opioid use (Table 3). Association between service and pain trajectory group did not reach statistical significance ($\chi^2 = 16.0$, df = 12, $P_{raw} = 0.173$; $P_{FDR} = 0.308$, Figure 4). Similar results were found for surgical procedure ($\chi^2 = 14.6$, df = 16, $P_{raw} = 0.552$).

Pain Trajectory Groups and Preoperative Mental Health

Trajectory groups were statistically significantly associated with each preoperative mental health and behavior measure (Figure 5). Higher patient anxiety ($F_{(4,352)} = 13.7$, P_{raw} & $P_{FDR} < 0.001$), depression ($F_{(4,349)} = 8.9$, P_{raw} & $P_{FDR} < 0.001$), pain behaviors ($F_{(4,349)} = 9.3$, P_{raw} & $P_{FDR} < 0.001$), and pain catastrophizing ($F_{(4,342)} = 10.8$, P_{raw} & $P_{FDR} < 0.001$) were associated with trajectories with higher pain. Interestingly, for all measures, patients in the decreasing pain group had similar scores to patients in the low and moderate-low groups.

Multivariable Analyses

Variables entered into multinomial logistic regression were, age, sex, PROMIS anxiety, PROMIS pain behaviors, pain catastrophizing, service, and intraoperative oral morphine milligram equivalents. Additionally, while intraoperative ketamine and lidocaine did not reach the defined threshold for inclusion ($P < 0.25$), they were also included due to clinical relevance. For surgical service, spine and orthopedic were combined, pancreas, biliary, and transplant were combined, and colorectal and urology were combined. Low and decreasing pain trajectory were combined as reference group for multinomial logistic regression. No other variables were recoded for this analysis. Table 4 reports full results from analysis, with bootstrapped estimates and 95%CIs; Appendix 2 reports estimates from original analyses compared to bootstrapped estimates. From this analysis, age, sex, PROMIS Anxiety, and PROMIS Pain Behavior emerged as independent predictors of pain trajectory. Specifically, lower age (OR: 0.94, 95%CI: 0.91–0.99), female sex (OR: 6.4, 95%CI: 1.49–15.6), higher anxiety (OR: 1.08, 95%CI: 1.01–1.14), and more pain behaviors (OR: 1.10, 95%CI: 1.02–1.18) were related to increased likelihood of being in high pain trajectory. Table 4 also includes the frequency of which variables were selected for model in bootstrap analysis (n = 500 samples).

Discussion

This study used group-based trajectory analysis to identify five distinct pain trajectory groups in the first 7 days following surgery. Four trajectories identified patients with low, moderate-low, moderate-high, and high pain over time, with one trajectory identifying

patients with drastically decreasing postoperative pain. Women and younger patients were more likely to be in the stable moderate-high and high pain groups. Patients in the stable high group also had higher anxiety and depression and greater pain behaviors and pain catastrophizing preoperatively. Additionally, patients in the moderate-high and high pain groups had greater opioid requirements postoperatively.

In the regional anesthesiology literature, heuristics on approaches to perioperative pain control largely center on surgical procedure type. This is a logical first step in regional anesthetic decisions because many regional anesthetics are predicated on anatomical considerations related to surgery type, and certain surgeries tend to result in more acute postoperative pain.[31,32] However, once anatomical location is determined, anesthesiologists have numerous options regarding desired block kinetics, ranging from minutes to days, through local anesthetic selection, additives to local anesthetics, delayed-release local anesthetic formulations, and continuous catheter-based techniques.[9,10,33–35] To aid patients in selecting a kinetically rational approach to regional anesthesia for their procedure, anesthesiologists must first understand the anticipated postoperative acute pain trajectory.[9,11,12,19] Although procedure-based heuristics offer important information for population-based recommendations, consideration of patient sociodemographic, medical, and behavioral factors becomes necessary to enable personalized regional anesthetics that are optimized for the individual.[36–38] This is increasingly important in the design of randomized controlled trials given accumulating evidence on the lack of true randomization of patients with relevant features.[39,40]

Sociodemographic and behavioral factors have been strongly associated with acute postoperative pain intensity over the last few decades.[41,42] However, much of this early work on preoperative predictors of acute postoperative pain used pain intensity assessments on a single day after surgery or aggregates over the first few days after surgery.[43–45] Early work by Thomas *et al.* first posed outcomes directly related to postoperative pain changes over time, uncovering significant differences in the slopes of acute pain trajectories.[14,16] Althaus *et al.* extended this work to demonstrate that the parameter estimates for certain behavioral risk factors for acute postoperative pain could invert when the outcome of interest was the rate of recovery rather than initial pain intensity.[13] For instance, preoperative anxiety was associated with greater initial postoperative pain intensity but also a more rapid rate of resolution of acute postoperative pain. Recent work using growth mixture modeling in a mixed surgical cohort suggested three postoperative pain trajectories compared to the five identified here.[17] However, this analysis did not describe the patient or procedural characteristics of the patient pain trajectory groups.

One of the key contributions of this analysis is the relative impact of patient sociodemographic and behavioral factors over procedural factors in assigning patients to a postoperative pain trajectory group. Despite work by Gerbershagen *et al.*, which shows differences in acute postoperative pain intensity across a range of surgical procedures, procedure type was not a key determinant of trajectory group assignment in our results.[31,32] This is noteworthy given that our cohort included several procedure categories such as spine, thoracic, and orthopedic surgeries, commonly associated with high, prolonged acute postoperative pain.[31] This discrepancy also applied to regional anesthesia; while regional

anesthesia is robustly associated with decreased postoperative pain intensity in many surgical procedures, using a preoperative nerve block was not associated with trajectory group assignment. Preoperative nerve block was confounded with surgical service and could not be included in multivariable analysis. This discrepancy in regional anesthetics could be related to the fact that 76% of patients received some type of preoperative nerve block, thus minimizing potential variability across the groups. Similarly, we did not identify any difference in the use of ketamine or lidocaine between different trajectory groups. To be clear, our results do not suggest that surgical procedure type, regional anesthesia, or multimodal analgesia are not associated with greater or lesser postoperative pain, but rather that these factors were not key differentiators of trajectory group assignments for acute postoperative pain. Furthermore, given the availability of opioids for breakthrough pain and identification of differences in intraoperative and postoperative oral morphine milligram equivalents between trajectory groups, the effects of multimodal analgesics may be best borne out in weighted composite endpoints encompassing pain intensity, opioid reduction, and functional improvement.

Multivariable modeling showed that sex, anxiety, and pain behaviors were independently associated with group trajectory assignment. Female sex has previously shown a strong association with increased postoperative pain intensity across a variety of surgical procedures.[46–48] By contrast, despite the strong associations reported between catastrophizing and postoperative pain intensity, catastrophizing was not associated with group trajectory assignment.[23,49,50] A study in breast cancer surgery patients suggests that pain catastrophizing may be a full mediator between preoperative anxiety and acute postoperative pain assessed 48 hours after surgery.[51] This discrepancy in findings on catastrophizing may also be interpreted in a similar manner as surgical procedures, whereby trajectory distinction remains conceptually different than pain intensity itself. Additionally, our logistic regression considered each group in equipoise rather than in an ordinal fashion, given difficulties in quantifying the “worseness” of the different trajectories.

Our finding regarding the role of pain behaviors, as assessed using the Patient-Reported Outcomes Measurement Information System Pain Behavior item bank, was surprising in its ability to distinguish among the group trajectories in a multivariable model. Pain behaviors are those physical or verbal, voluntary or involuntary, external manifestations of pain assessed using self-report.[21] To the best of our knowledge, prior reports examining postoperative trajectories have not included pain behaviors alongside assessments of catastrophizing. One possible explanation for the lack of significance regarding catastrophizing in multivariable analysis could be that the information contained in the pain catastrophizing measure that is relevant to pain trajectory group assignment is better captured within the assessment of pain behavior. Further work is necessary to more fully explore the relationships between catastrophizing and pain behaviors in the surgical population.

In our analysis, group assignment was performed only using postoperative pain intensity time series data, with post hoc analysis of inter-group differences, rather than inclusion of patient and procedural factors in the group classification itself. This approach allowed us to focus on the postoperative pain experience of patients in a manner similar to a

clinical decision framework. Our analyses also examined a range of relationships including linear and polynomial functions. These polynomial functions proved illustrative given the nonlinear shapes of the stable low and decreasing categories. Notably, across all groups except the decreasing group, there was minimal to absent overlap in the CI of each postoperative day between each group. In total, this interpretation suggests face validity in addition to the Bayes Factor optimization steps.

Overall, our results contain many similarities to that of Gan *et al.*'s survey of postoperative pain experience.[1] In their survey of 146 patients who received an inpatient surgical procedure within the prior 14 months, 47% reported moderate pain, 20.2% severe pain, and 11.9% extreme pain following surgery. In comparison, our results had 46% in the moderate-high pain group and 16.9% in the sustained high pain group. Only 7% of patients in our cohort were in a sustained low pain group, which is less than the 20.9% of patients reporting only slight postoperative pain from Gan *et al.*, but similar to the 8.2% who did not report postoperative pain. Similar work by Buvanendran *et al.* examining pain intensity on the day of discharge following inpatient surgery found 12% of patients reported "severe to extreme" pain and 54% "moderate to extreme pain."[52] Notably, Gan *et al.* reported that 90% of surveyed patients reported being "somewhat" or "very" satisfied with their pain management. In our sample, 37% of patients still reported moderate to severe pain (pain rating 5–10) at discharge. While significant differences in methodologies make direct comparisons difficult and fail to consider related differences to functional outcomes and opioid requirements, our findings suggest a lack of overall progress in pain intensity reduction.

Our study had several limitations. Although our prospective study design permitted collection of extra-clinical variables such as preoperative behavioral factors and post-discharge pain assessments, this limited the number of subjects, constraining the number of factors considered for multivariable modeling. Additionally, we examined only acute postoperative pain intensity; thus, these results cannot yet inform extrapolations to pain beyond the first 7 days after surgery. Our selection of a multi-surgical cohort presented several tradeoffs. The overall goal was to examine both inter- and intra-procedural differences in postoperative pain trajectories; thus, capturing multiple surgical procedures permitted such comparisons across multiple patterns of tissue injury. However, within each type of surgery, there remains the potential for considerable heterogeneity as well. For instance, a "revision total hip arthroplasty" can yield blood losses ranging from less than hundreds of milliliters to multiple liters, depending on the clinical and procedural circumstances of the revision. Furthermore, although these results point toward methodologies that can enable kinetically rationale block selection to minimize postoperative opioid requirements for the duration of anticipated maximal pain intensities, we have yet to examine trajectories that incorporate pain interference with function, nor to test the responsiveness of trajectory group assignments to improvements in postoperative functioning and pain.

In conclusion, our results demonstrate the existence of at least five categories of acute postoperative pain trajectories defined predominantly by patient factors rather than type of surgery and intraoperative medications. Further work is necessary to better specify the

patient and analgesic requirements across these groups as well as to understand the role of such group assignments in the risk of persistent postsurgical pain.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of interest statement:

Patrick J. Tighe, M.D., M.S., is a Director at Large for the American Academy of Pain Medicine, serves on the editorial board for Pain Medicine, and is the PI of a federal grant (NIH 5R01GM114290) that funded the study. The other authors have no conflicts of interest to declare.

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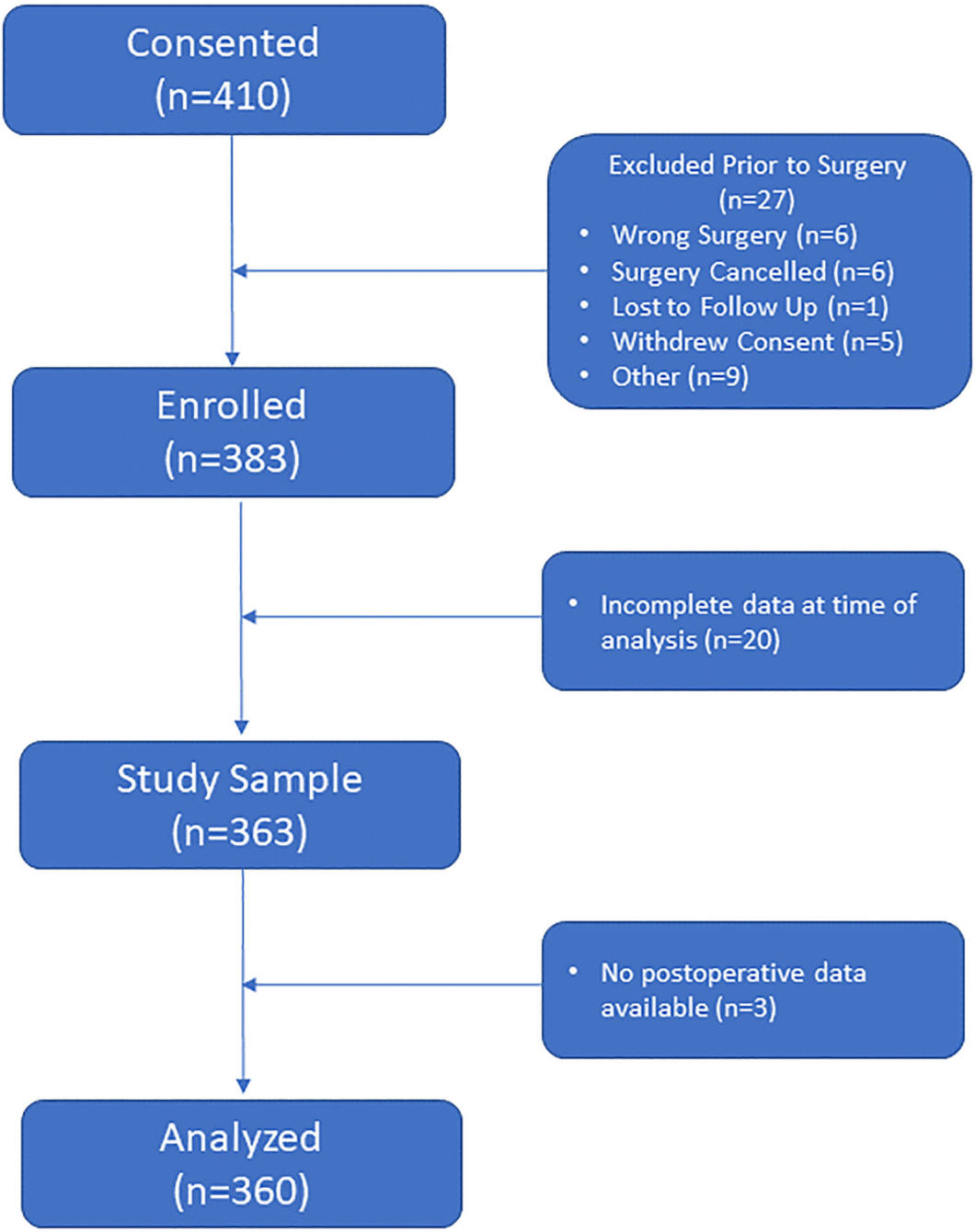

Fig. 1.
Study flow diagram for analytical sample.

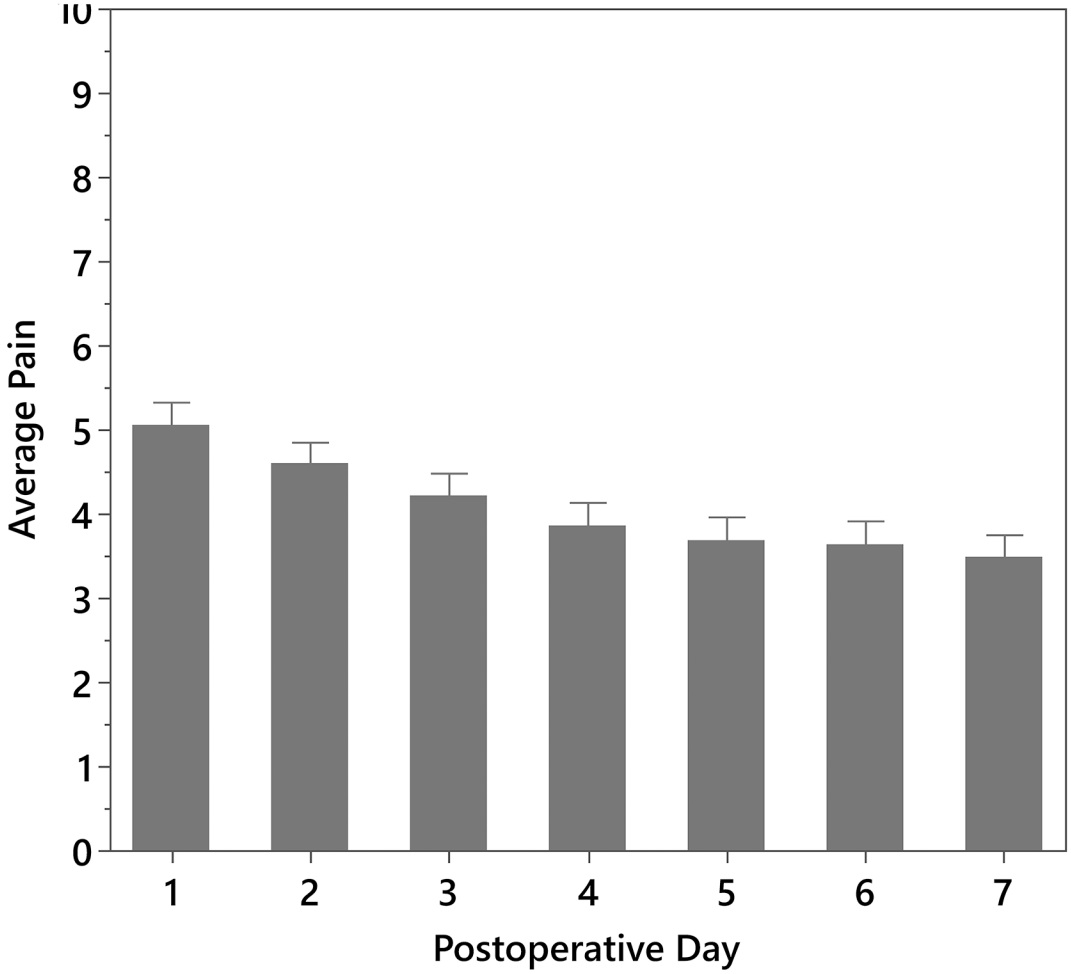

Fig. 2.

Average daily pain across first 7 days following surgery, with overall trajectory for entire sample. Error bars indicate 95%CIs.

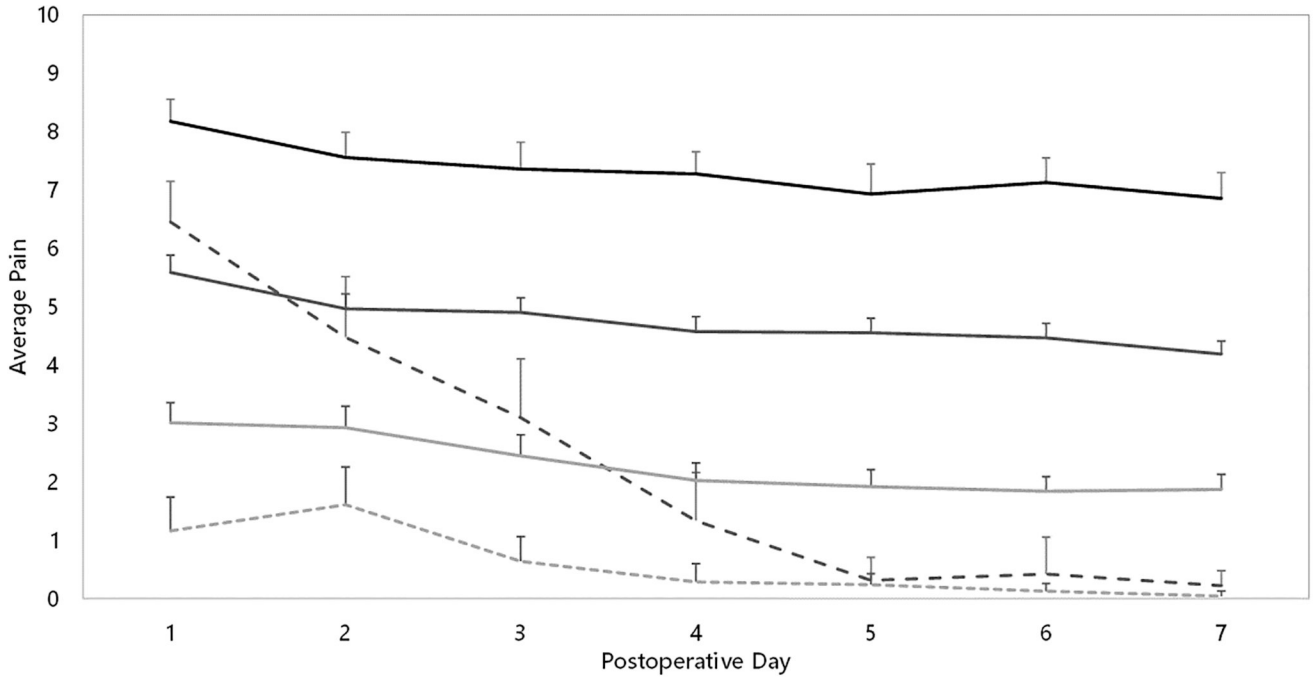

Fig. 3.
Group-based pain trajectories for first 7 days following surgery. Error bars indicate 95%CIs.

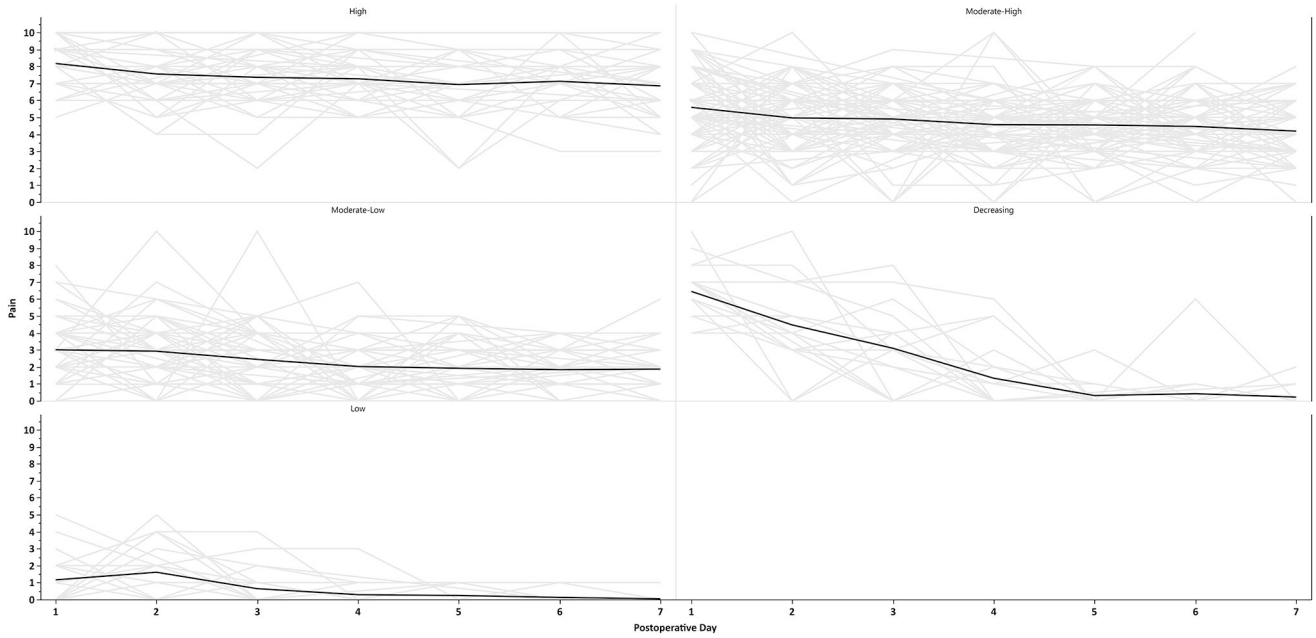

Fig. 4.
Spaghetti plots for individual trajectories within each pain trajectory group.

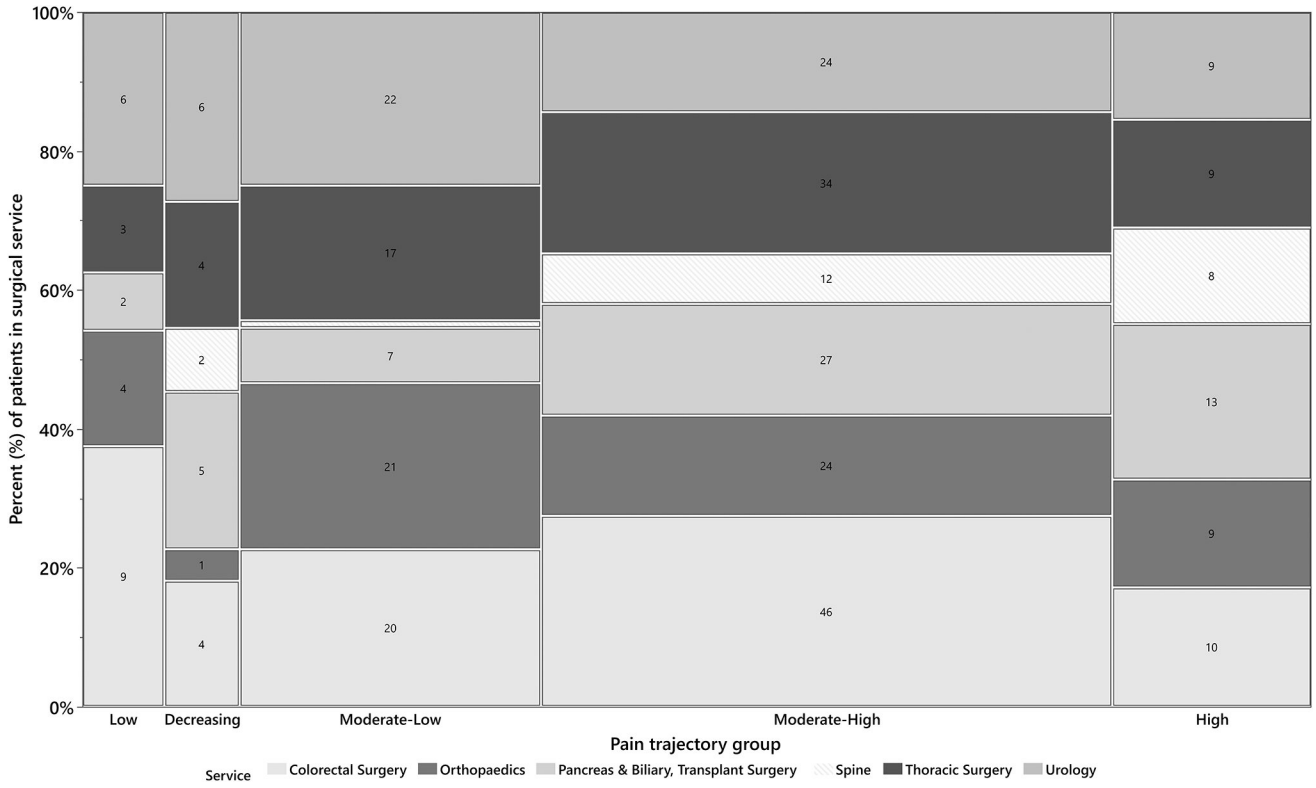

Fig. 5.

Mosaic plot for surgical service and pain trajectory groups, numbers in each cell are number of patients in that group. Vascular service (n = 1) was not included in this analysis.

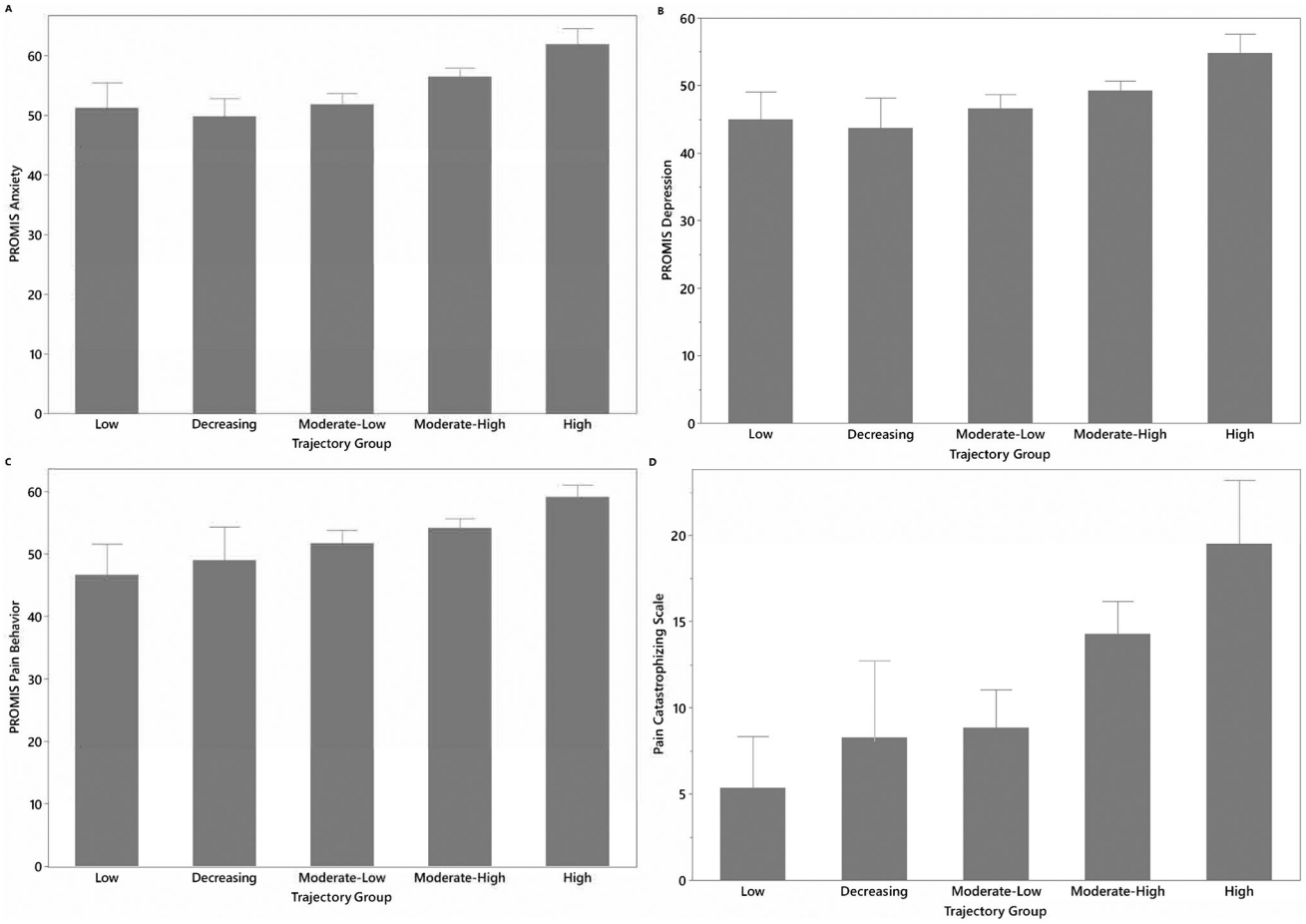

Fig. 6.

Mean score for Patient-Reported Outcomes Measurement Information System Anxiety (A), Depression (B), and Pain Behavior Scales (C), and Mean Pain Catastrophizing Scale score (D) across pain trajectory groups. Error bars indicate 95%CIs.

Table 1.

Patient Demographics

Patient Demographics	Summary (N=363)
Age, mean years ± SD	59 ± 13
Sex, n (%)	
M	181/363 (50%)
F	182/363 (50%)
Race, n (%)	
White	312/363 (86%)
Black	32/363 (9%)
Other	19/363 (5%)
Ethnicity, n (%)	
Hispanic	14/363 (4%)
Non-Hispanic	348/363 (96%)
Body mass index, mean ± SD	29.6 ± 6.6
Service, n (%)	
Colorectal surgery	90/363 (25%)
Neurosurgery	23/363 (6%)
Orthopaedics	60/363 (17%)
Pancreas and biliary surgery	44/363 (12%)
Thoracic cardiovascular surgery	67/363 (18%)
Transplant surgery	11/363 (3%)
Urology	67/363 (18%)
Vascular surgery	1/363 (.3%)
Preoperative block, n (%) yes	275/363 (76%)
Preoperative opioids, n (%) yes	
Total	72/160 (45%)
Hydrocodone	18/160 (12%)
Oxycodone	30/160 (19%)
Morphine	6/160 (4%)
Hydromorphone	5/160 (3%)
Tramadol	16/160 (10%)
Codeine	2/160 (1%)
Methadone	2/160 (.5%)
Fentanyl	1/160 (.6%)
Preoperative non-opioid analgesics, n (%) yes	
NSAIDs	28/160 (18%)
Acetaminophen	30160 (19%)
Gabapentinoids	9/160 (6%)
Intraoperative ketamine, n (%) yes	95/363 (26%)
Ketamine dose, mean mg ± SD	52.5 ± 41.8
Intraoperative lidocaine, n (%) yes	282/363 (78%)

Patient Demographics	Summary (N=363)
Lidocaine dose, mean mg ± SD	80.9 ± 31.8
Intravenous fentanyl (total), mean mg ± SD	0.23 ± 0.20
Intraoperative opioids, median oral morphine equivalents (interquartile range)	60.0 (70.5)
Total postoperative opioids, median oral morphine equivalents (interquartile range)	129.0 (175.5)

NSAIDs, non-steroidal ant-inflammatory drugs. Preoperative pain medication reporting was available in n = 160. Intraoperative doses only calculated in patients who received specified medication. For oral morphine milligram equivalents, median and interquartile range (quartile 3 – quartile 1) was used due to non-normality. Total postoperative opioids is the sum of recorded oral morphine equivalents across postoperative days 1 to 7. Note: many patients on multiple analgesics.

Table 2.

Trajectory Model Fitting

Model	Number of groups	Bayesian Information Criteria	Δ Bayesian Information Criteria	Bayes Factor (2×Δ Bayesian Information Criteria)
1	1 group	−5077.44	–	–
2	2 groups	−4659.35	418.09	836.18
3	3 groups	−4520.44	138.91	277.82
4	4 groups	−4480	40.44	80.88
5	**5 groups**	**−4467.75**	**12.25**	**24.5**
6	6 groups	−4468.14	−0.39	−0.78

Note: The order for all groups in above models were set to quartic to first determine number of groups. More complex models (i.e. more groups) were compared with previous, simpler models (# groups – 1) using difference in BIC. For the final model, the best fit was a 5-group model with three linear groups and two quadratic groups (Bayesian Information Criteria = −4440.04)

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Table 3.

Patient Demographics by Group

Patient Demographics	Low (n = 25)	Decreasing (n = 22)	Moderate-Low (n = 88)	Moderate-High (n = 167)	High (n = 58)	*P (raw)*	*P (False discovery rate)*
Age, mean years ± SD	66 ± 13	63 ± 10	61 ± 13	58 ± 12	54 ± 12	<0.001	<0.001
Sex, n (%)						0.002	0.005
M	19 (76%)	15 (68%)	49 (56%)	78 (47%)	20 (35%)		
F	6 (24%)	7 (32%)	39 (44%)	89 (53%)	38 (65%)		
Race, n (%)						0.584	0.755
White	21 (84%)	19 (86%)	81 (92%)	138 (83%)	50 (86%)		
Black	2 (8%)	2 (9%)	3 (3%)	20 (12%)	2 (9%)		
Other	2 (8%)	1 (5%)	4 (5%)	9 (5%)	3 (5%)		
Ethnicity, n (%)						0.648	0.755
Hispanic	0 (0%)	0 (0%)	4 (5%)	6 (4%)	4 (7%)		
Non-Hispanic	25 (100%)	22 (100%)	84 (95%)	161 (96%)	54 (93%)		
Body mass index, mean ± SD	28.2 ± 5.4	29.9 ± 6.2	29.2 ± 6.9	29.7 ± 6.4	30.1 ± 6.8	0.821	0.821
Preoperative nerve block, n (%)	20 (80%)	16 (73%)	70 (80%)	125 (75%)	41 (71%)	0.750	0.800
Preoperative opioids, (n=160), n (%)	1/4 (2%)	4/10 (6%)	13/35 (19%)	30/71 (44%)	21/39 (30%)	0.616	0.755
Intraoperative ketamine, n (%)	6 (24%)	4 (18%)	20 (23%)	47 (28%)	18 (31%)	0.661	0.755
Intraoperative lidocaine, n (%)	6 (24%)	4 (18%)	25 (28%)	33 (20%)	12 (21%)	0.596	0.755
Intraoperative opioids, median oral morphine equivalents (interquartile range)	55.0 (68.6)	63.5 (53.6)	45.0 (52.0)	65.0 (75.0)	78.0 (81.1)	0.047	0.094
Total postoperative opioids, median oral morphine equivalents (interquartile range)	60.0 (70.6)	68.8 (199.5)	73.5 (108.3)	136.3 (165.9)	249.5 (330.3)	<0.001	<0.001

Note: *P* (FDR) adjusted for multiple comparisons using false-discovery rate. Preoperative nerve block indicates a neuraxial or perineural catheter(s) were placed prior to surgery. Please see Appendix 1 for additional details on the use of regional anesthetics in this cohort. All denominators are n's listed in column labels unless otherwise noted. For oral morphine milligram equivalents, median and interquartile range (quartile 3 – quartile 1) are reported and Kruskal-Wallis test was used due to non-normality.

Table 4.

Results from Multinomial Logistic Regression (Estimates from Bootstrap Analysis, n = 500 samples)

Patient Demographics	Moderate-Low Bootstrapped Odds ratio (95%CIs)	Moderate-High Bootstrapped Odds ratio (95%CIs)	High Bootstrapped Odds ratio (95%CIs)	Frequency (%) of Variable Selection
Age (years)	0.97 (0.93−1.02)	0.96 (0.93−1.00)	**0.94 (0.91–0.99)**	71%
Sex (ref: male)				90%
Female	2.49 (0.91−6.3)	**3.52 (1.40−8.5)**	**6.4 (1.49–15.6)**	
Patient-Reported Outcomes Measurement Information System Anxiety	1.00 (0.95−1.04)	1.02 (0.98−1.08)	**1.08 (1.01–1.14)**	85%
Patient-Reported Outcomes Measurement Information System Pain Behavior	1.03 (0.98−1.09)	1.04 (0.99−1.08)	**1.10 (1.02–1.18)**	77%
Pain Catastrophizing Scale	1.00 (0.94−1.06)	1.03 (0.98−1.09)	1.01 (0.95–1.08)	18%
Intraoperative opioids (oral morphine equivalents)	1.00 (0.99−1.01)	1.00 (0.99−1.01)	1.01 (1.00–1.01)	50%
Intraoperative ketamine (mg)	0.99 (0.97−1.02)	1.01 (0.99−1.02)	1.00 (0.98–1.03)	13%
Intraoperative lidocaine (mg)	1.00 (0.99−1.01)	1.00 (0.99−1.01)	0.99 (0.98–1.01)	17%
Surgical Service (ref: colorectal and urology surgery)				75%
Orthopedics and spine	1.21 (0.318−4.3)	1.30 (0.316−4.8)	2.38 (0.46–8.7)	
Pancreas, biliary, and transplant	0.63 (0.171−4.9)	1.80 (0.56−8.7)	4.2 (0.91–21.0)	
Thoracic	1.55 (0.359−5.5)	2.38 (0.71−9.1)	1.96 (0.261–9.0)	

Note: Combined low/decreasing pain group was reference group for trajectory outcome. Odds ratios with 95%CI represent estimates following bootstrapping (n = 500 samples); Appendix 3 contains estimates from original analysis. Age, Patient-Reported Outcomes Measurement Information System Anxiety, Patient-Reported Outcomes Measurement Information System Pain Behaviors, Pain Catastrophizing Scale, intraoperative opioids, ketamine, and lidocaine were modeled as continuous measures, with odds ratios representing likelihood of group membership per unit increase in measure. Ref, reference value for categorical measures. Bolded parameters indicate odds ratios in which 95%CI does not include one.