Research Paper

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Clinically derived early postoperative pain trajectories differ by age, sex, and type of surgery

Patrick J. Tighe[a,*], Linda T. Le-Wendling[a], Ameet Patel[b], Baiming Zou[c], Roger B. Fillingim[d]

Abstract

The objective of this study was to determine the effects of age, sex, and type of surgery on postoperative pain trajectories derived in a clinical setting from pain assessments in the first 24 hours after surgery. This study is a retrospective cohort study using a large electronic medical records system to collect and analyze surgical case data. The sample population included adult patients undergoing nonambulatory nonobstetric surgery in a single institution over a 1-year period. Analyses of postoperative pain trajectories were performed using a linear mixed-effects model. Pain score observations (91,708) from 7293 patients were included in the statistical analysis. On average, the pain score decreased about 0.042 (95% confidence interval [CI]: −0.044 to −0.040) points on the numerical rating scale (NRS) per hour after surgery for the first 24 postoperative hours. The pain score reported by male patients was approximately 0.27 (95% CI: −0.380 to −0.168) NRS points lower than that reported by females. Pain scores significantly decreased over time in all age groups, with a slightly more rapid decrease for younger patients. Pain trajectories differed by anatomic location of surgery, ranging from −0.054 (95% CI: −0.062 to −0.046) NRS units per hour for integumentary and nervous surgery to −0.104 (95% CI: −0.110 to −0.098) NRS units per hour for digestive surgery, and a positive trajectory (0.02 [95% CI: 0.016 to 0.024] NRS units per hour) for musculoskeletal surgery. Our data support the important role of time after surgery in considering the influence of biopsychosocial and clinical factors on acute postoperative pain.

Keywords: Pain trajectory, Postoperative pain, Postoperative pain trajectory

1. Introduction

Acute postoperative pain occurs in 80% of patients, with 86% of these patients experiencing moderate to severe pain.[2] Given the approximately 234 million surgeries performed worldwide each year, acute postoperative pain is an important public health problem.[36] Acute postoperative pain is often quantified using single pain intensity scores.[8] The "snapshot" nature of this assessment method may limit its usefulness, both managing daily pain and in determining optimal pain regimens for patients at a more systematic level.[7,8,19,20,22,23] Accurately characterizing the postoperative pain course, by characterizing temporal trends in pain scores, is important given uncontrolled acute postoperative pain has been linked to persistent postsurgical pain afflicting between 10% and 50% of surgical patients.[24,27]

Pain trajectories have emerged as a novel way to characterize the postoperative pain experience.[9] Using linear models, patients have been categorized into 1 of 3 trajectories: those with negative slopes (pain decreases with time), flat trajectories, or positive slopes (pain increases with time). Indeed, certain pain trajectories have been linked to chronification of acute postoperative pain.[1] Previous work involving trajectory calculations has relied on daily averages of pain scores. However, such methodology fails to capture the daily fluctuations in pain with sufficient resolution to assist with clinical decision making.[15,26,29,32] The increasingly widespread availability of electronic medical record (EMR) systems creates the opportunity to collect very large numbers of clinical postoperative pain intensity assessments at multiple time points.[6] Using pain assessments obtained from routine postoperative nursing inquiries, the results can be compared with previously reported findings from more tightly controlled research settings to determine the potential for widespread clinical implementation of research findings, as well as to allow high-resolution analysis of how acute postoperative pain changes over time.

Previous work by our group has demonstrated that although early postoperative pain scores measured in the first and second hours after surgery correlate highly with each other, these pain scores correlate poorly with pain scores measured later in the recovery period on postoperative days 1 through 5.[34] The aim of this project was to determine the effects of age, sex, and type of surgery on postoperative pain trajectories derived from a large collection of clinical pain assessments in a mixed surgical population within the first 24 hours after surgery to examine this initial hinge point in the correlation of early vs late pain assessment. We first hypothesized that patients would generally have negative pain trajectories and that females would exhibit greater initial pain scores and less negative slopes in comparison with males, given prior data suggesting that female sex is associated with higher postoperative pain scores.[16] Next, we hypothesized that younger patients would exhibit higher initial pain scores and smaller negative slopes in comparison with older

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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patients given previous findings on pain perception and analgesic pharmacokinetics in older patients.[13] Our third hypothesis was that certain types of surgeries would be associated with pain trajectories with more positive slopes, given previous work demonstrating that spine and orthopedic procedures often result in significant postoperative.[18]

2. Methods

2.1. Study design

The Institutional Review Board (IRB-01) at the University of Florida approved this study. This study is a retrospective cohort study of surgical case data using a large EMR system that was designed to examine the roles of age, sex, and the type of surgical procedure on postoperative pain trajectory in an adult population undergoing a variety of surgical procedures. Results were reported in accordance with the STROBE criteria, a 22-point checklist of recommendations designed to guide researchers toward improved quality of reporting of observational studies in epidemiology (http://www.strobe-statement.org/fileadmin/Strobe/uploads/checklists/STROBE_checklist_v4_cohort.pdf).

2.2. Description of data

Surgical case data were obtained from the University of Florida's Integrated Data Repository. The Integrated Data Repository is a large database of validated fields obtained from EMR systems used for patient tracking, billing, surgery, and hospital documentation purposes. We chose patients who were aged 21 years or above undergoing nonambulatory surgery at UF Health at the University of Florida over a 1-year period beginning May of 2011. Surgical case exclusion criteria were obstetric surgery, as well as those patients who received multiple separate surgeries within the study period to avoid contamination of pain scores from the effects of surgeries preceding or after the case of interest.

All pain scores were documented by clinical staff using the numeric rating scale (NRS) on an 11-point system ranging from 0 to 10. Pain scores were entered using the Epic EMR system (Epic Systems Corporation, Verona, WI); this particular implementation provides education on the administration of the NRS query at the point of data entry to improve the veracity of collected data and constrains the options for data entry to avoid aberrant entries (eg, pain score of 77 instead of 7). Pain scores were generally recorded every 15 minutes within the recovery room, and then every 4 hours per nursing protocol, with a repeat query within 1 hour after administration of analgesic medications for breakthrough pain. When the clinical staff documented a pain score as "patient asleep," the pain score was converted to a missing value rather than 0/10 to account for the fact that some patients had received additional sedatives that may have facilitated sleep despite an otherwise large nociceptive load. All pain scores were recorded with a corresponding date/time stamp, as were the start and end times of the related surgical procedure. End of surgery times are defined in this system as the application of dressing over the surgical site after wound closure. For each pain score, the time in minutes after the end of surgery was calculated to enable a stable reference point from which to calculate pain trajectories. Pain scores were filtered to include only those obtained after the listed end-surgery time through 24 hours after the documented end of surgery. In this system, analgesic protocols were not adjusted for adults based on age or sex, and opioid therapies generally followed hospital-based protocols that were not surgery specific. The use of multimodal analgesics was surgeon dependent with the exception of regional anesthesia, which was used in the majority of orthopedic surgical patients. Pain scores were restricted to the first 24 hours after surgery to focus on early opportunities to modify the ensuing pain trajectories on postoperative days 2 through 7; this restriction had the salutary benefit of minimizing the effect of censuring within the mixed-model framework described below. Specific details on the type of anesthesia and analgesic medications were not available although patients within each type of surgery were generally cared for within specific analgesic frameworks that included or precluded the use of neuraxial, paraneuraxial, and perineural catheters and/or single-injection nerve blocks on the basis of the type of surgery.

Types of surgery were identified using current procedural terminology (CPT) codes published by the American Medical Association. Given the large number of CPT codes, surgeries were grouped into separate categories based on their anatomic location according to the first digits of the CPT code. For patients with multiple CPT codes, only the primary CPT code was used for definition of the type of surgery. The total number of CPT codes used to describe each surgery was included as an index of the complexity of the surgical procedure. Patient comorbidity was scored by first extracting up to 50 comorbid diagnoses as coded by the *International Classification of Disease 9, Clinical Modification* (*ICD-9-CM*) for each patient. The *ICD-9-CM* codes were then converted into a Charlson Comorbidity Score.[10] Sex was defined as male or female. Age was defined in separate models as a continuous variable.

Observations with missing pain scores or missing measurement time points for pain scores were removed from the analysis set. Additionally, anatomic types of surgery with less than 300 patients within the cohort were removed from the analysis set.

Table 1

Univariate Analysis of Study Sample

Variable	Category	Statistic, n (%)
Gender	Male	3740 (51.28)
	Female	3553 (48.72)
Anatomic type of surgery	Cardiovascular	993 (13.62)
	Digestive	1727 (23.68)
	Integumentary	582 (7.98)
	Musculoskeletal	1949 (26.72)
	Nervous	1150 (15.77)
	Pulmonary	281 (3.85)
	Urinary	611 (8.38)
BMI group	Morbidly obese	505 (6.92)
	Normal	1507 (20.66)
	Obese	1766 (24.22)
	Overweight	1664 (22.82)
	Underweight	1007 (13.81)
	Unknown	844 (11.57)
Age group	21-39	1266 (17.36)
	40-64	3469 (47.57)
	65-84	2378 (32.61)
	>85	180 (2.47)
No. of *ICD-9* comorbidity diagnoses	>20	596 (8.17)
	10-19	2444 (33.51)
	5-9	2523 (34.59)
	<5	1730 (23.72)
No. of CPT codes to describe surgery	>5	109 (1.49)
	3-5	1192 (16.34)
	<3	5992 (82.16)
Charlson comorbidity index	<3	6403 (87.80)
	3-6	858 (11.76)
	7-10	12 (0.16)
	Unknown	20 (0.27)

CPT, current procedural terminology; *ICD-9, International Classification of Disease 9.*

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2.3. Statistical analysis

Analyses of postoperative pain trajectories were performed using the following linear mixed-effects model framework. A mixed-effects model was used because of the multiple continuous NRS pain intensity ratings reported from each patient, where the pain intensity ratings reported within each patient are correlated. This approach allowed us to examine within-patient changes of pain scores rather than simply examining changes in pain scores across the aggregate sample. We used the following model:

$$Y_{ij} = \alpha_0 + \alpha_1 \times t_{ij} + \alpha_2 \bar{t}_i + X_{ij} \times \alpha + u_i + \varepsilon_{ij},$$

where Y_{ij} represents the pain score measured for subject i at the jth measurement. t_{ij} is the actual time (in the unit of hours) after the surgery for the pain score being measured for subject i at the jth measurement. $u_i \sim N(0,\sigma^2)$ is the unobserved random cluster effect due to subject i representing a source of variation and the heterogeneity for the pain score from the patient i, ie, each patient may have their specific feelings of the pain that follows a normal distribution with mean zero, which is a common assumption made in a traditional mixed-effects model that is used to describe the correlated responses.[25] X_{ij} are all other observed covariates listed in **Table 1**. $\varepsilon_{ij} \sim N(0,\sigma^2)$ is the random measurement error and $\bar{t}_i$ is the average time from end of surgery to NRS measurement (in the unit of hours) for subject i. This term is added to relax the independence assumption made in the traditional linear mixed-effects model that the random effects (eg, u_i) is independent of the fixed-effects covariates (eg, t_{ij} in this study). This assumption rarely holds in practice. Adding this term makes the traditional mixed-effects model (ie, the above model without $\bar{t}_i$) a special case that will allow one to obtain the consistent fixed-effects parameter estimates regardless of whether the independence assumption holds or not. Starting with a grand full model by including all the observed covariates listed in **Table 1**, a model selection process is conducted through a likelihood ratio test to obtain the optimal model deemed for the data. A residual Q-Q plot is obtained, and it follows the theoretical normal distribution reasonably well as shown in the supplementary materials.[14]

In addition to the consideration of the correlation among repeated measurements, our model relaxes the independence assumption between the random cluster effects and fixed-effects covariates by introducing the average time measured for each subject. This modeling scheme allows for the small and unequal spacing between repeated measurements, which are an expected feature of clinically acquired pain score observations. The need to include the extracted average time term per subject and/or cluster was tested through likelihood ratio statistics with a degree of freedom of 1.

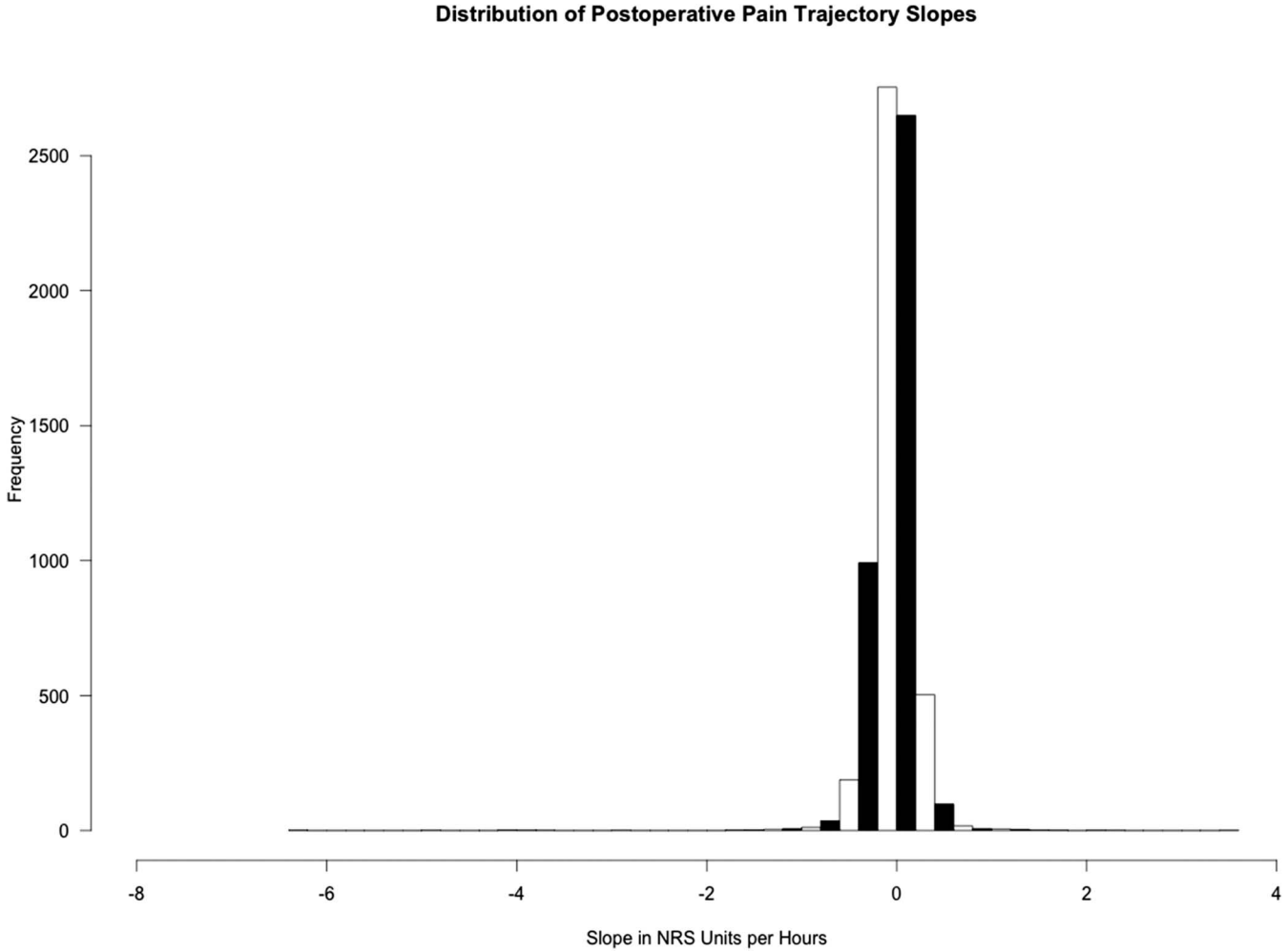


Figure 1. Distribution of postoperative pain trajectory slopes for cohort of analyzed surgical patients. The distribution of slopes ranged from −6.3 numerical rating scale (NRS) units per hour to 3.5 NRS units per hour, with a median of −0.023 NRS units per hour. Notably, of 7293 subjects, only 22 had an NRS trajectory slope of less than −1 NRS units per hour, and only 15 had an NRS trajectory slope of greater than 1 NRS units per hour.

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To investigate the association between the pain score and measurement time and other covariates, we used a linear mixed-effects model as mentioned before in which pain score was the outcome variable. We first fitted an oversaturated model (full model) that included time (t_{ij}), age, gender, average time ($\overline{t}_i$), Charlson comorbidity index, the total number of coded comorbidities, the total number of CPT codes, body mass index category, type of surgery by anatomic location, ie, all the observed covariates summarized in **Table 1**, and their mutual interactions, and the random cluster effects of the subject. We then used the log-likelihood ratio test to select the optimal model deemed for the data. The final selected optimal model included the following covariates: intercept, time (t_{ij}), age, gender, average time ($\overline{t}_i$), Charlson comorbidity index, total number of *ICD-9*-coded comorbidities, total number of CPT codes used to describe the surgical procedure, the anatomic type of surgery, and age and gender interaction. The need for average time term ($\overline{t}_i$) in the model was justified by a likelihood ratio test with a $P < 10^{-10}$.

Given the large number of observations considered, $P < 0.01$ was chosen for statistical significance. All analyses were conducted using the open source statistical analysis software R[33] with the lme4 package for the mixed-effects model fitting (http://cran.r-project.org/web/packages/lme4/lme4.pdf).

3. Results

3.1. Demographics

Raw data included 389,617 records with 8346 patients. However, after removing observations with missing pain scores or missing measurement time points for pain score and those surgical procedures with less than 300 cases per type of surgery, a linear mixed model of 91,708 pain score observations from 7293 patients was made. Patient ages ranged from a minimum

Table 2

Parameter estimates for age, sex, and time after surgery.

Variable	Estimate	Std Err	*P*
Intercept	10.263	1.561	$<10^{-10}$
t_{ij}	−0.042	0.001	$<10^{-10}$
Age_{ij}	−0.053	0.002	$<10^{-10}$
$Gender_i$ (male)	−0.274	0.054	$3.3 \times <10^{-7}$
t_i	−0.054	0.008	$<10^{-10}$
CCI group (vs 0)	1: −0.246	1: 0.069	1: 3.56×10^{-4}
	2: −0.299	2: 0.087	2: 6.26×10^{-4}
	3: −0.534	3: 0.122	3: 1.18×10^{-5}
	4: −0.317	4: 0.170	4: 0.062
	5: −0.429	5: 0.294	5: 0.145
	6: −1.018	6: 0.579	6: 0.079
	7: −1.466	7: 0.726	7: 0.043
	9: 0.472	9: 2.343	9: 0.840
Total CPT count (vs 1)	2: 0.300	2: 0.068	2: 9.69×10^{-6}
	3: 0.174	3: 0.089	3: 0.050
	4: 0.731	4: 0.145	4: 4.18×10^{-7}
	5: 0.753	5: 0.205	5: 2.38×10^{-4}
	6: 1.419	6: 0.264	6: 7.98×10^{-8}
	7: 1.397	7: 0.540	7: 0.010
	8: 0.781	8: 0.746	8: 0.295
	9: −0.006	9: 1.138	9: 0.996
	10: 0.387	10: 1.564	10: 0.805
Anatos (vs Cardiovascular)	Digestive: 0.472	Digestive: 0.096	Digestive: 9.97×10^{-7}
	Integumentary: 0.828	Integumentary: 0.124	Integumentary: 2.48×10^{-11}
	Musculoskeletal: 0.540	Musculoskeletal: 0.094	Musculoskeletal: 1.09×10^{-8}
	Nervous: 0.243	Nervous: 0.104	Nervous: 0.019
	Pulmonary: −0.155	Pulmonary: −0.156	Pulmonary: 0.320
	Urinary: 0.405	Urinary: 0.121	Urinary: 0.001

Anatos, Anatomic Type of Surgery; CCI, Charlson Comorbidity Index; CPT, current procedural terminology.

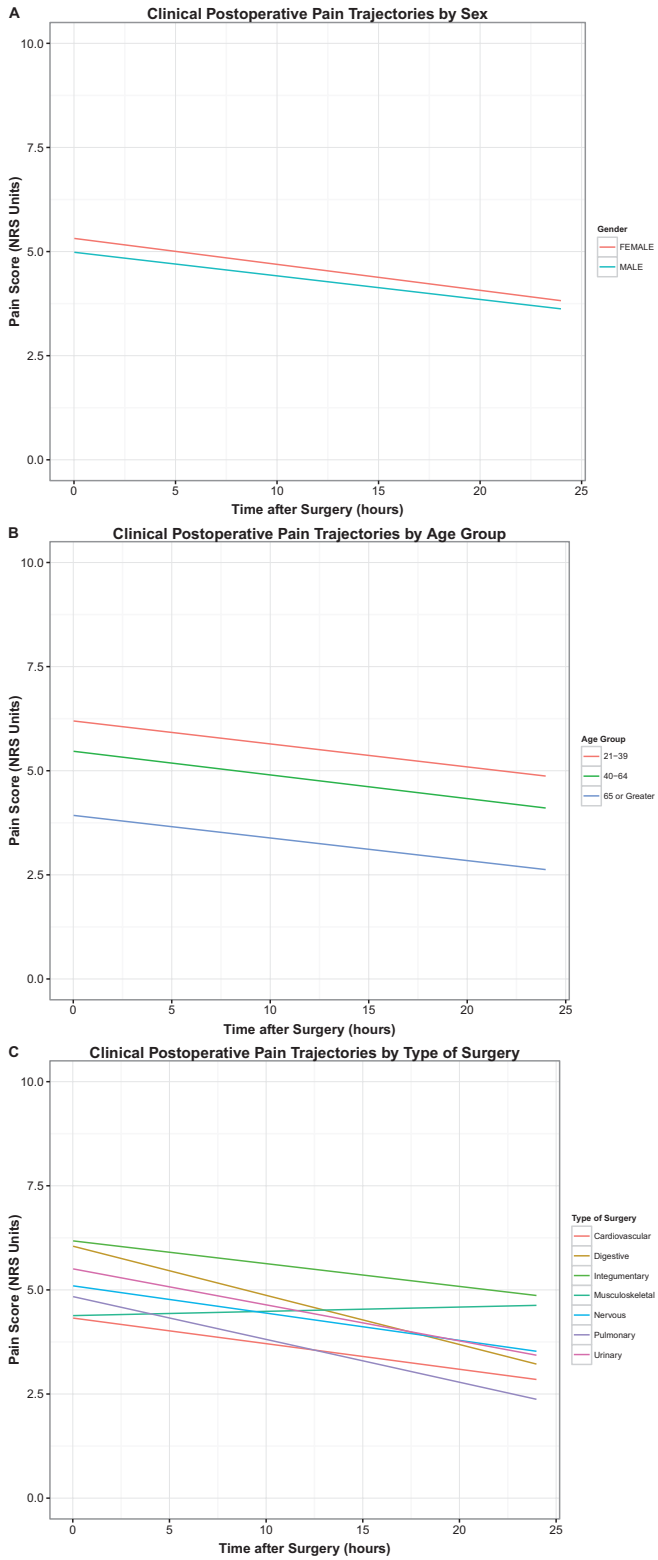


Figure 2. Overview of early postoperative pain trajectories by sex (A), age (B), and the type of surgery (C). Group comparisons within each stratification for sex, age, and type of surgery visually depict differences in the y-intercept and slopes of early postoperative pain trajectories measured from clinical pain assessments within the first 24 hours after surgery. NRS, Numerical Rating Scale.

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Table 3

Postoperative pain trajectories by sex.

Gender	Variable	Estimate	Std Err	*P*
Male	Intercept	10.089	2.185	3.9×10^{-6}
	t_{ij}	−0.041	0.002	$<10^{-10}$
	Age_{ij}	−0.056	0.003	$<10^{-10}$
	t_i	−0.031	0.012	7.9×10^{-3}
Female	Intercept	10.35	2.216	3.0×10^{-6}
	t_{ij}	−0.043	0.002	$<10^{-10}$
	Age_{ij}	−0.05	0.003	$<10^{-10}$
	t_i	−0.079	0.012	$<10^{-10}$

21 years to a maximum 97 years (mean ± SD, 56.4 ± 16.4 years). Because there were only 180 patients in the 85-year-and-greater age group, we combined groups 65 to 84 years and >85 years into ≥65 years (**Table 1**).

3.2. Trajectory model

The model for postoperative pain trajectory suggests that after controlling for other covariates at the same level, on average, the pain score decreased about 0.042 points on the NRS per hour (95% confidence interval [CI]: −0.044 to −0.040) after the surgery (**Fig. 1**). Similarly, after controlling for other covariates at the same level, including time after surgery, the pain score reported by male patients was approximately 0.27 NRS points (95% CI: −0.380 to −0.168) lower than that reported by females (**Table 2**). With every year increase in age, the initial pain score decreased by 0.053 NRS points (95% CI: −0.057 to −0.049) while controlling for other factors, including time after surgery at the same level (**Fig. 2**).

3.3. Stratification by sex

We conducted the same analysis using the same model without separation for male and female patients to better characterize the effects of sex on postoperative pain trajectories (**Table 3**). Our data reveal that for male and female surgical patients, the pain score decreased with time after surgery (−0.041 NRS points per hour [95% CI: −0.045 to −0.037] for male surgical patients [$P < 1 \times 10E - 10$]; −0.043 NRS points per hour [95% CI: −0.047 to −0.039] for female surgical patients [$P < 1 \times 10e - 10$]; **Figure 3**). Furthermore, for both male and female surgical patients, increases in age were associated with more negative postoperative pain trajectories (−0.056 NRS points [95% CI: −0.062 to −0.050] per year of age for males [$P < 1 \times 10E - 10$]; −0.05 NRS points [95% CI: −0.056 to −0.044] per year of age for females [$P < 1 \times 10E - 10$]). This reflects how the pain score will change per year of age increase, at exactly the same time point, within the sex stratification.

3.4. Stratification by age group

Similar to the approach of stratification by sex, we restratified the cohort according to the following age groups: 21 to 39 years, 40 to 64 years, and ≥65 years (**Table 4**). Pain scores significantly decreased over time in all age groups, with a slightly more rapid decrease for younger patients (pain trajectory slope of −0.046 NRS units per hour [95% CI: −0.052 to −0.040] in the 21-to-39-year age group, −0.042 [95% CI: −0.046 to −0.038] in the 40-to-64-year age group, and −0.041 [95% CI: −0.045 to −0.037] in the ≥65-year age group, $P < 1E - 10$ for each group; **Figure 4**). When the effect of sex was considered within each age group, male sex was associated with lower pain scores compared with female sex only in the ≥65-year age group (−0.459 NRS units in males vs females, $P = 4.8E - 7$). This effect was roughly equivalent to the same decrement seen 11 hours after surgery in this age group based on the parameter estimates of time vs gender.

3.5. Stratification by type of surgery

Similar to the approach of stratification by sex, we restratified the cohort according to the following types of surgery: cardiovascular, digestive, integumentary, musculoskeletal, nervous, pulmonary,

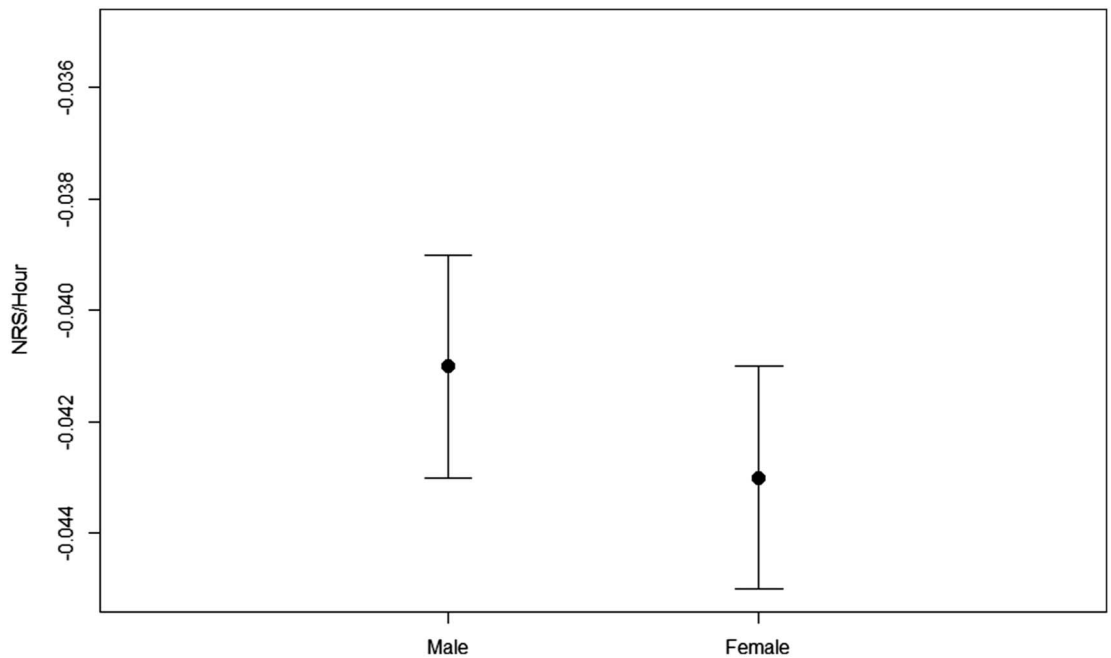


Figure 3. Differences in postoperative pain trajectory slopes for male and female patients. NRS/Hour = change in numerical rating scale units per hour after surgery. The mean and standard error are plotted for each group.

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Table 4

Postoperative pain trajectories by age group.

Age group	Variable	Estimate	Std Err	*P*
21-39	Intercept	8.174	2.086	8.9×10^{-5}
	t_{ij}	−0.046	0.003	$<10^{-10}$
	$Gender_i$ (male)	−0.143	0.121	0.236
	t_i	−0.028	0.021	0.17
40-64	Intercept	4.986	0.28	$<10^{-10}$
	t_{ij}	−0.042	0.002	$<10^{-10}$
	$Gender_i$ (male)	−0.185	0.08	0.021
	t_i	−0.062	0.012	6.3×10^{-7}
≥65	Intercept	6.69	2.16	2.0×10^{-3}
	t_{ij}	−0.041	0.002	$<10^{-10}$
	$Gender_i$ (male)	−0.459	0.091	4.8×10^{-7}
	t_i	−0.05	0.013	1.4×10^{-4}

and urinary (**Table 5**). The effect of time after surgery was significant for all types of surgery ($P < 1E-10$) and negative in slope ranging from −0.054 NRS units per hour (95% CI: −0.062 to −0.046) for integumentary and nervous surgery to −0.104 NRS units per hour (95% CI: −0.110 to −0.098) for digestive surgery. An important exception was musculoskeletal surgery, with a positive trajectory of 0.02 (95% CI: 0.016 to 0.024) units per hour (**Figure 5**). Although the effect of age, after controlling for postoperative pain trajectory, on postoperative pain scores was consistent across all types of surgery, the effects of sex were not. Male patients had statistically significant lower pain scores than female patients only for cardiovascular (−0.447 [95% CI: −0.725 to −0.169], $P = 1.6E-3$), digestive (−0.326 [95% CI: −0.549 to −0.103], $P = 4.4E-3$), and nervous (−0.357 [95% CI: −0.626 to −0.088], $P = 0.009$) types of surgery. There were no types of surgery for which male patients had greater postoperative pain scores than female patients.

4. Discussion

Our results confirm previous findings that postoperative pain had a generally negative trajectory with a wide variance. However, our findings differed from previous reports by suggesting that although the effects of age, sex, and type of surgery were generally associated with postoperative pain after controlling for the effect of time after surgery, the effects of sex were quite variable within certain stratifications for age group and type of surgery.

Our results suggest that the effect of sex on pain trajectories may be conditional depending on the age group and the type of surgery. In the whole-model analysis, male patients had a substantially more rapid decrease in postoperative pain compared with female patients, even after controlling for age, comorbidity status, type of surgery, and surgical complexity. These findings extend previous work on sex differences in static pain scores in both experimental and clinical settings.[4,16,21,31,35] However, in age-stratified analyses, the effect of sex on postoperative pain was significant only in those greater than or equal to 65 years of age. Likewise, when examining each type of surgery, the effect of sex on postoperative pain was negligible for integumentary, musculoskeletal, pulmonary, and urinary surgery. Such differences could conceivably point to an interaction between sex and type of surgery, which we were unable to explore despite the large number of observations available. Alternatively, it may be that for surgeries where the effect of sex was negligible, the procedures resulted in nociceptive levels sufficiently high to abolish the effect of sex.

Our results did point to a consistent effect of age on postoperative pain trajectories and postoperative pain at any given time point after surgery. In our whole-model analysis, each year of increasing age leads to lower postoperative pain scores after controlling for the effects of time after surgery, sex, comorbidity status, type of surgery, and surgical complexity. These effects were maintained when considering male and female patients separately. However, when examining each age group, younger patients in the 21-to-39-year age group had slightly more negative postoperative pain trajectories than patients in the 40-to-64 and ≥65-year categories. Examining the marginal mean estimate of NRS at time zero, these data

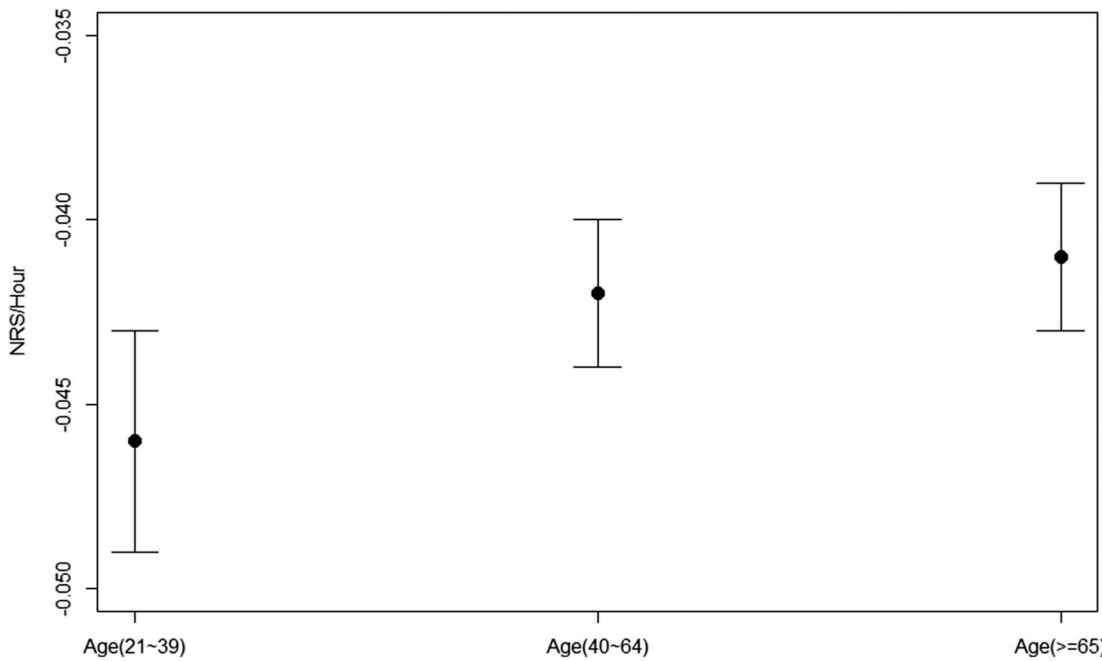


Figure 4. Differences in postoperative pain trajectory slopes by age group. NRS/Hour = change in numerical rating scale units per hour after surgery. The mean and standard error are plotted for each group.

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Table 5

Postoperative pain trajectories by type of surgery.

Type of survey	Variable	Estimate	Lower 95% CI	Upper 95% CI	*P*
Cardiovascular	Intercept	10.742	6.71028	14.77372	1.8×10^{-7}
	t_{ij}	−0.055	−0.06088	−0.04912	$<10^{-10}$
	Age_{ij}	−0.054	−0.0638	−0.0442	$<10^{-10}$
	$Gender_i$ (male)	−0.447	−0.72532	−0.16868	1.6×10^{-3}
	t_i	0.007	−0.02632	0.04032	0.702
Digestive	Intercept	10.825	6.40324	15.24676	1.6×10^{-6}
	t_{ij}	−0.104	−0.10988	−0.09812	$<10^{-10}$
	Age_{ij}	−0.052	−0.05984	−0.04416	$<10^{-10}$
	$Gender_i$ (male)	−0.326	−0.54944	−0.10256	4.4×10^{-3}
	t_i	−0.022	−0.05532	0.01132	0.196
Integumentary	Intercept	6.827	5.4844	8.1696	$<10^{-10}$
	t_{ij}	−0.054	−0.06184	−0.04616	$<10^{-10}$
	Age_{ij}	−0.041	−0.05276	−0.02924	$<10^{-10}$
	$Gender_i$ (male)	−0.104	−0.45484	0.24684	0.561
	t_i	0.005	−0.05772	0.06772	0.871
Musculoskeletal	Intercept	7.173	6.44976	7.89624	$<10^{-10}$
	t_{ij}	0.02	0.01608	0.02392	$<10^{-10}$
	Age_{ij}	−0.061	−0.06688	−0.05512	$<10^{-10}$
	$Gender_i$ (male)	−0.187	−0.39084	0.01684	0.071
	t_i	−0.072	−0.10924	−0.03476	1.5×10^{-4}
Nervous	Intercept	7.658	6.79168	8.52432	$<10^{-10}$
	t_{ij}	−0.054	−0.05988	−0.04812	$<10^{-10}$
	Age_{ij}	−0.046	−0.0558	−0.0362	$<10^{-10}$
	$Gender_i$ (male)	−0.357	−0.62552	−0.08848	0.009
	t_i	−0.058	−0.10504	−0.01096	0.015
Pulmonary	Intercept	8.201	6.31548	10.08652	$<10^{-10}$
	t_{ij}	−0.094	−0.10576	−0.08224	$<10^{-10}$
	Age_{ij}	−0.049	−0.06664	−0.03136	3.3×10^{-8}
	$Gender_i$ (male)	0.347	−0.18416	0.87816	0.2
	t_i	0.009	−0.06156	0.07956	0.791
Urinary	Intercept	9.223	8.29396	10.15204	$<10^{-10}$
	t_{ij}	−0.062	−0.0718	−0.0522	$<10^{-10}$
	Age_{ij}	−0.058	−0.06976	−0.04624	$<10^{-10}$
	$Gender_i$ (male)	−0.127	−0.47196	0.21796	0.469
	t_i	−0.074	−0.12888	−0.01912	0.008

suggest that older patients may start with a lower postoperative pain score but that their postoperative pain resolves at a slower rate. This finding may help explain the conflicting data on the effect of age on postoperative pain.[3,5,17,28,30]

No association emerged between comorbidity and surgical complexity on postoperative pain trajectories, although specific comorbidities may have different effects on postoperative pain. An obvious example would be the presence of chronic pain conditions requiring the use of high-dose systemic opioids before surgery that would increase the likelihood of persistent post-surgical pain. It is quite possible that more specific targeted measures of both pain-related comorbidities and surgical complexity would have offered improved insight into the role of these factors in postoperative pain trajectories by teasing out specific mechanistic attributes that were not diluted by a plethora of other comorbidity and complexity attributes that do not alter pain trajectories. Altogether, these results suggest the need to consider additional clinical and biopsychosocial factors, in a more targeted fashion, that are not routinely captured by the EMR.

Information on postoperative pain trajectories may offer a wealth of support in the clinical decision-making process. For instance, early postoperative trajectories that are nonnegative may point to opportunities to use extended-release/long-acting formulations of opioid and nonopioid analgesics. Additionally, anesthesiologists may wish to include perioperative regional anesthetics, especially considering those options that include longer-acting local anesthetics and/or continuous catheter-based interventions. Patients in the highest risk categories for postoperative pain trajectories can have earlier disposition arrangements to rehabilitation centers rather than home care environments to assist with continued optimization of pain management and functional status in a supervised environment.

The use of pain trajectories to describe postoperative pain is an emerging and innovative way to characterize acute postoperative pain.[1,9] Chapman et al. introduced the use of postoperative pain trajectories with a prospective observational approach using initial pain intensity (intercept) and rate of pain resolution (slope) to describe the course of pain over a period of 6 days. Patients provided daily reports of pain, and once discharged, provided pain scores at their convenience. Using completed NRS data for 502 patients, these authors noted a similar effect of age and gender on pain trajectories as in our study. Their surgical cases were categorized by the surgical site instead of organ system, and they noted that chest surgery resulted in the highest initial pain intensity with the quickest decline in pain intensity over time. In our study, surgery of the digestive system resulted in the steepest decline in pain. An additional difference included the issue of preexisting chronic pain; patients with a history of treatment for chronic pain were excluded from the report of Chapman et al., whereas no such exclusion occurred in our

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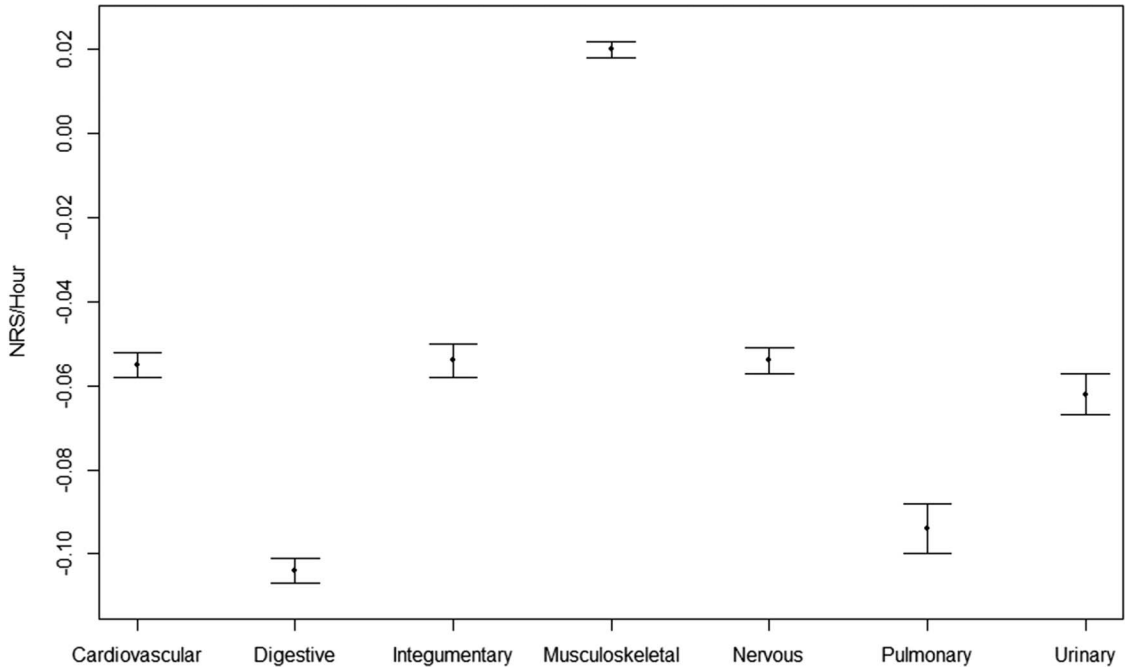


Figure 5. Differences in postoperative pain trajectory by type of surgery. NRS/Hour = change in numerical rating scale units per hour after surgery. The mean and standard error are plotted for each group.

study. The presence of chronic pain may influence pain scores and trajectories in that these patients may have lower thresholds for pain perception, increased tolerance to opioids, and opioid-induced hyperalgesia, all of which would result in higher initial pain scores and pain trajectories with positive slopes or less negative slopes.[11,12] This will need to be examined in greater detail in future studies because our current model did not include information on home opioid use and/or histories of chronic pain.

Work by Althaus et al. emphasized the use of acute pain trajectories in identifying patients at risk for chronic postsurgical surgical pain (CPSP) at 6 months, noting that higher initial pain intensity and slower resolution of acute pain were predictors for CPSP. The authors noted that patients with anxiety had higher initial pain scores and steeper declines in pain, whereas patients with depression had slightly lower initial pain scores with slower declines in pain. Neither anxiety nor depression was associated with CPSP at 6 months. The works of Chapman et al. and Althaus et al. highlight the important role that time plays in predicting postoperative pain and how time can modulate the role of other important predictive factors.

Our study differed in many ways from the studies by Chapman et al. and Althaus et al. Our sample size was significantly greater than either study, by an order of magnitude, through our use of a large clinical data repository. In addition, values for pain were clinically derived by routine nursing care at our institution; therefore, NRS data included a time stamp that allowed for accurate collection of pain scores as a function of time with the hours as the unit of measurement. In addition, our study examined the potential effects of the Charlson comorbidity index, a measure of comorbidity, as well as the relative complexity of surgery on postoperative pain trajectories.[10] Our results offered a high-resolution analysis of how postoperative pain scores change within the earliest postoperative time epochs.

Although data gathered prospectively in the context of a clinical research protocol may allow more accuracy in data collection, such a resource-intensive approach can limit sample size and clinical generalizability of findings. However, clinical data may be inaccurate based on the heterogeneity of backgrounds of medical providers who are performing the pain assessments and the patients' understanding of the NRS scale. These additional sources of variability in existing clinical data point to a growing need to reconcile clinical observations with experimental findings on a more robust scale. Nevertheless, applied analytics for quality improvement will inevitably rely on clinical data rather than experimentally derived data, and the gap between clinical data as opposed to experimentally derived data will need to be bridged in future research.

The limitations of our study include the shortened time frame of data acquisition, which is limited by the date of initiation of our electronic record system. Despite this, we were able to collect data at a higher resolution than in previous studies. However, there were an insufficient number of patients to allow assessment of more specific surgery types and to better delineate postoperative pain trajectories in the greatest age groups. In addition, our mixed model fails to fully capture differences due to pain assessments at irregular intervals, and it is possible that more advanced modeling methods, including Markov models and dynamic time warping, could offer additional insights into the observed time–domain variance. Our data set did not include sufficient information on the dose, timing, and route of administration of perioperative analgesics, thus this information was not included in our analyses. This is an important limitation that will need to be investigated in greater detail with more complicated and dedicated analyses given that pain intensity ratings and analgesic medications have alternating causal relationships over multiple windows of time.

In conclusion, our data support the important role that time plays after surgery in considering the influence of biopsychosocial and clinical factors on acute postoperative pain. Future work is necessary to determine how these very early differences in postoperative pain trajectories lead to the resolution of acute postoperative pain beyond postoperative day 1. Furthermore, much work is necessary to examine the agreement between

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clinically and experimentally derived measures of postoperative pain trajectories.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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