Distinguishing problematic from nonproblematic postsurgical pain: a pain trajectory analysis after total knee arthroplasty

M. Gabrielle Pagé[a,b], Joel Katz[a,b], E. Manolo Romero Escobar[b], Noga Lutzky-Cohen[a,b], Kathryn Curtis[a,b], Samantha Fuss[a,b], Hance A. Clarke[a,*]

Abstract

The goal of this study was to follow a cohort of patients undergoing total knee arthroplasty over time to: (1) identify and describe the various pain trajectories beginning preoperatively and for up to 12 months after surgery, (2) identify baseline predictors of trajectory group membership, and (3) identify trajectory groups associated with poor psychosocial outcomes 12 months after surgery. One hundred seventy-three participants (female = 85 [49%]; mean age [years] = 62.9, SD = 6.8) completed pain and psychological questionnaires and functional performance tests preoperatively and 4 days, 6 weeks, and 3 and 12 months after total knee arthroplasty. Using growth mixture modeling, results showed that a 4-group model, with a quadratic slope and baseline pain data predicting trajectory group membership, best fit the data (Akaike information criterion = 2772.27). The first 3 pain trajectories represent various rates of recovery ending with relatively low levels of pain 12 months after surgery. Group 4, the constant high pain group, comprises patients who have a neutral or positive pain slope and do not show improvement in their pain experience over the first year after surgery. This model suggests that preoperative pain levels are predictive of pain trajectory group membership and moderate preoperative pain, as opposed to low or high pain, is a risk factor for a neutral or positive pain trajectory postoperatively. Consistent with previous studies, these results show that postoperative pain is not a homogeneous condition and point to the importance of examining intraindividual pain fluctuations as they relate to pain interventions and prevention strategies.

Keywords: Acute pain, Chronic postsurgical pain, Pain trajectories, Total knee arthroplasty

1. Background

Chronic postsurgical pain (CPSP) is a prevalent pain condition that affects between 1.5% and 10% of adults one year after undergoing surgery.[30] Chronic postsurgical pain is typically defined as persistent pain that continues for longer than 2 months after surgery and cannot be attributed to a preexisting pain condition or causes other than surgery.[39] A significant proportion of patients, however, undergo surgery with one of the goals being a reduction in their preexisting pain. Total knee arthroplasty (TKA) is one such example. Total knee arthroplasty is a surgical procedure that is often preceded by moderate to severe pain, which has a significant impact on rehabilitation and hospital discharge. A large proportion of patients continue to experience pain after TKA.[11]

Acute postoperative pain is one of the most consistent predictors of the development of CPSP or continuation of the pain experience.[28,29,31,48] However, not all patients with moderate/severe acute postoperative pain will develop CPSP. Examining risk factors (eg, single pain intensity score) without considering rates of postoperative pain resolution limits the effectiveness of prevention and treatment approaches.[14] In addition, the development of chronic pain is a dynamic process in which the progression from acute to chronic pain is as important as the maintenance of chronic pain.[28] Examining pain as it evolves over time (ie, along a time continuum) as opposed to at discrete time points will contribute to identifying broader causal and associative risk factors that are involved in the development and maintenance of chronic pain.[28,36]

The examination of pain trajectories not only improves detection of problematic pain outcomes but also improves precision of pain measurement.[14] This approach can provide valuable information to help identify patients whose postoperative pain follows a favorable path to recovery vs patients whose pain remains stable or worsens and eventually transitions into CPSP.[15,55]

Chapman et al.[14] examined individual pain trajectories in the first 6 days after surgery and found 3 distinct patient groups: negative pain slope, stable pain slope, and increased pain slope.[14] Similar results were obtained in a sample of adults undergoing cardiac surgery.[16] Another study of pain trajectories of liver donor patients showed that patients who developed CPSP had higher pain intensity trajectories in the first 24 hours after surgery or an abnormal resolution of their acute pain.[10]

The goals of this study were to: (1) identify and describe the various pain trajectories beginning preoperatively and for up to 12 months after surgery, (2) identify baseline predictors of trajectory group membership, and (3) identify trajectory groups

that are associated with poor psychosocial outcomes 12 months after surgery in a cohort of patients undergoing TKA.

The prevalence rate of TKAs varies between 8.6 (Romania) and 213.3 (United States) per 100,000 population,[34] with an average hospital length stays of 7.7 days.[38] Osteoarthritis, the primary reason for TKA, is associated with mobility difficulties.[22,25] As such, this study will examine the presence of CPSP after TKA and functional outcomes.

2. Methods

2.1. Participants

Adults between the ages of 18 and 75 years with an American Society of Anesthesiology physical status I to III and scheduled to undergo unilateral TKA were eligible to participate in this study. Patients were excluded from this study if they had a history of drug or alcohol abuse, had a known allergy to medications being used in this study, had chronic pain on slow-release preparations of opioid, had rheumatoid arthritis, had a history of psychiatric disorders, were unable to use patient-controlled analgesia, were diabetic or had impaired renal function, or had a body mass index greater than 40. Patients were excluded postoperatively if they had additional operative procedures requiring modification of the usual rehabilitation standard of care.

2.2. Questionnaires

2.2.1. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC LK3.1)

The WOMAC is a 24-item Likert scale that assesses the extent to which patients with knee and/or hip osteoarthritis experience pain, stiffness, and physical functional impairment.[3,4] The WOMAC comprises 3 subscales, namely pain (5 items), stiffness (2 items), and physical function (17 items). For each item, patients are asked to rate the extent to which they experience pain, stiffness, and physical limitations on a scale ranging from 0 (none) to 4 (extreme). Total scores range from 0 to 20 for the pain subscale, 0 to 8 for the stiffness subscale, and 0 to 68 for the physical function subscale with higher scores indicating worse pain, stiffness, and physical limitations. The WOMAC subscales have very good internal consistency (α = 0.86-0.95),[5] adequate test–retest reliability (intra-class correlation coefficient = 0.74-0.95),[21,52] good sensitivity and responsiveness to change over time,[12,40,59] and adequate face,[4] construct,[9,12,53] and criterion[9,13,51] validity. The WOMAC subscale has adequate reliability (α = 0.84) to measure pain related to physical functioning and correlates moderately with the visual analog scale.[24]

2.2.2. Lower Extremity Functional Scale

The Lower Extremity Functional Scale is a 20-item Likert scale that assesses a patient's difficulties to perform everyday tasks because of his or her knee problem.[6] For each item, patients are asked to rate the extent to which they are having difficulties performing the tasks using a scale from 0 (extreme difficulty or unable to perform activity) to 4 (no difficulty). Total scores range from 0 to 80 with lower scores indicating greater lower extremity impairment. The Lower Extremity Functional Scale has good test–retest reliability (r = 0.94), sensitivity to change, and adequate convergent and discriminant validity.[6,60]

2.2.3. Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale (HADS) is a 14-item Likert scale that assesses an individual's levels of depression (7-item subscale) and anxiety (7-item subscale) in nonpsychiatric hospital patients (physical symptoms of anxiety and disorders, such as fatigue, dizziness, and insomnia, are excluded).[61] For each item, patients are asked to check the answer that most closely describes how they have been feeling in the past week on a scale from 0 to 3. Total scores for each subscale range from 0 to 21 with higher scores indicating higher levels of anxiety or depression. The internal consistency of the depression (α = 0.67-0.90) and anxiety (α = 0.68-0.93) subscales of the HADS is adequate.[7] The HADS also has good discriminant and convergent validity as well as specificity and sensitivity in detecting clinically significant levels of depression and anxiety.[7]

2.2.4. Pain Disability Index

The Pain Disability Index (PDI) is a 7-item scale that measures the extent to which pain is interfering with everyday tasks (family and home responsibilities, recreation, social activity, occupation, sexual behavior, self-care, and life-support activity).[49] Patients answer each item on a scale from 0 (no disability) to 10 (worst disability) with total scores ranging from 0 to 70, higher scores indicating higher levels of pain-related disability. The Pain Disability Index has adequate internal consistency (α = 0.86), fair test–retest reliability (r = 0.44), and adequate concurrent validity.[17,49,56,57]

2.3. Functional outcomes

The timed get up and go test (TUG), 6-minute walk test, and the stair test were used to evaluate functional performance. These measures have shown to have adequate reliability and sensitivity to change over time in an arthroplasty population.[33]

2.3.1. Timed get up and go test

Patients are asked to rise from a standard arm chair, walk at a safe and comfortable pace for 3 m, and then return to a sitting position in the chair.[23,45] Length of time to complete the test, use of armrest to get up and sit down, and pain intensity at the site of surgery were recorded.

2.3.2. Six-minute walk test

Patients are asked to walk to cover as much distance as possible during 6 minutes, with the possibility to stop and rest as needed during the test.[8,35,47] Standardized encouragement is offered every 60 seconds as research has shown that encouragement improves performance.[26] Total distance walked, test completion, and pain intensity at the site of surgery were recorded.

2.3.3. Stair test

Patients are asked to ascend and descend 1 flight of 9 stairs in their usual manner, at a safe and comfortable pace.[32,58] Test completion, length of time to complete the test, aids used (crutches, cane, railing), ascending and descending pattern, and pain intensity at the site of surgery were recorded.

2.3.4. Knee range motion

Active assisted knee flexion and active knee extensions were recorded. As soon as the measurement of knee flexion is complete, patients are asked to rate the intensity of their pain. Knee range motion has been shown to have good reliability among patients with knee osteoarthritis.[33]

2.4. Procedure

The study was approved by the Research Ethics Board of the Sunnybrook Hospital Health Sciences Center. Eligible participants were recruited from the preassessment clinic or the preoperative rehabilitation education session and provided written and informed consent. Data from the first 3 months of this analysis were part of a randomized controlled trial[18] examining the effect of perioperative gabapentin use on rehabilitation outcomes, functional status, and evoked pain. A separate Research Ethics Board (REB) submission was approved by the REB to gather postoperative pain data from these participants 1 year after surgery. Preoperatively, participants received either 400 mg of celecoxib and 600 mg of gabapentin or 400 mg of celecoxib and a placebo. Postoperatively, all participants, regardless of treatment group, received a standard postoperative regimen of celecoxib 200 mg b.i.d. for 3 days and were given intravenous patient-controlled analgesia with morphine for the first 24 hours. Participants also received either placebo or gabapentin 200 mg t.i.d. as per randomization starting 8 hours after the preoperative dose and continuing for 4 days. Participants completed a series of questionnaires and functional performance measures preoperatively and postoperatively on days 1 to 4, and at 6 weeks and 3 months. One year after surgery, patients were contacted and the full series of questionnaires was completed over the phone. Physical function data were not collected at this point. Details and time of administration of questionnaires and functional performance tests performed are shown in **Table 1**.

2.5. Data analysis

2.5.1. Pain trajectories

Pain trajectory analyses were performed using growth mixture modeling (GMM).[2,42,43] Growth mixture modeling is a longitudinal analysis methodology in which a latent membership to discrete trajectories is estimated. Mixture refers to the use of categorical (discrete) and continuous variables, either as observed or latent. Growth mixture modeling allows for individual variation within trajectory groups, which is defined as random effects as in longitudinal data analysis with continuous variables. Mplus (Version 7, Muthen & Muthen, Los Angeles, CA)[44] was used to test several models in which number of groups and model structure were evaluated empirically. Scores on the pain subscale of the WOMAC collected at a total of 5 time points were used to estimate pain trajectories. The 2 main aspects that varied across models were the role of the baseline WOMAC pain score and the inclusion of a quadratic term into the longitudinal measurement portion of the model. Akaike Information Criterion (AIC)[1,20] was used to determine the best model fit. Lower AIC values are associated with better fit to the data. In addition, model selection should also be determined by interpretability of the resulting membership groups, not unlike the practice in factor analysis.[37] Pearson χ^2 test was used to examine differences in pain trajectory group membership across randomization conditions (gabapentin vs placebo), and if a significant difference was found this variable was entered in the pain trajectory model.

2.5.2. Differences in pain, psychological, and functional outcomes based on pain trajectory group membership

When appropriate, analyses compared the treatment and placebo groups to rule out group differences before analyzing the sample as a whole.

Pearson χ^2 test examined differences in the presence/absence of pain at the surgery site 12 months after surgery across trajectory group membership. Univariate 1-way analysis of variance (ANOVA) was used to examine differences in average pain intensity (Numeric Rating Scale [NRS]) at 12 months across trajectory group membership. Alpha level was set at 0.025 to control for multiple comparisons.

Univariate 1-way ANOVA examined differences in baseline pain levels (WOMAC–Pain) across trajectory group.

Multivariate ANOVAs were used to examine differences in trajectory group membership in levels of: (1) anxiety, depression, lower-extremity functioning, stiffness, functioning difficulty, and pain disability (12 months only) at baseline and 12 months after surgery, (2) functional performance outcome measures (distance completed during the 6-minute walk test, time to complete the TUG test, time to complete stair test) at baseline, and (3) assisted knee flexion and knee extension at baseline. Significant overall models ($\alpha = 0.017$ to account for multiple comparisons) were followed up with Bonferroni post hoc tests.

2.6. Sample size estimation

Sample size was estimated a priori for Pearson χ^2 test, 2-tailed multivariate ANOVA, and univariate 1-way ANOVA using G*Power (version 3.1; G*Power Team, Dusseldorf, Germany). There are no general rules on minimum sample size required for GMM; sample size requirements will depend on theoretical foundations of the study, data characteristics, models being tested, between-group differences, and reliability of measurement.[50] Simulation data suggest that sample sizes of 200 participants with 5 time points offer a power greater than 80%.[27]

Sample size estimation for Pearson χ^2 test showed that a sample size of 122 participants would be required to detect a medium effect size (w = 0.3) with $\alpha = 0.05$, power = 80%, and $df = 3$. Sample size estimation showed that 152 participants would be required for a univariate 1-way ANOVA to ensure $\alpha = 0.025$, power = 80% with a medium effect size ($f = 0.3$), and 4 groups. Sample size estimation for multivariate ANOVA showed

	Baseline	POD1	POD2	POD3	POD4	6 wk	3 mo	12 mo
Questionnaires								
WOMAC	√					√	√	√
HADS	√					√	√	√
LEFS	√					√	√	√
PDI								√
Knee arthroplasty pain questionnaire								√
Functional performance tests								
Timed get up and go test	√		√		√	√	√	
Stair test	√				√	√	
6-minute walk test	√					√	√	
Range of motion	√	√	√	√	√	√	√	

HADS, Hospital Anxiety and Depression Scale; LEFS, Lower Extremity Function Scale; PDI, Pain Disability Index; range of motion: assisted active knee flexion and active knee extension; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

that a sample size of 40 participants would be required to detect a medium effect size ($v = 0.25$) with $\alpha = 0.017$, power = 80%, number of groups = 4, and with 6 response variables.

3. Results

3.1. Recruitment

Recruitment took place between November 2007 and March 2012. Details of the recruitment process and patient retention are presented in **Figure 1**.

There were no significant differences in baseline measures of anxiety, depression, or lower-extremity function between patients who completed vs those who did not complete the postoperative day 4 (POD4) assessment, 6-week follow-up, 3-month follow-up, or 12-month follow-up. Patients who completed the POD4 assessment walked a significantly greater distance on the 6-minute walk test at baseline ($P = 0.027$) and reported significantly less pain intensity ($P = 0.038$) after the knee flexion test at baseline compared with patients who did not complete the POD4 assessment. There were no other statistically significant differences in pain intensity scores during functional tests between those who completed the POD4 assessment vs patients who did not complete the POD4 assessment. Patients who completed the 6-week follow-up walked a significantly greater distance on the 6-minute walk test ($P = 0.027$) and took significantly less time to complete the stairs test ($P = 0.040$) at baseline compared with patients who did not complete the 6-week follow-up. Patients who completed the 3-month tests climbed a significantly greater number of stairs ($P = 0.015$) at baseline compared with patients who did not complete the 3-month follow-up.

3.2. Descriptive statistics

The final sample comprised 173 adults (female = 85 [49%]) aged between 37 and 76 years (mean age in years = 62.9, SD = 6.8). Four part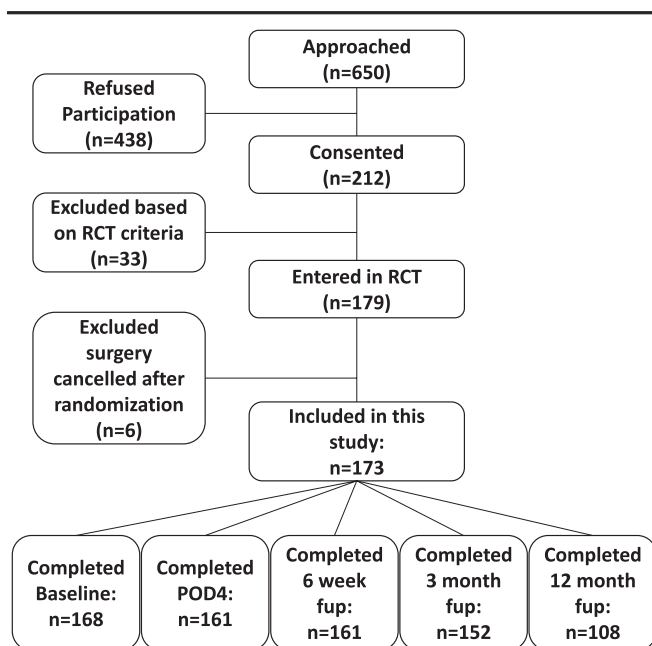icipants (2.3%) had previously undergone foot/ankle surgery, 61 participants (35.3%) had previously undergone lower-extremity surgery, and 25 participants (14.5%) had previously undergone TKA. Twenty-three (21.3%) of the participants who completed the 12-month follow-up underwent another surgical procedure in the first 12 months after the present surgery, but none of these 23 patients had another surgery at the site of the TKA.

Overall, patients in this sample reported gradually decreasing pain from baseline (WOMAC–pain mean = 9.81; SD = 3.1) to 4 days (WOMAC–pain mean = 8.36; SD = 3.1) and 6 weeks (WOMAC–pain mean = 6.76; SD = 3.2) after surgery; the pain intensity sharply decreased from 6 weeks to 3 (WOMAC–pain mean = 3.84; SD = 3.3) and 12 months (WOMAC–pain mean = 2.54; SD = 3.3) after surgery.

Mean and SD values for questionnaires and functional performance tests are presented in **Table 2** and pain outcomes at the 12-month follow-up are presented in **Table 3**.

3.3. Pain trajectories

Eight different models were tested based on different combinations of the following factors: (1) baseline data used either as the initial time point of the trajectory or not in the trajectory itself but rather as a predictor of trajectory group membership, (2) presence or absence of a quadratic slope, and (3) 3 or 4 trajectory group memberships. The number of groups tested was between 3 and 4 as other options produced large errors of estimation. **Table 4** shows the characteristics of these 8 models.

The final model (based on the lowest AIC value) comprised 4 groups, used baseline data as a predictor of trajectory group membership, and included a quadratic slope. The use of baseline data as a predictor, rather than as part of the trajectory, makes the trajectory group membership statistically independent of pre-operative pain level. Five participants were excluded from the final model because they did not have baseline data. The structure of the final model is illustrated in **Figure 2** and the characteristics and parameter estimates of the regression equation for each group are shown in **Table 5**.

Pearson χ^2 test showed no significant differences between the control and gabapentin groups in pain trajectory group membership ($P = 0.715$) and as such group randomization (placebo vs gabapentin) was not entered as a variable in the trajectory model.

The pain trajectories of the 4 groups are shown in **Figure 3**. Group 1 (n = 27), named high baseline pain early and late decrease group, is characterized by high preoperative pain intensity, lower acute postoperative pain intensity that remains
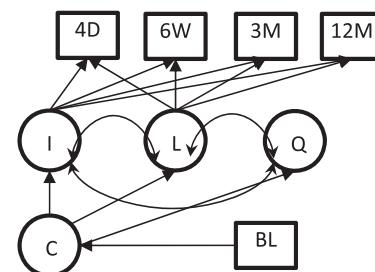
Figure 1. Details of recruitment process.

Figure 2. Representation of the final growth mixture model. Baseline is used as a predictor of trajectory group membership and a quadratic slope is added. The latent trajectory group membership is tested using 4 different groups. BL, baseline; 4D, 4 days postoperatively; 6W, 6-week follow-up; 3M, 3-month follow-up; 12M, 12-month follow-up; I, intercept; L, linear slope; Q, quadratic slope; C, latent group membership based on longitudinal measurement model.

Mean (SD) values of pain, psychological variables, and functional performance outcomes measured preoperatively, 4 d, 6 wk, 3 mo, and 12 mo after surgery.

	Baseline	POD4	6 wk	3 mo	12 mo
Pain outcomes					
WOMAC–Pain*	9.80 (3.2)	8.36 (3.1)	6.76 (3.2)	3.84 (3.3)	2.55 (3.3)
Stair test–Pain*	4.49 (2.4)	4.15 (2.4)	2.50 (2.0)	1.46 (1.7)	
TUG test–Pain*	3.33 (2.4)	4.27 (2.3)	1.83 (1.9)	0.79 (1.3)	
Walk test–Pain*	5.21 (2.3)		2.91 (2.1)	1.33 (1.8)	
Knee flexion–Pain*	4.19 (2.1)	5.59 (2.6)	2.42 (1.9)	1.19 (1.8)	
Psychological and functional variables					
HADS–anxiety	5.92 (3.5)	5.49 (3.1)	4.75 (3.5)	3.68 (3.0)	3.64 (3.2)
HADS–D	4.31 (2.6)	4.64 (3.0)	4.01 (2.9)	5.38 (2.3)	2.71 (2.9)
WOMAC–stiffness	4.51 (1.6)	4.22 (1.3)	3.38 (1.5)	2.39 (1.5)	1.59 (1.5)
WOMAC–difficulty	33.51 (11.1)	34.49 (9.4)	22.02 (12.2)	14.43 (11.3)	9.40 (11.4)
LEFS	29.18 (11.5)	17.55 (11.4)	35.59 (16.2)	48.40 (14.3)	22.03 (15.7)
PDI					9.13 (13.4)
Assisted knee flexion		86.10 (10.8)			
Assisted knee extension		3.65 (3.1)			

* Pain intensity measured using the 11-point Numeric Rating Scale.
HADS-Anxiety, Hospital Anxiety and Depression Scale—Anxiety Subscale; HADS-D, Hospital Anxiety and Depression Scale—Depression Subscale; LEFS, Lower Extremity Function Scale; PDI, Pain Disability Index; TUG, timed get up and go test; WOMAC–difficulty, Western Ontario and McMaster Universities Osteoarthritis Index—difficulty subscale; WOMAC–Pain, Western Ontario and McMaster Universities Osteoarthritis Index—Pain subscale; WOMAC–stiffness, Western Ontario and McMaster Universities Osteoarthritis Index—stiffness subscale.

constant up to 3 months after surgery, and then shows a second drop in pain intensity at 12 months after surgery. Group 2 (n = 66), named low baseline pain gradual decrease group, is characterized by a relatively low level of preoperative pain that remains constant across the first few days after surgery and subsequently gradually decreases up to 12 months after surgery. Group 3 (n = 60), named high baseline pain gradual decrease group, is characterized by a higher level of pre-operative pain compared with group 2. Patients in this group reported a lower level of pain in the first 4 days after surgery compared with their baseline pain level, and this decrease continued up to 12 months after surgery. Group 4 (n = 15), named high pain group, is characterized by moderate levels of pain preoperatively and relatively constant pain of moderate intensity up to 12 months after surgery.

Unlike patients in groups 1 to 3 who show a decrease in pain levels over time (negative slopes), patients in group 4 have a neutral or positive pain slope and do not show a decrease in pain over time. There were no significant age ($P = 0.149$) or gender ($P = 0.064$) differences between patients in the 4 different pain trajectories.

3.4. Differences in pain, psychological, and functional outcomes based on pain trajectory group membership

Results of Pearson χ^2 test (see **Table 3** for additional details) showed significant differences in the presence of pain at the surgery site in the week before the 12-month follow-up across pain trajectories: A significantly smaller proportion of patients in group 2 reported the presence of pain 12 months after surgery in contrast to group 4 where a significantly greater proportion reported pain 12 months after surgery. In addition, 1-way ANOVA showed significant differences in average pain intensity 12 months after surgery ($F_{(3,73)} = 5.24$, $P = 0.002$) across trajectory group membership such that patients in group 4 reported higher average pain intensity compared with patients in group 2 (NRS mean difference = 2.87, $P = 0.001$) and group 3 (NRS mean difference = 2.24, $P = 0.016$).

Given the number of participants per trajectory group member-ship in the final model (27, 66, 60, and 15, respectively), the GMM model was unable to estimate all necessary parameters when the relationships between pain trajectories and psychological and functional variables were entered. As such, these relationships were explored separately through ANOVAs.

Pain outcomes at the 12-mo follow-up across pain trajectory classes and for the total sample.

		Pain trajectory classes				Total sample	χ^2	P
		High baseline pain, early and late decrease	Low baseline pain, gradual decrease	High baseline pain, gradual decrease	Constant high pain			
Ever feel pain (n)	Yes	6	18†	20*	8*	54	5.72	0.126
	No	9	23*	14†	2†	50		
Had pain in last wk (n)	Yes	4	9†	8	7*	29	8.45	0.038
	No	13	32*	27	4†	79		
Pain right now (n)	Yes	2	0†	3	4*	9	14.78	0.002
	No	15	41*	32	7†	99		

	Pain trajectory classes				Total sample	F (df)	P
	High baseline pain, early and late decrease	Low baseline pain, gradual decrease	High baseline pain, gradual decrease	Constant high pain			
Average pain intensity (mean, (SD))	2.50 (2.7)	1.77 (1.5)	2.39 (1.9)	4.64 (2.7)	2.52 (2.2)	5.24 (3, 73)	0.002

* Fewer patients than expected by chance endorsed this category.
† More patients than expected by chance endorsed this category.

3.5. Group differences in baseline variables

Mean values on the psychological and functional outcome measures across trajectory group membership are shown in **Table 6**.

One-way ANOVA showed significant differences between pain trajectory groups in baseline pain levels ($F_{(3,164)} = 82.44$, $P < 0.001$). Bonferroni post hoc analyses showed that patients in group 4 had significantly lower pain scores compared with patients in group 1 ($P = 0.001$) and significantly higher pain scores compared with patients in group 2 ($P < 0.001$).

Multivariate ANOVA ($F_{(15,459)} = 5.48$, $P < 0.001$) showed significant differences among pain trajectory groups in baseline levels of anxiety ($F_{(3,155)} = 5.54$, $P = 0.001$), stiffness ($F_{(3,155)} = 11.42$, $P < 0.001$), functional difficulty ($F_{(3,155)} = 24.90$, $P < 0.001$), and lower-extremity functioning ($F_{(3,155)} = 13.65$, $P < 0.001$) but not depression ($P = 0.099$). **Table 6** shows mean and SD values on all measures across pain trajectory groups at baseline and 12 months after surgery. Bonferroni post hoc tests, comparing group 4 with the other 3 groups showed that group 4 had significantly poorer lower-extremity functioning ($P = 0.020$), higher anxiety scores ($P = 0.006$), and higher levels of functioning difficulty ($P = 0.001$) compared with group 2.

Multivariate ANOVA ($F_{(9,462)} = 3.36$, $P = 0.001$) showed an overall significant difference in functional performance outcomes at baseline (time to complete stair test, time to complete TUG test, and total distance walked in 6-minute walk test) across groups. Bonferroni post hoc tests, comparing group 4 with the other 3 groups, showed that patients in group 4 took significantly longer period to complete the stairs test compared with patients in group 2 (mean difference = 10.11, $P = 0.004$).

Multivariate ANOVA ($F_{(6,258)} = 1.23$, $P = 0.291$) showed no significant differences in knee flexion and knee extension at baseline across groups.

3.6. Group differences in 12-month variables

Multivariate ANOVA ($F_{(18,231)} = 4.52$, $P < 0.001$) showed significant difference between pain trajectory groups in 12-month levels of depression ($F_{(3,80)} = 5.36$, $P = 0.002$), anxiety

($F_{(3,80)} = 3.06$, $P = 0.033$), stiffness ($F_{(3,80)} = 9.84$, $P < 0.001$), functional difficulty ($F_{(3,80)} = 28.56$, $P < 0.001$), lower-extremity functioning ($F_{(3,80)} = 11.01$, $P < 0.001$), and pain disability ($F_{(3,80)} = 6.71$, $P < 0.001$). Bonferroni post hoc tests, comparing group 4 with the other 3 groups showed that group 4 had significantly (1) worse lower-extremity functioning compared with group 2 ($P < 0.001$) and group 3 ($P < 0.001$), (2) higher levels of stiffness compared with group 1 ($P = 0.002$), group 2 ($P < 0.001$), and group 3 ($P < 0.001$), (3) higher levels of functioning difficulty compared with group 1 ($P < 0.001$), group 2 ($P < 0.001$), and group 3 ($P < 0.001$), and (4) higher levels of pain disability compared with group 2.

4. Discussion

The aims of this study were to examine pain trajectories over the first 12 months after TKA and to identify predictors of pain trajectory group membership. Results showed that a 4-group model with a quadratic slope and with baseline data as predictor of trajectory group membership had the best fit to the data. Consistent with previous studies,[14,36,55] these results show that postoperative pain is not a homogeneous condition and point to the importance of examining intraindividual postoperative pain fluctuations. This model also indicated that preoperative pain levels are predictive of pain trajectory group membership. The present results suggest that moderate preoperative pain, as opposed to low or high pain, is one of the risk factors for a poorer pain trajectory postoperatively and a poorer pain status outcome 12 months after surgery. These results are consistent with another study examining acute pain trajectories in patients undergoing TKA. Morze et al.[41] found the presence of 4 different pain trajectories in the first 3 months after TKA; preoperative "best" and "worst" pain scores ≤4 of 10 were a risk factor for initially higher postoperative pain, slower rates of pain decline, and a longer time to experience a 50% reduction in pain scores.

Previous research has shown that acute postoperative pain intensity scores predict the development of CPSP.[28,29,31,48] Results from this study provide a more refined view of the role of acute postoperative pain in the development of CPSP. Results from this study showed that patients in groups 1 to 4 had similar levels of acute postoperative pain 4 days after surgery; however, only patients in group 4 continued to experience similar levels of pain 12 months after surgery. What seems to differentiate patients in group 4 from the other groups is that these patients on average did not report a change in their pain score from baseline to the first 2 postoperative time points (4 days and 6 weeks after surgery). In contrast to patients in group 2 and group 3, patients in group 4 did not report a decrease in pain intensity during the first 6 weeks postoperatively; they reported a neutral or positive pain slope and continued to experience pain 12 months after surgery.

Results also showed that 6 weeks after surgery, patients in group 4 had significantly higher pain scores compared with

Table 5

Pain trajectories model descriptions and goodness of fit indicators.

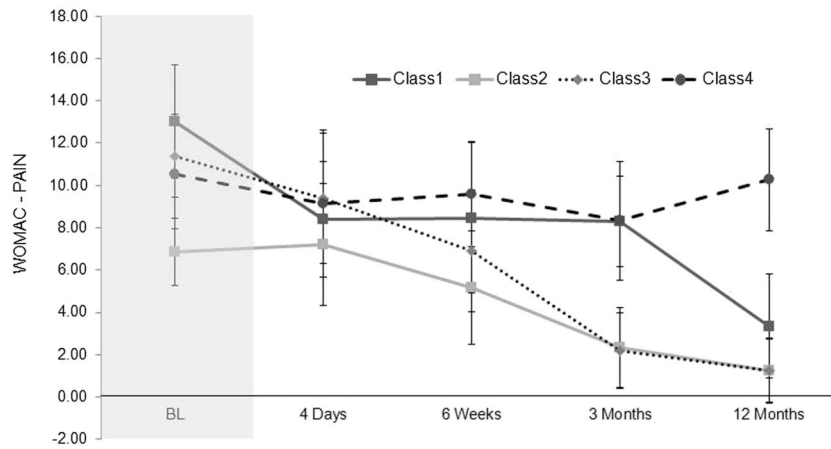| Trajectory group	n	Intercept	Slopes		Predicted values			
			Linear	Quadratic	4 d	6 wk	3 mo	12 mo
1	27	8.663	−0.088	−0.031	8.65	8.46	8.12	3.14
2	66	7.816	−2.211	0.138	7.49	4.81	2.43	1.16
3	60	9.834	−3.072	0.195	9.38	5.66	2.37	1.05
4	15	9.102	−0.287	0.031	9.06	8.74	8.52	10.12

Figure 3. Results of pain trajectories analysis showed 4 different subgroups of patients. Group 1 (n = 27), high baseline pain early and late decrease group; group 2 (n = 66), low baseline pain gradual decrease group; group 3 (n = 60), high baseline pain gradual decrease group; group 4 (n = 15), high pain group.

patients in the other 3 groups, suggesting that by the end of the acute postoperative period, patients with a neutral or positive pain slope (1) experience higher levels of pain and (2) will continue to experience this level of pain 12 months after surgery. These results are consistent with a recent study of CPSP in children in which pain intensity and unpleasantness scores at 2 weeks after surgery predicted who would go on to develop CPSP at the 12-month follow-up.[46] Designing interventions for patients with a neutral or positive pain slope in the first few weeks after surgery could potentially prevent these patients with acute pain from transitioning into CPSP.

Patients in group 4 did not differ significantly from patients in groups 1 and 3 on functional outcome measures or on most psychological variables preoperatively; however, they had poorer lower-extremity functioning, higher levels of anxiety, higher levels of functioning difficulty, and walked a shorter distance on the

6-minute walk test compared with patients in group 2. These results suggest that in addition to levels of preoperative pain, other preoperative functional and psychological variables influence the pain reports of patients postoperatively and their risk of developing CPSP.

Results of this study failed to show that age or gender is a risk factor for persistent postsurgical pain. This contrasts with other studies, which found that younger age and female gender are risk factors for the development of CPSP and persistent opioid use greater than 3 months after major surgery.[19] Results from this study are consistent with a prospective study of TKA, however, showing that neither age nor gender is associated with CPSP after TKA.[11]

Patients in group 4 not only reported higher levels of pain 12 months after surgery compared with patients in the other 3 groups but also showed a lower level of lower-extremity functioning

Table 6

Mean (SD) values and statistical differences in psychological and functional outcomes at baseline and 12 mo after surgery based on pain trajectory class membership.

	Baseline					12 mo				
	Group 1	Group 2	Group 3	Group 4	Sig*	Group 1	Group 2	Group 3	Group 4	Sig*
Age	60.93 (6.9)	63.97 (5.8)	62.22 (7.5)	64.47 (7.2)	NS					
WOMAC–Pain	13.00 (2.7)	6.86 (1.6)	11.40 (1.9)	10.53 (2.6)	1-4 2-4	3.35 (2.4)	1.23 (1.5)	1.23 (1.5)	10.27 (2.4)	1-4 2-4 3-4
WOMAC–stiffness	5.30 (1.8)	3.71 (1.5)	5.15 (1.2)	4.13 (1.6)	NS	1.82 (1.5)	1.24 (1.2)	1.26 (1.4)	3.63 (1.6)	1-4 2-4 3-4
WOMAC–difficulty	41.70 (11.1)	25.95 (8.7)	47.51 (8.7)	36.60 (8.7)	2-4	14.00 (10.2)	5.23 (6.4)	5.00 (6.3)	32.18 (12.1)	1-4 2-4 3-4
HADS-D	4.44 (2.4)	3.74 (2.5)	4.82 (2.6)	4.87 (2.8)	NS	4.12 (2.9)	1.90 (1.8)	2.17 (2.6)	5.64 (4.3)	NS
HADS-A	6.74 (2.9)	4.82 (3.0)	6.00 (3.2)	7.60 (3.3)	2-4	5.59 (3.8)	2.90 (2.7)	3.20 (2.30)	5.45 (4.8)	NS
LEFS	21.41 (11.1)	35.02 (9.8)	26.05 (1.02)	25.94 (9.7)	2-4	33.69 (15.4)	16.23 (11.0)	18.37 (13.7)	40.02 (17.8)	2-4 3-4
PDI						17.00 (15.4)	4.44 (7.9)	6.30 (11.0)	24.18 (19.1)	2-4
TUG–Time	12.79 (4.5)	11.16 (3.7)	13.27 (5.7)	13.60 (2.9)	NS					
Stairs–Time	26.47 (14.1)	16.90 (5.9)	23.20 (10.2)	27.02 (12.9)	2-4					
Walk test–distance	318.85 (143.1)	409.32 (110.8)	323.53 (139.5)	323.71 (141.8)	NS					
Knee flexion	108.35 (15.6)	116.64 (12.9)	111.13 (18.5)	109.86 (15.92)	NS					
Knee extension	2.70 (3.3)	3.43 (4.0)	2.80 (3.5)	3.07 (4.6)	NS					

* Statistically significant differences between pain trajectory groups using Bonferroni post hoc test. Only differences between group 4 and the other 3 groups were examined.
HADS-Anxiety, Hospital Anxiety and Depression Scale—Anxiety Subscale; HADS-D, Hospital Anxiety and Depression Scale—Depression Subscale; LEFS, lower extremity function scale; NS, not significant; PDI, Pain Disability Index; TUG, timed get up and go test; WOMAC–difficulty, Western Ontario and McMaster Universities Osteoarthritis Index—difficulty subscale; WOMAC–Pain, Western Ontario and McMaster Universities Osteoarthritis Index—Pain subscale; WOMAC–stiffness, Western Ontario and McMaster Universities Osteoarthritis Index—stiffness subscale.

and reported higher levels of stiffness, functioning difficulty, and pain-related disability. These results suggest that these patients recover poorly from the surgery in other domains of life besides pain. It is unclear, however, whether the stiffness and functioning difficulty reported are a consequence of the pain experienced or whether they contribute to the development of CPSP.

It is important to note that our cohort identified 15/168 (9%) group 4 patients (ie, those who remained in the study until POD4) who could potentially benefit from more aggressive therapies perioperatively. Recently, a growing body of evidence suggests that fitness improvements achieved through total-body pre-operative physical conditioning can significantly impact peri- and postoperative health.[54] Future studies may consider identifying patients with high pain and poor preoperative function (group 4) and then tailor prehabilitation programs toward improving function and decreasing pain in an attempt to improve baseline function and potentially modify/improve their postoperative pain trajectory.

5. Limitations

First, patients in this study participated in a randomized controlled trial of the efficacy of gabapentin in reducing postoperative pain.[18] Results of this RCT found that gabapentin improved early in-hospital knee function, although this early gain in function did not translate into improved functional status after hospital discharge.[18] Although no group differences were found in pain trajectories between patients who received gabapentin vs placebo, it would be important to replicate the current findings with a homogenous sample of patients receiving uniform post-operative care. Second, sample size of this study did not allow for the examination of the relationships between pain trajectories and functional and psychological variables within the GMM. It would be interesting for future studies to examine how these additional variables can directly impact pain trajectories. Third, no intra-operative data (eg, surgeon who performed TKAs, length of surgery, technical difficulties during surgery) were collected and as such these variables could not be controlled for in the trajectory model.

In summary, results showed that 4 different pain trajectories could be identified, one of which includes approximately 9% of patients who display a neutral or positive pain slope over the first year after TKA. Results suggest that a neutral or positive pain slope in the first few weeks after surgery leads to the continuation of the pain experience and the development of CPSP. In addition to levels of acute postoperative pain, levels of preoperative pain can also influence patients' pain trajectories. Future research directions include replication of this pain trajectory model in other postoperative populations and examination of functional and psychological variables that can influence pain trajectories. Furthermore, early identification of patients with a flat pain trajectory in the weeks after surgery could lead to the development of programs that are aimed at aggressively in-tervening in an attempt to decrease the development of a persistent postsurgical pain problem.

Conflict of interest statement

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