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ORIGINAL ARTICLE

Preoperative risk factors associated with chronic pain profiles following total knee arthroplasty

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ABSTRACT

Background: One in five patients experience chronic pain 12 months following total knee arthroplasty (TKA). This longitudinal study used a person-centred approach to identify subgroups of patients with distinct chronic pain profiles following TKA and identified preoperative characteristics associated with these profiles.

Methods: On the day before surgery, 202 patients completed questionnaires that assessed pain, interference with functioning, fatigue, anxiety, depression and illness perceptions. Average and worst pain were assessed prior to surgery, on postoperative day 4, at 6 week and at 3 and 12 months following surgery. Using growth mixture modelling, two subgroups with distinct average and worst pain profiles were identified.

Results: Patients in the "lower average" and "lower worst" pain classes had moderate preoperative pain scores that decreased over the remaining 9 months following TKA. Patients in the "higher average" and "higher worst" pain classes had relatively higher preoperative pain scores that increased during the first three months and then decreased slightly over the remaining 9 months. Patients in the higher pain classes had higher interference with function scores; used opioids prior to surgery more often, were more likely to receive a continuous nerve block and ketamine; had higher preoperative fatigue severity and interference scores; and had worse perceptions of illness than patients in the lower pain classes.

Conclusions: These risk factors may be used to identify subgroups of patients at higher risk for more severe pain after TKA. Future studies should test whether modifying these risk factors can improve patients' outcomes after TKA.

Significance statement: The present study provides a novel and original analysis of pain profiles following total knee arthroplasty that may contribute to our understanding of the transition from acute to chronic pain. Our results may be used to identify patients at higher risk for poorer outcomes based on preoperative risk factors.

1 | INTRODUCTION

Chronic pain and dissatisfaction with the outcome occur in 10% to 34% of patients 12 months after total knee arthroplasty (TKA; Beswick et al., 2012). With an estimated threefold increase in the incidence of primary TKA by 2040 (Singh et al., 2019), the number of patients living with chronic pain will grow exponentially. Chronic pain has negative effects on function (Lindberg, Miaskowski, Rustøen, et al., 2016), mental health and quality of life (QOL), and can increase opioid consumption and healthcare costs (Wylde et al., 2018). A variety of risk factors for the development of chronic pain following TKA have been identified, including multiple painful sites (Lewis et al., 2015), lower grade of osteoarthritis (OA) (Dowsey et al., 2012; Niinimaki et al., 2011), female gender, younger age (Singh et al., 2008), previous knee surgeries (Skou et al., 2013), higher preoperative (Noiseux et al., 2014) and perioperative pain intensity (Puolakka et al., 2010) and poorer psychological state (Lewis et al., 2015). However, as noted in three systematic reviews (Chodor & Kruczynski, 2016; Harmelink et al., 2017; Wylde et al., 2018), a large amount of heterogeneity exists across studies; they focused mainly on biomechanical factors; and were primarily registry-based, retrospective, or secondary analyses of randomized controlled trials. Therefore, the fundamental processes that underlie the transition from acute to chronic pain after TKA are poorly understood (Katz & Seltzer, 2009) and the evidence on risk factors is weak (Harmelink et al., 2017). Well-designed studies of inter-individual variability in patients' pain experiences and identification of associated modifiable characteristics may provide important information for clinicians to use to individualize follow-up care.

To date, two studies have evaluated pain profiles during the first year after TKA. The first study (Page et al., 2015) identified a subgroup of patients with moderate and relatively constant levels of pain that lasted for 12 months after surgery. Compared to three subgroups characterized by distinct rates of decreasing pain, the patients with constant levels of pain had poorer lower extremity function, shorter walking distances and higher anxiety levels prior to surgery. In the second study that evaluated pain and functional trajectories following TKA, (Dumenci et al., 2019) 20% of the patients reported chronic pain, impaired function, or both at 12 months. Both of these studies were secondary analyses of randomized controlled trials with strict inclusion and exclusion criteria; patients were included based on levels of pain catastrophising (Dumenci et al., 2019); and were excluded if they were older than 75 years, had diabetes or used controlled-release opioids prior to surgery (Page et al., 2015). Therefore, these patients may not be representative of the general population of individuals who undergo TKA.

Given the paucity of research that used patient-centred analytic approaches like growth mixture modelling (GMM) and a comprehensive list of potential risk factors, the purposes of this study were to identify subgroups of patients with distinct pain profiles during 12 months following TKA and to identify preoperative demographic, clinical, symptom and psychological characteristics associated with these subgroups.

2 | MATERIALS AND METHODS

2.1 | Patients and procedures

This longitudinal analysis is part of a larger longitudinal study that evaluated pain, symptoms and QOL in patients undergoing TKA whose details are described previously (Lindberg, Miaskowski, Rustøen, et al., 2016). Patients ($n = 202$) were included if they: were >18 years of age, were able to read, write and understand Norwegian, were scheduled for primary TKA and did not have a diagnosis of dementia. The study was approved by the Regional Medical Research Ethics Committee of Health South East of Norway (#2011/1755).

Patients who met the inclusion criteria were approached by a nurse on the day of admission, invited to participate and provided written informed consent. Then, patients completed the enrollment questionnaires that assessed average and worst pain using a 0 to 10 numeric rating scale (NRS), as well as demographic, clinical, symptom and psychological characteristics. Medical records were reviewed for preoperative and perioperative information. Patients rated their average and worst postoperative pain on postoperative day (POD) 4, and at 6 week, 3 months and 12 months after surgery. Patients completed mailed questionnaires and returned them in sealed prepaid envelopes.

2.2 | Surgical and pain management procedures

The procedures for anaesthesia, surgery and postoperative pain management were standardized. All patients received the same posterior cruciate-retaining fixed modular-bearing implant for the TKA (Profix CR, Smith&Nephew Inc., USA) using hybrid fixation. All surgeons ($n = 7$) used the same surgical technique. A tourniquet was applied and the joint was accessed through a medial parapatellar approach. A mechanical alignment technique was employed in all cases. The tibial plateau was fixed using PALACOS® R + G cement (Heraeus, Hanau, Germany). The femoral component was implanted without the use of cement. The patella was not resurfaced in any of the patients. A drain was placed and removed on POD1. Weight bearing as tolerated was allowed.

Spinal anaesthesia with bupivacaine and sedation was the first choice for anaesthesia. Epidural analgesia (EDA) with a continuous infusion of bupivacaine 1 milligram/millilitre (mg/ml), adrenaline 2 micrograms (μg)/ml and fentanyl 2 μg/ml (5–12 ml/hr) was the first choice for postoperative pain management. If neuraxial blockade was contraindicated, patients received total intravenous anaesthesia and a continuous femoral nerve block (CFNB) with bupivacaine 2.5 mg/ml at 4–10 ml/hr for postoperative pain management. In most cases, the epidural and femoral catheters were removed on POD2. Oral acetaminophen 1 g was given every 6 hr and celecoxib 200 mg and controlled-release oxycodone 5–20 mg was given every 12 hr unless contraindicated. Immediate-release oxycodone 5 mg tablets or intravenous ketobemidone 2.5–5 mg were available as rescue medications. If pain control was not satisfactory, low dose ketamine 1.5 μg/kg/min was administered as a short-term intravenous infusion (usually on the day of surgery). Pain medication prescribed at discharge usually consisted of a combination of acetaminophen and tramadol.

Mobilisation and physical therapy (PT) were standardized. All patients were allowed full weight bearing on the operated knee and received PT on a daily basis with walking, flexion and extension of the knee beginning on POD1. Most patients were discharged directly to home on POD 4 and continued to receive PT on a weekly basis for up to 4 months after surgery.

2.3 | Measures

2.3.1 | Symptom measures

2.3.1.1 | *Pain intensity*
The Brief Pain Inventory (BPI) was used to measure pain intensity, impact of pain on function and number of painful sites (Cleeland, 1985). The BPI consists of four items that assess pain intensity using a 0 to 10 NRS (i.e. pain right now, least, average, worst), seven items that assess pain interference with function, one item that assesses pain relief and a body map that assesses pain locations. In this analysis, the ratings of average and worst pain intensity were used in the GMM based on the IMMPACT recommendations for assessing pain in clinical trials, which recommends using average and worst pain to describe pain severity (Turk et al., 2006). The validity and reliability of the Norwegian version of the BPI are well established (Klepstad et al., 2002).

2.3.1.2 | *Fatigue severity*
The 5-item Lee Fatigue Scale (LFS) was used to evaluate fatigue severity. Each item was rated on a 0 to 10 NRS. A total score was calculated as the mean of the five items with higher scores indicating higher fatigue severity. The LFS has satisfactory validity and reliability (Lee et al., 1991; Lerdal et al., 2013). In this study, its Cronbach's alpha was 0.91.

2.3.1.3 | *Fatigue interference*
The 7-item Fatigue Severity Scale (FSS-7) was used to evaluate fatigue interference during the past week. Patients rated their agreement with seven statements, using a 7-point Likert scale that ranged from disagree to agree. A total score can range from 1 to 7 with higher scores indicating higher levels of interference. The Norwegian version of the FSS-7 has good psychometric properties (Lerdal et al., 2005). In this study, its Cronbach's alpha was 0.93.

Mood states: The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) was used to evaluate depression and anxiety. The scale consists of seven items for depression and seven items for anxiety. Scores can range from 0 to 21 on each subscale, with higher scores indicating higher levels of depression and anxiety. Psychometric properties of the Norwegian version of the HADS were excellent in a large population-based study (Mykletun et al., 2001). In this study, the Cronbach's alphas for the depression and the anxiety scales were 79.2 and 84.4, respectively.

2.3.2 | Psychological measure

The Brief Illness Perception Questionnaire (BIPQ; Broadbent et al., 2006) was used to measure self-reported illness perception. The scale consists of eight items that measure different dimensions of self-reported illness perception (i.e. consequences, timeline, personal control, treatment control, identity, illness concern, coherence, emotional response). Each item was rated on a 0 to 10 NRS. For this analysis, patients rated their illness perception in relationship to their OA knee. Five items from the BIPQ (i.e. consequences, personal control, identity, concern, emotional response) were used in the statistical analyses because these specific items are sensitive to changes over time in patients with traumatic injuries (Lee et al., 2010).

2.4 | Statistical analyses

Data analyses were performed using Statistical Package for Social Science (IBM, Armonk, NY) version 22 and Mplus Version 7.3 (Muthén & Muthén, 2015). Frequency distributions and descriptive statistics were generated on sample characteristics and average and worst pain scores.

GMM with robust maximum likelihood estimation was used to identify latent classes (i.e. subgroups of patients) with distinct average and worst pain profiles. GMM allows for the estimation of more than one growth curve over time which facilitates the identification of subgroups of patients that change differently over time. The initial status of the estimation of a growth curve (i.e. intercept) represents the predicted mean for the dependent variable at the first assessment (e.g.

average pain prior to surgery). The slope represents the rate of change predicted for each unit of time. A detailed description of the GMM procedure is published elsewhere (Dunn et al., 2012). Separate GMM analyses were performed for average and worst pain. First, for average and worst pain, one single growth curve that represented each variable's mean change trajectory was estimated. Subsequently, iterative models with increasing number of classes were fit to the data until the final iteration of the model was not supported. The number of latent growth curves (generated by different latent classes) that best fit the data was identified based on lower Bayesian information criterion (BIC) and a statistically significant Vuong-Lo-Mendell-Rubin (VLMR) likelihood test for the K versus K-1 model suggesting a better model fit (Jung & Wickrama, 2008; Nylund et al., 2007), combined with visual inspections of plots of predicted values against observed values. After identifying the latent class solution that best fit our data, differences between the predicted growth classes were evaluated for important covariates (i.e. demographic, clinical, symptom and psychological characteristics) outside our models using Independent samples t tests, Mann–Whitney U tests and Chi-square analyses. Level of statistical significance was set at $p < 0.05$ (two-sided). Because of the exploratory nature of our study, we did not correct for multiple testing. To facilitate the interpretation of the clinical meaningfulness of our findings (Page, 2014), effect sizes were calculated on differences in symptom scores between the pain classes, according to Cohen's coefficient d (i.e. small = >.2; medium = >.5; large = >.8) (Cohen, 1992).

3 | RESULTS

Of the 245 patients who were invited to participate, 33 declined and 6 had their surgery cancelled. Of the 206 patients who agreed to participate and enrolled in the study, two patients were excluded after surgery because of postoperative disorientation and another was excluded because of revision surgery on the same knee. One patient died from postoperative complications, leaving a total of 202 patients for this analysis.

The majority of the sample was female (68%), lived with a partner (60%) and had completed higher education (51%). The patients' mean age was 68 (SD = 9.2) years and most were not employed (64%).

3.1 | GMM analysis

As shown in Tables S1 and S2, for both average and worst pain, a 2-class model was selected because the VLMR test indicated a better model fit. For both the average and worst pain models, the VLMR for the 3-class model indicated that

too many classes had been extracted. The BIC for 2-classes was smaller than for the 1 and 3-class average pain models indicating better fit; however, the BIC combined with the VLMR was ambiguous for the worst pain 3-class model. In addition, visual inspection of the plots with the observed values against the estimated values supported the choice of a 2-class model. The parameter estimates for the average and worst pain analyses are shown in Tables S3 and S4.

3.2 | Average pain

Figure 1a displays the unconditional model for average pain. The total sample had an average pain score of 5.3 on POD 4 that gradually decreased over the 12 months following TKA. Using GMM, two distinct classes were identified (Figure 1b). Class 1 was named the "lower average pain class." Patients in this class (69.8%) had moderate preoperative pain scores that decreased over the 12 months following TKA. However, most of the reduction in pain score was observed during the first three months (Figure 1b). Class 2 was named the "higher average pain class." Patients in this class (30.2%) had relatively higher preoperative pain scores compared to the lower pain class. Their pain scores increased during the first three months followed by a slight decrease over the remaining 9 months.

3.2.1 | Differences in pre-and postoperative characteristics between the average pain classes

As shown in Table 1, compared to the lower pain class, patients in the higher class had a higher number of comorbidities, higher preoperative average (Cohen's $d = .66$) and worst (Cohen's $d = .48$) pain scores, and higher preoperative pain interference with function (Cohen's $d = .75$). In addition, patients in the higher pain class used opioids prior to surgery more often, received epidural analgesics for fewer days, had a CFNB for more days and needed ketamine for a higher number of days. Finally, patients in the higher pain class had higher preoperative fatigue severity (Cohen's $d = .40$) and interference (Cohen's $d = .50$) scores, higher depression (Cohen's $d = .47$) and anxiety (Cohen's $d = .42$) scores, and higher preoperative BIPQ scores for consequences (Cohen's $d = .38$), personal control (Cohen's $d = .41$), illness concern (Cohen's $d = .46$) and emotional response (Cohen's $d = .54$).

3.3 | Worst pain

Figure 2a displays the unconditional model for worst pain. The total sample had a worst pain score of 5.5 on POD 4 that gradually decreased over the 12 months following TKA.
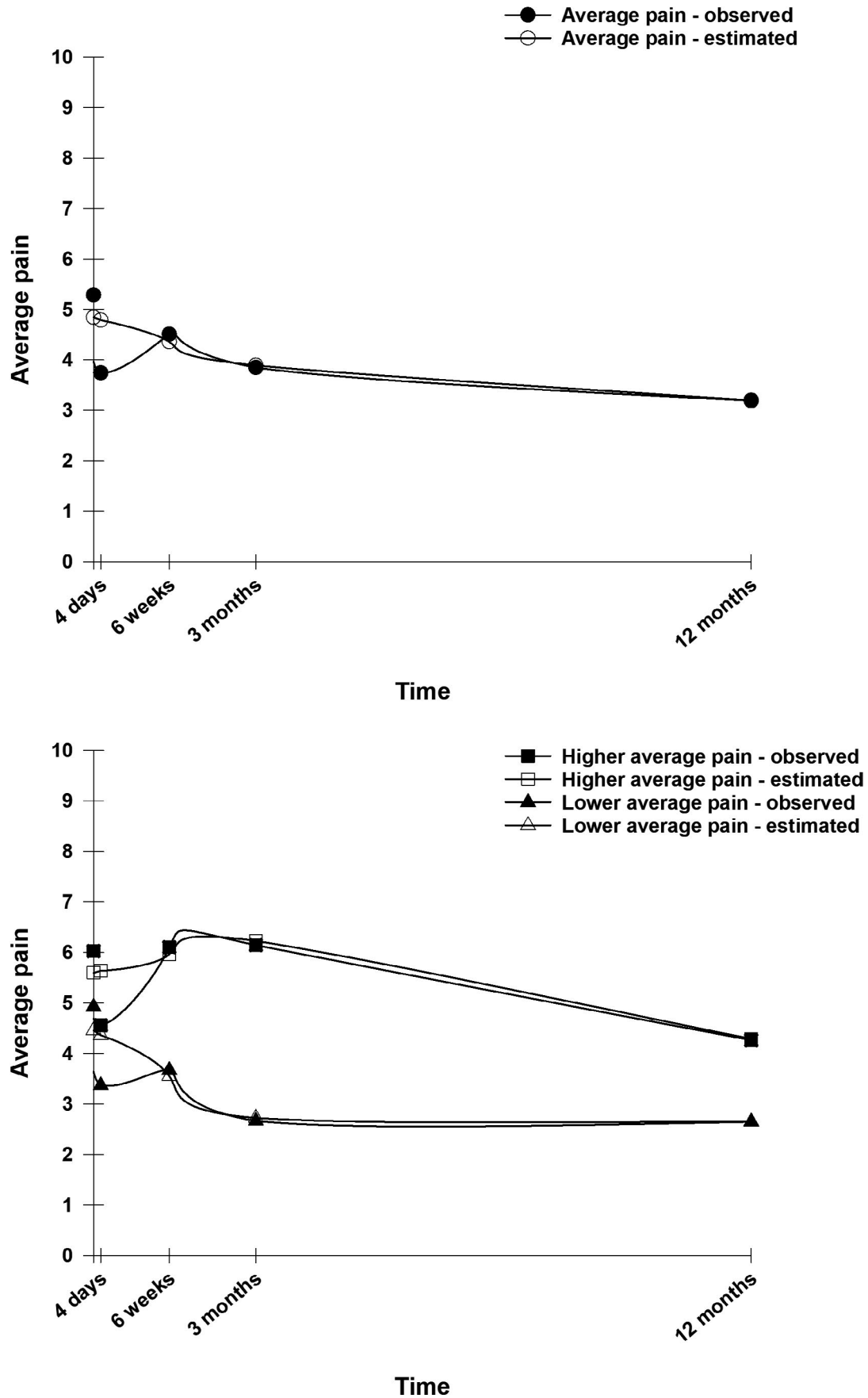
FIGURE 1 (a) Observed and estimated scores for the unconditional model of average pain; (b) Observed and estimated scores for the latent classes of average pain

TABLE 1 Differences in demographic, clinical, symptom, and psychological characteristics between the lower and higher average pain classes

	Lower 69.8 % (n = 141)	Higher 30.2 % (n = 61)	Statistics
Demographic characteristics	Mean (SD)	Mean (SD)	
Age (year)	68.0 (9.3)	68.6 (9.0)	$t = -.45, p = .65$
	% (n)	% (n)	
Women (comp: male)	66.7 (94)	72.1 (44)	$\chi^2 = .36, p = .51$
Lives alone (comp: lives with partner)	39.0 (55)	41.0 (25)	$\chi2 = .11, p = .91$
No paid work (comp: paid work)	60.3 (85)	73.8 (45)	$\chi^2 = 2.81, p = .09$
Higher education (comp: lower education)	55.8 (77)	41.0 (25)	$\chi^2 = 3.15, p = .08$
Preoperative clinical characteristics	Mean (SD)	Mean (SD)	
Body mass index (kg/m^2)	29.0 (4.8)	29.7 (4.8)	$t = -.97, p = .33$
Number of comorbidities	1.0 (0.9)	1.5 (1.1)	*$p = .001$
ASA score (1-4)	2.0 (0.5)	2.1 (0.5)	*$p = .63$
Systolic blood pressure (mm/hg)	137.7 (15.5)	138.3 (17.6)	$t = -.23, p = .82$
Diastolic blood pressure (mm/hg)	81.9 (10.6)	79.3 (13.0)	$t = -1.52, p = .13$
C-reactive protein	3.1 (2.9)	3.7 (3.2)	$t = -1.36, p = .18$
Hemoglobin (g/dL)	13.9 (1.1)	13.9 (1.2)	$t = -.11, p = .91$
Pain characteristics			
Average pain prior to surgery	4.9 (1.7)	6.1 (1.8)	$t = -4.6, p < .001$
Worst pain prior to surgery	5.2 (2.1)	6.2 (2.1)	$t = -3.3, p = .001$
Pain interference with function prior to surgery	4.0 (1.8)	5.5 (2.0)	$t = -5.1, p < .001$
Number of painful sites, preoperative	2.2 (1.8)	2.2 (1.5)	*$p = .47$
Number of painful sites, 12 months after surgery	1.9 (1.2)	2.0 (1.3)	*$p = .70$
Perioperative characteristics			
Length of surgery (min)	65.3 (13.7)	65.5 (13.4)	$t = -.09, p = .93$
	% (n)	% (n)	
Left knee (49%) (comp: right knee)	46.1 (65)	54.1 (33)	$\chi^2 = .79, p = .36$
Regional anaesthesia (87%) (comp: total intravenous)	89.4 (126)	80.3 (49)	$\chi^2 = 2.27, p = .13$
Pain management characteristics			
Preoperative opioid use	5.7 (8)	16.4 (10)	$\chi^2 = .4.7, p = .03$
	Mean (SD)	Mean (SD)	
Number of days with epidural analgesia (n=172)	1.9 (0.7)	1.5 (1.0)	*$p = .002$
Number of days with a continuous femoral nerve block	0.2 (0.6)	0.7 (1.0)	*$p < .001$
Number of days with ketamine	0.2 (0.5)	0.3 (.61)	*$p = .04$
Average dose of opioids over 4 days	12.8 (7.7)	13.4 (6.7)	$t = -.52, p = .61$
Preoperative symptoms			$t = -3.27, p = .001$
Fatigue severity	2.4 (2.1)	3.5 (2.2)	$t = -2.77, p = .006$
Fatigue interference	3.8 (1.5)	4.4 (1.5)	$t = -2.64, p = .009$
Depression	3.1 (2.7)	4.6 (3.9)	$t = -2.38, p = .02$
Anxiety	4.2 (3.2)	5.7 (4.3)	
Preoperative psychological characteristics from the BIPQ			
Consequences	6.1 (1.7)	6.8 (1.8)	$t = -2.76, p = .006$
Personal control	5.2 (2.3)	5.6 (2.6)	$t = -1.02, p = .31$
Identity	6.4 (1.6)	7.1 (1.7)	$t = -2.59, p = .01$
Concern	4.7 (2.6)	5.9 (2.5)	$t = -2.97, p = .003$
Emotional response	4.1 (2.6)	5.5 (2.4)	$t = -3.60, p < .001$

Abbreviations: ASA, American Society of Anaesthesiologists' physical status classification; BIPQ, Brief Illness Perception Questionnaire; comp, comparison, dL, decilitre; kg, kilogram; m, metre; mg, milligram; SD, standard deviation.

*Mann–Whitney U tests

Using GMM, two distinct classes were identified. Class 1 was named the "lower worst pain class." Patients in this class (68.8%) had moderate preoperative pain scores that decreased over the 12 months following TKA (Figure 2b). Class 2 was named the "higher worst pain class." Patients in this class (31.2%) had higher preoperative pain scores compared to the lower pain class. Their pain scores increased during the first three months followed by a slight decrease over the remaining 9 months.

3.3.1 | Differences in pre-and postoperative characteristics between the worst pain classes

As shown in Table 2, no differences were found in any demographic or clinical characteristics between the two classes. Compared to the lower pain class, patients in the higher class had higher preoperative average (Cohen's $d = .44$) and worst pain (Cohen's $d = .29$) scores, higher pain interference with function scores (Cohen's $d = .50$) and a higher number of painful sites at 12 months after surgery (Cohen's $d = .29$). In addition, patients in the higher pain class used opioids prior to surgery more often, had a CFNB for more days and needed ketamine for a higher number of days. Finally, patients in the higher pain class had higher preoperative fatigue severity (Cohen's $d = .46$) and interference (Cohen's $d = .36$) scores, and higher preoperative BIPQ scores for consequences (Cohen's $d = .33$), personal control (Cohen's $d = .33$), identity (Cohen's $d = .35$), illness concern (Cohen's $d = .42$) and emotional response (Cohen's $d = .42$).

3.4 | Differences in characteristics associated with average and worst pain class membership

As shown in Table 3, twelve characteristics were associated with membership of both the average and worst higher pain classes. These characteristics were: higher preoperative average and worst pain and interference with function scores, more use of opioids prior to surgery, higher number of days with a CFNB, higher number of days with ketamine, higher preoperative fatigue severity and interference scores, and more severe preoperative scores for illness perceptions (i.e. consequences, identity, illness concern, emotional response).

4 | DISCUSSION

This study is the first to use a person-centred statistical analysis to identify a chronic pain phenotype for average and worst pain during the first year following TKA. Our

findings provide new information on the time course and risk factors associated with the transition from acute to chronic pain following TKA surgery (Burns et al., 2015; Harmelink et al., 2017; Kim et al., 2018; Lewis et al., 2015; Wylde et al., 2018). We identified several modifiable and non-modifiable characteristics associated with two chronic pain phenotypes that clinicians can use to identify high-risk patients.

For approximately 30% of the patients, their pain increased from prior to surgery through 3 months after surgery, followed by only slight decreases over the remaining nine months. Consistent with our findings, one in three patients had slow decreases in pain intensity during the first 8 week following TKA (Singh, Lemay, et al., 2019) and had more severe pain 6 months following surgery compared to patients with fast decreases. Similarly, another study (Page et al., 2015) describes a constant high pain subgroup that was characterized by a neutral or positive pain slope with no improvement during the first 12 months following surgery.

Higher preoperative pain interference with function had the largest effect size amongst all the factors associated with chronic pain phenotypes. Similarly, a number of previous reports found that poor preoperative function predicts chronic pain (Dowsey et al., 2012; Sullivan et al., 2011; Tilbury et al., 2018). However, pain interference is not the same concept as function, but rather a measure of a limiting factor for participation in everyday life (Karayannis et al., 2017). Pain interference is not well studied as a predictor for chronic pain after TKA. The large effect size for this risk factor suggests that it should be evaluated in future studies.

Similar to our findings, several studies have identified higher preoperative pain as a risk factor for chronic pain after TKA (Kim et al., 2018; Lewis et al., 2015; Noiseux et al., 2014; Page et al., 2015). Preemptive pain management to modify patients' pain levels prior to surgery is an option to reduce the risk of chronic pain following surgery (Lavand'homme & Thienpont, 2015). Pain medication is initiated prior to surgery (Pogatzki-Zahn & Zahn, 2006) to prevent the production of inflammatory substances, as well as pain sensitisation and hypersensitivity (Penprase et al., 2015). Combined with a postoperative multimodal pain management regimen, preemptive pain management is now the standard procedure in many surgical clinics (Moucha et al., 2016). Of note, while all of the patients in this study had chronic OA pain prior to surgery, only 22% ($n = 45$) used pain medication prior to surgery and only 7% ($n = 15$) used opioids. Not surprisingly, preoperative opioid consumption was identified as a risk factor for a more severe pain profile. In line with our results, preoperative opioid use was associated with early revision (Ben-Ari et al., 2017) as well as complications and a painful recovery (Zywiel et al., 2011) after TKA. Updated guidelines strongly recommend against preoperative use of opioids because of the weak evidence of the benefits of opioids on OA
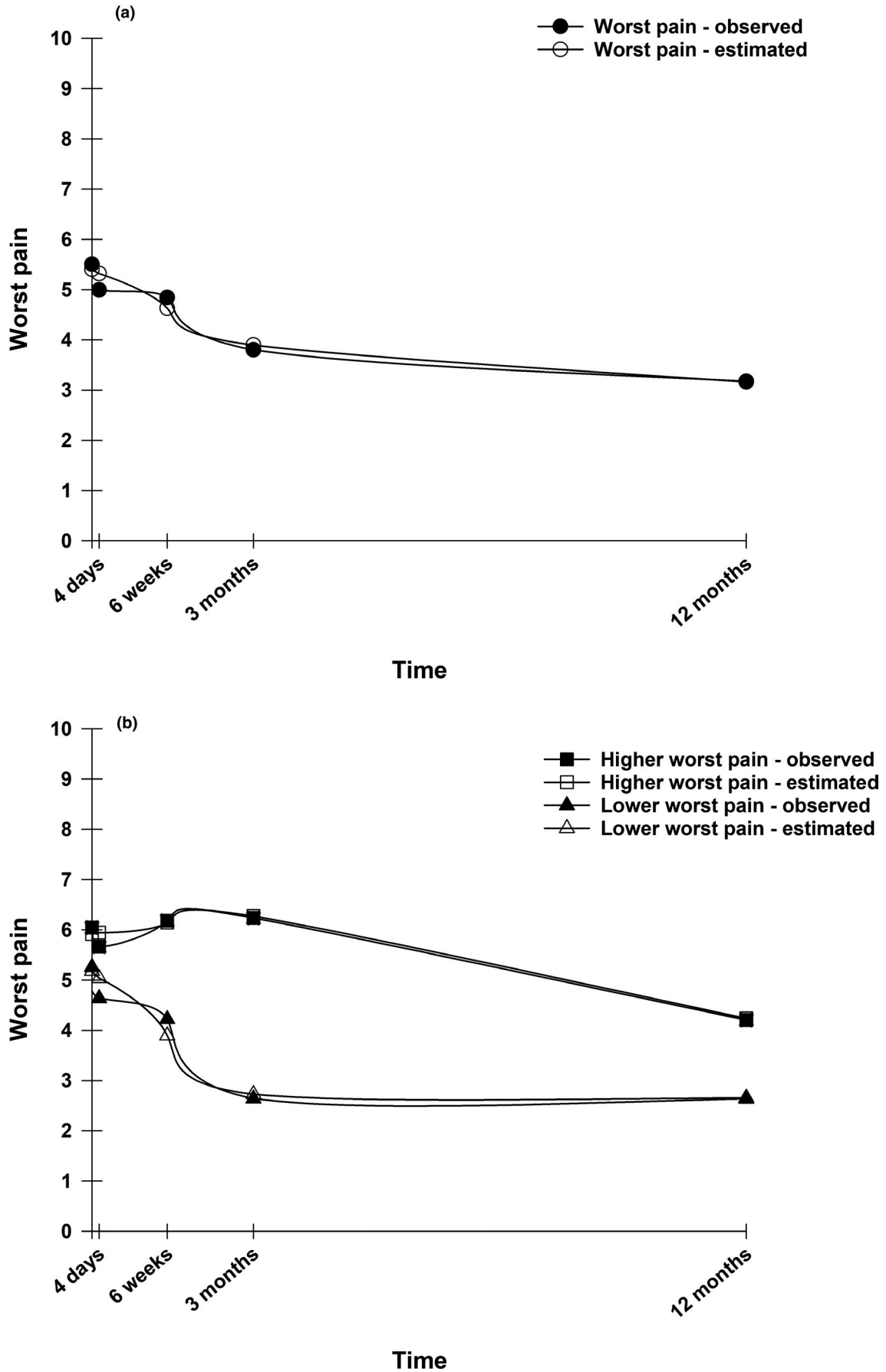
FIGURE 2 (a) Observed and estimated scores for the unconditional model of worst pain; (b) Observed and estimated scores for the latent classes of worst pain

TABLE 2 Differences in demographic, clinical, symptom, and psychological characteristics between the lower and higher worst pain classes

	Lower 68.8 % (*n* = 139)	Higher 31.2 % (*n* = 63)	Statistics
Demographic characteristics	Mean (SD)	Mean (SD)	
Age (year)	68.9 (8.6)	66.8 (10.3)	$t = 1.4, p = .16$
	% (*n*)	% (*n*)	
Women (comp: male)	67.6 (94)	69.8 (44)	$\chi^2 = .02, p = .88$
Lives alone (comp: lives with partner)	40.3 (56)	38.1 (24)	$\chi^2 = .02, p = .89$
No paid work (comp: paid work)	64.0 (89)	65.1 (41)	$\chi^2 = .001, p = 1.0$
Higher education (comp: lower education)	55.9 (76)	41.3 (26)	$\chi^2 = 3.12, p = .07$
Preoperative clinical characteristics	Mean (SD)	Mean (SD)	
Body mass index (kg/m^2)	29.2 (4.9)	29.3 (4.6)	$t = -.15, p = .88$
Number of comorbidities	1.10 (0.9)	1.3 (1.1)	$^*p = .33$
ASA score (1–4)	2.0 (0.5)	2.0 (0.5)	$^*p = .86$
Systolic blood pressure (mm/hg)	137.8 (15.7)	138.1 (17.2)	$t = -.13, p = .90$
Diastolic blood pressure (mm/hg)	81.5 (10.8)	80.3 (12.5)	$t = .69, p = .49$
C-reactive protein	3.1 (2.4)	3.7 (4.1)	$t = -1.09, p = .28$
Hemoglobin (g/dL)	13.8 (1.1)	14.0 (1.1)	$t = -.93, p = .35$
Pain characteristics			
Average pain prior to surgery	5.3 (2.1)	6.1 (1.9)	$t = -2.1, p = .04$
Worst pain prior to surgery	5.1 (1.8)	5.7 (1.7)	$t = -2.6, p = .01$
Pain interference with function prior to surgery	4.1 (1.9)	5.1 (1.9)	$t = -3.6, p < .001$
Number of painful sites, preoperative	2.1 (1.8)	2.2 (1.5)	$^*p = .35$
Number of painful sites, 12 month after surgery	1.8 (1.1)	2.3 (1.3)	$^*p = .03$
Perioperative characteristics	Mean (SD)	Mean (SD)	
Length of surgery (min)	65.3 (14.0)	65.6 (12.6)	$t = -.11, p = .92$
	% (*n*)	% (*n*)	
Left knee (49%) (comp: right knee)	50.4 (70)	44.4 (28)	$\chi^2 = .34, p = .53$
Regional anaesthesia (87%) (comp: total intravenous)	88.5 (123)	82.5 (52)	$\chi^2 = .86 p = .35$
Pain management characteristics			
Preoperative opioid use (comp: no opioids)	4.3 (6)	19.0 (12)	$\chi2 = .9.8, p = .002$
Number of days with epidural analgesia (*n* = 172)	1.8 (0.8)	1.6 (0.9)	$^*p = .10$
Number of days with a continuous femoral block	0.2 (0.7)	0.5 (0.9)	$^*p = .03$
Number of days with ketamine	0.1 (0.4)	0.3 (0.6)	$^*p = .02$
Average dose of opioids over 4 day	12.5 (6.3)	14.1 (9.4)	$t = -1.39, p = .17$
Preoperative symptoms			
Fatigue severity	2.5 (2.2)	3.3 (2.0)	$t = -2.49, p = .01$
Fatigue interference	3.7 (1.5)	4.4 (1.6)	$t = -2.92, p = .004$
Depression	3.3 (2.8)	4.1 (3.8)	$t = -1.58. p = .12$
Anxiety	4.4 (3.4)	5.1 (4.1)	$t = -1.16, p = .25$
Preoperative psychological characteristics from the BIPQ			
Consequences	6.1 (1.8)	6.7 (1.8)	$t = -2.14, p = .03$
Personal control	5.1 (2.4)	5.9 (2.4)	$t = -2.21, p = .03$
Identity	6.4 (1.7)	7.0 (1.6)	$t = -2.42, p = .02$
Concern	4.7 (2.6)	5.8 (2.6)	$t = -2.90, p = .004$
Emotional response	4.2 (2.5)	5.3 (2.7)	$t = -3.00, p = .003$

Abbreviations: ASA, American Society of Anaesthesiologists' physical status classification; BIPQ, Brief Illness Perception Questionnaire; comp, comparison; dL, decilitre; kg, kilogram; m, metre; mg, milligram; SD, standard deviation.

*Mann–Whitney *U* tests.

TABLE 3 Comparison of characteristics associated with membership of the higher average and worst pain classes

Characteristic	Higher average pain class	Higher worst pain class
Preoperative clinical characteristics		
Higher number of comorbidities	◆	
Pain characteristics		
Higher average pain prior to surgery	◆	◆
Higher worst pain prior to surgery	◆	◆
Higher preoperative pain interference with function	◆	◆
Higher number of painful sites 12 months after surgery		◆
Pain management characteristics		
Use of opioids prior to surgery	◆	◆
Fewer number of days with epidural analgesia	◆	
Higher number of days with a continuous femoral nerve block	◆	◆
Higher number of days with ketamine	◆	◆
Preoperative symptoms		
Higher fatigue severity scores	◆	◆
Higher fatigue interference scores	◆	◆
Higher depression scores	◆	
Higher anxiety scores	◆	
Psychological characteristics from the BIPQ		
Higher consequences scores	◆	◆
Higher personal control scores		◆
Higher identity scores	◆	◆
Higher concern scores	◆	◆
Higher emotional response scores	◆	◆

Abbreviation: BIPQ, Brief Illness Perception Questionnaire.

symptoms as well as the potential risk for developing opioid dependency. (Bannuru et al., 2019)

Interestingly, while a Cochrane review (Chaparro et al., 2013) found a significant preventive effect of ketamine on the development of chronic pain at 3 and 6 months after surgery, patients in the higher pain class received supplemental doses of ketamine for a higher number of days than those in the lower pain class. Our results reflect pain management in a non-experimental setting using a relatively standardized regimen. The relatively high pain scores on POD 4 suggest the need for even more individualized adjustments for effective pain management. For example, the patients who received ketamine in our study required additional analgesics beyond the standard regimen. However, this drug was usually limited to the day of surgery. Our finding is consistent with previous studies that found that higher acute postoperative pain (Puolakka et al., 2010; Thomazeau et al., 2016) and analgesic consumption (Kehlet et al., 2006) were risk factors for chronic pain after TKA.

Similarly, CFNB was used more frequently by patients in higher pain classes. This result may be related to the higher number of comorbidities in patients' higher worst pain class. For example, neuraxial blocks are contraindicated in patients on anticoagulants or with certain spinal diseases. Similarly, in a systematic review (Calders & Van Ginckel, 2018), a higher number of comorbidities was associated with increased pain severity and worse physical function after total hip and knee replacement. Clinicians may optimize patients' comorbidity status by planning an individual risk modification programme for each patient based on the preoperative assessment of their specific comorbidities (Georgiev & Angelov, 2019).

Higher preoperative fatigue scores were associated with membership in the higher pain classes. Fatigue is a common symptom in OA patients with between 35% and 41% of them reporting clinically meaningful levels of fatigue (Overman et al., 2016) that persists after TKA (Aarons et al., 1996). Of note, in our previous studies,

higher levels of fatigue were associated with higher acute pain scores (Lindberg, Miaskowski, Rustøen, et al., 2016) and increased pain with walking 12 months after surgery (Lindberg, Miaskowski, RustøEn, et al., 2016). Fatigue is a modifiable risk factor. Exercise therapy is a safe and effective intervention to decrease fatigue (Hackney et al., 2019). Clinicians who consider whether a patient with high fatigue levels is a candidate for TKA may recommend prehabilitation (Moyer et al., 2017) consisting of an individualized plan for preoperative exercise therapy adjusted to each patients' ability (Hackney et al., 2019; Murphy et al., 2012). The evidence for the effectiveness of prehabilitation on outcomes after TKA is weak to moderate.

This study is the first to evaluate associations between preoperative illness perceptions and chronic pain following TKA. Patients in the higher pain classes had worse illness perceptions (i.e. consequences, identity, illness concern, emotional response) than those in the lower pain classes. Of note, these same factors were associated with a lack of improvement in pain's interference with walking 12 months after TKA (Lindberg, Miaskowski, Rustøen, et al., 2016). Higher preoperative emotional responses and perceived consequences were associated with poorer knee function 12 months after TKA (Hanusch et al., 2014). Furthermore, illness concern predicted poorer functional results after TKA. Patients' beliefs about their illness are important determinants of how they cope with their illness and adhere to treatment (Petrie & Weinman, 2006), are related to individuals' perceived general health (Lerdal et al., 2019) and can be modified (Petrie & Weinman, 2006). Clinicians should address patients' erroneous beliefs and promote more positive health behaviours (Hurley et al., 2018). While prehabilitation including patient education is a promising option that improves functional outcomes following TKA, its effectiveness on pain outcomes remains unclear (Moyer et al., 2017).

In a systematic review (Khatib et al., 2015), higher levels of depression and anxiety were associated with more severe pain after TKA. In another systematic review (Alattas et al., 2017), preoperative anxiety was a specific risk factor for increased pain, poorer function and decreased QOL at 6 months following surgery. Furthermore, the absence of anxiety predicted lower pain scores and better function 12 months following TKA (Harmelink et al., 2017). It is interesting to note that in our study, anxiety and depression were only associated with membership in the higher average pain class. This finding suggests that average and worst pain represent distinct dimensions of the pain experience, with distinct risk factors. OA patients describe two distinct types of pain: a dull, aching constant pain and shorter episodes of more intense, acute pain (Hawker et al., 2008).

The comprehensive list of potential risk factors, the prospective design and 12-month follow-up, and the use of a patient-centred analysis are major strengths of this study. The large convenience sample from all regions of Norway increases the generalisability of our findings. All patients received the same implant, a standardized pain management regimen and physiotherapy. Some limitations warrant consideration. Several potentially important risk factors were not assessed including neuropathic pain features, pain catastrophising, expectations and amount and adherence with physiotherapy. We did not measure pain with rest and activity; however, average and worst pain are in line with the IMMPACT recommendations and may reflect similar concepts (Turk et al., 2006). Additional assessments of average and worst pain scores between 3 and 12 months would have provided a more detailed pain trajectory.

This study used a patient-centred analytic approach to identify distinct chronic pain phenotypes following TKA. Higher preoperative pain and interference scores, more opioid use prior to surgery, a higher number of days with CFNB or ketamine, higher preoperative fatigue scores and worse preoperative illness perception scores were associated with membership in the higher average and worst pain classes following TKA. These risk factors may be useful as part of an evidence-based preoperative screening tool to identify patients at higher risk for more severe pain following surgery. Future studies should test whether modifying these risk factors can improve patients' outcomes after TKA.

CONFLICTS OF INTEREST
The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS
MF. Lindberg, C. Miaskowski, T. Rustøen and A. Lerdal collaborated on the development and the design of the study. M.F. Lindberg performed the literature search and performed statistical analyses with B.A. Cooper. All authors were responsible for the data interpretation and preparation of the manuscript and have read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.