Received: 3 October 2020 | Accepted: 7 October 2020

DOI: 10.1002/msc.1522

RESEARCH ARTICLE

WILEY

High levels of preoperative pain and fatigue are red flags for moderate-severe pain 12 months after total knee arthroplasty—A longitudinal cohort study

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Funding information

The South-Easter Regional Health Authority, Grant/Award Number: 2018060; Norwegian Research Council, Grant/Award Number: 287816; The U.S. Norway Fulbright Foundation

Abstract

Background: Moderate/severe pain after total knee arthroplasty (TKA) is a poor surgical outcome. Many studies have identified preoperative risk factors of pain after TKA, but studies of the joint contributions of co-occurring symptoms are lacking.

Methods: Patients undergoing primary TKA ($n = 202$) were enrolled in a longitudinal cohort study. Preoperatively, patients completed questionnaires measuring demographics and symptoms (pain, fatigue, sleep problems and depression). Pain was re-assessed 12 months after TKA. Logistic regression analysis was used to compute the probabilities of moderate-severe pain at 12 months based on preoperative symptom levels, and results were combined into a risk matrix.

Results: More than one-third (40%) of patients ($n = 187$) reported moderate-severe pain after TKA. Among preoperative risk factors included in the logistic regression analyses were age, sex, pain, fatigue, sleep problems and depression. Adjusting for possible confounders, fatigue ($p = 0.02$) and pain ($p = 0.01$) were significant risk factors for moderate-severe pain at 12-months follow-up and were retained in the final risk matrix. The co-occurrence of high-preoperative fatigue and pain scores resulted in 57% estimated probability of moderate-severe pain at 12 months. Similarly, the co-occurrence of low-preoperative fatigue and pain scores resulted in 14% estimated probability of moderate-severe pain 12 months after TKA.

Conclusion: The combination of high fatigue and pain scores prior to surgery was a key risk factor for moderate-severe pain 12 months after TKA. Mapping of these factors could be used preoperatively to identify patients who are at risk to experience a poor outcome of TKA.

KEYWORDS

moderate-severe pain, preoperative fatigue, preoperative pain, risk factors, total knee arthroplasty

1 | INTRODUCTION

Knee osteoarthritis (OA) is associated with pain and functional impairment in patients' normal daily activities (Neogi, 2013). Total knee arthroplasty (TKA) is considered an effective intervention for improving pain and functional outcomes. Thus, the rate of utilization of TKA has increased steadily in developed countries (Pabinger, Lothaller, & Geissler, 2015), such as the United States (Inacio, Paxton, Graves, Namba, & Nemes, 2017) and Korea (Koh, Kim, Chang, Cho, & In, 2013) and the Nordic countries (NAR, 2019). Indeed, TKA has proved to be an effective therapy to lessen pain. However, this is not the case for all patients. A systematic review reported that 10%–34% of patients report chronic pain after TKA (Beswick, Wylde, Gooberman-Hill, Blom, & Dieppe, 2012). Due to this finding, the resolution of pain after TKA has become a major concern. Because pain is a multifactorial experience, the emphasis on identifying modifiable risk factors for pain 12 months after TKA is necessary to develop preventive interventions.

Previous studies have identified female gender, younger age (Singh, Gabriel, & Lewallen, 2008) and higher levels of preoperative pain (Lewis, Rice, McNair, & Kluger, 2015), pain catastrophizing (Edwards, Haythornthwaite, Smith, Klick, & Katz, 2009; Lewis et al., 2015), and anxiety and depression (Brander et al., 2003) as determinants of poor pain outcomes after TKA.

In OA patients, while pain is the predominant symptom, a number of studies have reported that depression (Han & Pae, 2015; Sharma, Kudesia, Shi, & Gandhi, 2016), fatigue (Cross, Lapsley, Barcenilla, Brooks, & March, 2008; Fishbain et al., 2003; Power, Badley, French, Wall, & Hawker, 2008) and sleep disturbances (Haack, Simpson, Sethna, Kaur, & Mullington, 2020; Irwin et al., 2012; Pickering, Chapurlat, Kocher, & Peter-Derex, 2016) are also common. These symptoms frequently occur among patients living with a chronic disease, including OA (Pickering et al., 2016; Power et al., 2008; Sharma et al., 2016). Furthermore, a number of studies have highlighted that each symptom has the potential to intensify the severity of other symptoms (Finan & Smith, 2013; Fishbain et al., 2003; Irwin et al., 2012), and in this way, co-occurring symptoms can exacerbate patients' pain severity (Haack et al., 2020; Irwin et al., 2012; Sharma et al., 2016).

Despite the knowledge that co-occurring symptoms can increase patients' experience of pain prior to surgery, possible associations between preoperative pain, fatigue, sleep problems, depression and postoperative pain after TKA have, to our knowledge, not been explored. Thus, the aim of this study was to test the hypothesis that the co-occurrence of high symptom levels prior to surgery is a risk factor for pain 12 months after TKA. Identification of possible risk factors and building a risk matrix model based on combinations of these symptoms would not only assist clinicians in determining each patient's risk profile and probable TKA pain outcomes, but would also provide critically useful information to patients weighing the potential risks versus rewards of surgery.

2 | METHODS

2.1 | Study design and setting

This study was part of 'a larger longitudinal cohort study at Lovisenberg Diaconal Hospital, Oslo, Norway' (Lindberg et al., 2016).

2.2 | Patient selection and procedures

A total of 245 patients referred from all parts of Norway scheduled for primary TKA, between October 2012 and September 2014 were invited to participate if they met the following eligibility criteria: age 18 years or older, able to understand and sign a Norwegian consent form, and no diagnosis of dementia. Of these, six patients were cancelled for surgery, and 33 patients declined to participate. Among the 206 patients who signed informed consent forms and were enrolled in the study, four patients were excluded, two due to postoperative disorientation, one had revision surgery on the same knee and one died from postoperative complications. The remaining 202 patients were included in the study and completed the baseline data. At the 12-months follow-up, 15 patients were lost (retention rate 93%), leaving a cohort of 187 patients to be included in this analysis.

On the day of admission to hospital, usually the day before surgery, patients completed the baseline questionnaires, which measured preoperative pain, fatigue, sleep problems and depression. Moreover, the demographic and clinical information (i.e., body mass index [BMI], number of comorbidities and American Society of Anesthesiologists physical status classification [ASA] score) were retrieved from their medical records. Twelve months after TKA surgery, patients were mailed the follow-up questionnaire, which measured pain, and returned it in a pre-paid envelope. Patients who did not respond received one reminder.

2.3 | Surgical and pain management procedures

The 'surgical technique, including anaesthesia, pain management and physiotherapy, were standardized' (Lindberg et al., 2016). In brief, all patients received similar posterior cruciate-retaining fixed modular-bearing implants for the TKA. A tourniquet was used in the course of surgery and drainage was placed and removed on postoperative day 1. Neuraxial block with bupivacaine and sedation were the first choice for anaesthesia. Epidural analgesia, with continuous infusion of bupivacaine 1 mg/ml, adrenaline 2 μg/ml and fentanyl 2 μg/ml (5–12 ml/h), was used for postoperative pain management. Patients for whom neuraxial blockade was contraindicated received total intravenous anaesthesia and a continuous femoral nerve block with bupivacaine 2.5 mg/ml (4–10 ml/h) for postoperative pain management. In most cases, the regional blocks were removed on postoperative day 2. Oral acetaminophen 1 g was given every 6 h and

celecoxib 200 mg and controlled-release oxycodone 5–20 mg was given every 12 h unless contraindicated. Supplementary treatment with low dose ketamine 1.5 μg/kg/min was available as a short-term intravenous infusion, usually on the day of surgery. All patients were mobilized out of bed and allowed full weight bearing on the operated knee on postoperative day 1. Patients received physical therapy on a daily basis with walking, flexion and extension of the knee beginning on postoperative day 1.

2.4 | Measurements

The Norwegian version (Klepstad et al., 2002) of the valid and reliable Brief Pain Inventory (BPI; Cleeland, 1985) was used to measure worst pain intensity both at baseline and at follow-up. The BPI consists of four items that measure 'worst', 'least', 'average' and 'now' pain intensity using an 11-point numeric rating scale (NRS) with endpoints of 0 (i.e., no pain) to 10 (i.e., worst imaginable pain), seven items that assess pain interference with function, one item that assesses pain relief, and a body map that assesses pain locations. For the purpose of this study, the 'worst pain intensity' item was used as the outcome (Atkinson et al., 2010). A worst pain intensity score ≥4 is indicative of moderate-severe pain (Atkinson et al., 2010; Gerbershagen, Rothaug, Kalkman, & Meissner, 2011; Kapstad, Hanestad, Langeland, Rustøen, & Stavem, 2008).

The Norwegian version of the Lee Fatigue Scale (LFS) was used to measure preoperative fatigue severity. Patients rated the severity of fatigue on five items on a 0–10 NRS. Higher scores indicate more severe fatigue. For this study, scores ≥5 were considered indicative of severe fatigue. The LFS has adequate psychometric properties (Lerdal, Kottorp, Gay, & Lee, 2013).

The Pittsburgh Sleep Quality Index (PSQI) was used to assess preoperative sleep quality. The 19-item self-rated questionnaire consists of seven sub-scores; each rated equally on a 0–3 scale. The sub-scores are summed to yield a global score that ranges from 0 to 21, with higher scores indicating worse sleep quality. PSQI global scores ≥5 is indicative of impaired sleep quality. The PSQI has been shown to be a reliable and valid tool for assessing sleep quality (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989).

The Norwegian version of the Hospital Anxiety and Depression Scale (HADS) was used to measure preoperative depressive symptoms. The psychometric properties of the HADS were acceptable in a large population-based study in Norway (Mykletun, Stordal, & Dahl, 2001). The depression subscale consists of seven items, rated on a 4-point Likert scale (0–3), then summed to a maximum of 21 points. Scores ≥8 indicate the presence of depressive symptoms (Zigmond & Snaith, 1983).

2.5 | Statistical analysis

Data were analysed using the Statistical Package for Social Sciences (SPSS), version 26 (IBM). Continuous variables were reported as means, standard deviations, medians and ranges and categorical variables as counts and percentages.

Variables were selected for testing in the risk matrix based on both available literature and statistical properties. We assessed crude associations between pairs of categorical variables using chi-square tests. Variables that reached a p-value <0.1 in the univariate analyses were entered into a multivariate model. Risk factors were excluded if they were highly correlated with each other to reduce the risk of multi-collinearity.

Several logistic regression models were fitted and the best model was chosen based on its predictive power and Akaike Information Criterion. The odds of having moderate-severe pain (worst pain intensity score ≥4) 12 months after TKA derived from the logistic regression models were then transformed into probabilities and the results were used to construct a risk matrix. p-values <0.05 were considered statistically significant. As all analyses were considered exploratory, no correction for multiple testing was performed. Imputation of missing data was not performed, as missingness was well below 10% for all variables.

3 | RESULTS

In total, there were 202 patients prior to surgery; with mean (SD) age of 68 (9), two thirds were female, 60% completed higher education, 60% were lived with partner and 64% were not working. Furthermore, the majority were overweight with a median BMI in kg/m^2 of 28 (19–43), mean number of comorbidities 1 (0–5) and a median ASA classification score of 2 (1–3).

Frequencies of the potential preoperative risk factors (i.e., pain, fatigue, depression and sleep disturbance) and the outcome variable (i.e., moderate-severe pain 12 months after TKA) are presented in (Table 1).

The initial multiple logistic regression analysis (Table 2) revealed no statistically significant associations between moderate-severe pain 12 months after TKA and the following baseline variables: age, depression and sleep quality. Thus, these three variables were not

TABLE 1 Frequencies of potential preoperative risk factors and postoperative outcome

Variables	Total	*n*	%
Preoperative symptoms			
Pain (BPI worst pain score ≥4)	202	162	80
Fatigue (LFS score ≥5)	198	38	19
Depression (HADS depression score ≥8)	191	24	13
Sleep disturbance (PSQI score ≥5)	172	153	89
Postoperative outcome (12 months after TKA)			
Pain (BPI worst pain score ≥4)	187	74	40

Abbreviations: BPI, Brief Pain Inventory; HADS, Hospital Anxiety and Depression Scale; LFS, Lee Fatigue Scale; PSQI, Pittsburgh Sleep Quality Index; TKA, total knee arthroplasty.

TABLE 2 Initial multiple logistic regression model of risk factors for moderate-severe pain (worst pain intensity score ≥4) 12 months after TKA

Preoperative predictors	Adjusted OR	95% CI	*p*-value
Pain (BPI worst pain score ≥4)	4.33	1.35–13.85	0.013[a]
Fatigue (LFS score ≥5)	2.93	1.20–7.17	0.018[a]
Depression (HADS depression score ≥8)	1.74	0.53–5.72	0.362
Sleep disturbance (PSQI score ≥5)	1.41	0.51–3.92	0.509
Age at admission, years	1.00	0.97–1.05	0.785
Sex (female)	0.49	0.22–1.10	0.086

Abbreviations: BPI, Brief Pain Inventory; CI, confidence interval; HADS, Hospital Anxiety and Depression Scale; LFS, Lee Fatigue Scale; OR, odds ratio; PSQI, Pittsburgh Sleep Quality Index; TKA, total knee arthroplasty.

[a]denotes statistically significant.

TABLE 3 Preoperative symptom risk factors for moderate-severe pain 12 months after TKA stratified by sex

Sex	Preoperative predictors	Adjusted OR	95% CI	*p*-value
Male	Fatigue (LFS score ≥5)	1.33	0.30–5.93	0.705
	Pain (BPI worst pain score ≥4)	15.94	1.88–134.95	0.011[a]
Female	Fatigue (LFS score ≥5)	2.17	0.99–4.76	0.054
	Pain (BPI worst pain score ≥4)	2.27	0.76–6.83	0.144

Abbreviations: BPI, Brief Pain Inventory; CI, confidence interval; LFS, Lee Fatigue Scale; OR, odds ratio; TKA, total knee arthroplasty.

[a]denotes statistically significant.

retained in the final regression model. Those with a high level of fatigue had almost three times higher odds for moderate-severe postoperative pain compared to those with low levels of fatigue odds ratio (OR) = 2.9 (95% confidence interval [CI] 1.2–7.2). Those with moderate-severe preoperative pain had more than four times higher odds for moderate-severe postoperative pain compared to those with no or mild preoperative pain OR = 4.3 (95% CI 1.4–13.9). Females were half as likely to have moderate-severe pain OR = 0.5 (95% CI 0.2–1.1) compared to males, however this association did not reach the level of statistical significance.

Regarding sex, females were much less likely than males to have moderate-severe pain 12 months after TKA. Thus, to further investigate the possible difference regarding sex, the analysis was stratified by sex and models with preoperative pain and fatigue were fitted separately for males and females (Table 3). For males, those who reported moderate-severe pain preoperatively were 16 times more likely to still experience moderate-severe pain 12 months after TKA OR = 15.9 (95% CI 1.9–134.9). In contrast, females who had severe fatigue preoperatively were two times more likely to experience moderate-severe pain 12 months after TKA OR = 2.2 (95% CI 0.9–4.8).

As displayed in the final multiple logistic regression model in (Table 4), preoperative fatigue and pain remained statistically significant in the model and were used to construct a risk matrix. All combinations of preoperative fatigue and pain levels are presented as probabilities for moderate-severe pain 12 months after TKA in (Table 5).

TABLE 4 Final multiple logistic regression model of risk factors for moderate-severe pain (worst pain intensity score ≥4) 12 months after TKA ($n = 187$)

Preoperative predictors	Adjusted OR	95% CI	*p*-value
Fatigue (LFS score ≥5)	2.08	1.03–4.19	0.042[a]
Pain (BPI worst pain score ≥4)	4.10	1.59–10.57	0.003[a]
Sex (Female)	0.88	0.44–1.76	0.724

Abbreviations: BPI, Brief Pain Inventory; CI, confidence interval; LFS, Lee Fatigue Scale; OR, odds ratio; TKA, total knee arthroplasty.

[a]denotes statistically significant.

4 | DISCUSSION

This study is the first to use preoperative symptoms to generate a risk matrix estimating probabilities of experiencing moderate-severe pain following TKA. Our findings revealed that higher levels of fatigue and pain prior to surgery are associated with higher odds of moderate—severe pain following TKA. This risk matrix model is a simple tool that can easily be implemented and used in clinical practice. Thus, our model may assist decision-making for clinicians and OA patients when considering knee replacement.

We found that more than one-third (40%) of patients reported moderate-severe pain 12 months after TKA. Our finding is somewhat higher than reported in a systematic review of studies (Beswick et al., 2012), which estimated a range of 10%–34% of patients experiencing the undesirable outcome of long-term pain. This discrepancy might

TABLE 5 Full risk matrix model for moderate-severe pain (worst pain intensity score ≥4) 12 months after TKA by preoperative fatigue and pain levels

Likelihood of moderate-severe pain 12 months after TKA			
		Preoperative pain level	
		Moderate-severe (NRS ≥4)	Mild (NRS <4)
Preoperative fatigue level	High (LFS ≥5)	57.3%	25.0%
	Low (LFS <5)	39.7%	14.1%

Abbreviations: LFS, Lee Fatigue Scale; NRS, 0–10 numeric rating scale; TKA, total knee arthroplasty.

reflect methodological differences across studies. Studies not only differ with respect to their patient populations and the length of their follow-up period, they also vary in how chronic pain is defined. Some studies define chronic pain as a lack of improvement in pain ratings over time, some define it as pain above a certain severity level at the time of follow-up, and still others specify a minimum duration of pain above a certain level (e.g., moderate or severe pain for at least 3 months). This study defined pain as a numerical rating ≥4 (on a 0–10 scale) for the patient's worst pain in the past 24 h. This definition of pain could include patients whose pain was significantly reduced following surgery or who might only be experiencing temporary pain, and thus, we might expect a higher proportion of patients identified as having moderate/severe pain 12 months after TKA compared with other studies that used a stricter definition.

Moreover, this study used ratings of 'worst pain intensity', which tend to be higher than the 'average pain intensity' ratings used in some other studies. However, the worst pain intensity measure was selected because it may capture different elements of pain such as movement-evoked pain. Reduced pain with movement is an important aspect of recovery after TKA. Furthermore, a systematic evaluation of the worst pain intensity rating (Atkinson et al., 2010) concluded that this measure satisfies most key recommendations for clinical trial endpoints, is simple and low demand to use and the cut-point levels were considered reasonable and valid for patient-based studies.

In this study, we did not find any statistically significant associations between moderate-severe pain at 12 months and the following preoperative variables, adjusted for other factors: patient age, depression and sleep quality. The lack of significant associations may reflect a lack of variability on these measures, as most patients in this sample were older, few had depressive symptoms, and most had sleep disturbance. A larger sample with more variation on these measures is needed to fully evaluate potential associations with pain outcomes following TKA.

Despite these negative findings, we did detect a strong association between moderate-severe preoperative pain and moderate-severe pain following TKA OR = 4.1 (95% CI 1.6–10.6), adjusting for other factors. This result is consistent with a meta-analysis focused on pain as an outcome variable (Lewis et al., 2015), which concluded that a high level of pain prior to surgery is often a risk factor for chronic pain across a number of surgical procedures.

Furthermore, we observed novel finding that a high level of preoperative fatigue was strongly associated with moderate-severe pain 12 months after TKA OR = 2.1 (95% CI 1.0–4.2). Because no previously published studies have explored the relationship between this common symptom and chronic pain, there is no existing literature with which to compare our result.

Moreover, we observed a significant sex difference with respect to the symptoms that were associated with pain after TKA. For males, only preoperative pain was statistically significant OR = 15.9 (95% CI 1.9–134.9), but the CI was quite broad. In contrast, for females, it was fatigue that was statistically significant OR = 2.2 (95% CI 1.0–4.8). Thus, this study raises the possibility that a sex difference exists, but we lack the statistical power due to our small sample size and under-representation of male patients, and are therefore unable to model the sex differences with sufficient statistical precision. Further research is needed with a larger sample to describe the potentially sex-specific influence of symptoms on pain outcomes.

Finally, we constructed a risk matrix with two variables, preoperative fatigue and pain. Both were statistically significant risk factors for moderate-severe pain 12 months after TKA and were therefore retained in the final model. When arranged in the risk matrix, our results indicated that patients with the co-occurrence of high scores on both fatigue and pain measures prior to surgery had 57% probability of experiencing moderate-severe pain 12 months after TKA. Similarly, patients with the co-occurrence of low scores on both fatigue and pain prior to surgery had only 14% probability of having moderate-severe pain 12 months after TKA. These results support our hypothesis that the presence of severe symptoms prior to surgery may be associated with significant pain 12 months after TKA.

We acknowledged that the study was conducted at one centre, which may limit the generalizability of the findings. However, the study centre admits patients from all regions of Norway. Furthermore, the relatively small sample size may have limited the statistical precision of the results, especially for analysing gender differences.

5 | CONCLUSION

High preoperative fatigue and pain scores are risk factors for moderate-severe pain 12 months after TKA. It is therefore useful to include these symptoms in preoperative screening for knee replacement therapy. Screening both fatigue and pain prior to surgery and

designing modifications for those patients at risk may reduce the likelihood of patients experiencing moderate-severe pain after TKA.

ACKNOWLEDGEMENTS

The research presented in this study was supported by funding from the Norwegian Research Council of Norway (grant #287816), the South-Easter Regional Health Authority (grant #2018060) and the U.S.–Norway Fulbright Foundation.

CONFLICT OF INTERESTS

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

ETHICAL STATEMENT

This study was conducted through an inter-university collaboration between Jimma University, Ethiopia, and University of Oslo, Norway. The study was conducted with approval from the Regional Committee for Medical Research Ethics—South-East Norway (2011/1755) and from the Institutional Review Board, Jimma University (JHRPGD/510/2018).

AUTHOR CONTRIBUTIONS

Anners Lerdal, Milada Cvancarova Småstuen, Maren Falch Lindberg, and Mestawet Getachew developed and designed the study. Milada Cvancarova Småstuen and Mestawet Getachew performed the statistical analyses. All authors appraised the data, contributed to the manuscript preparation, and have read and approved the final manuscript.

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How to cite this article: Getachew M, Lerdal A, Småstuen MC, et al. High levels of preoperative pain and fatigue are red flags for moderate-severe pain 12 months after total knee arthroplasty—A longitudinal cohort study. *Musculoskeletal Care*. 2020;1–7. https://doi.org/10.1002/msc.1522