Received: 12 September 2022 | Revised: 30 March 2023 | Accepted: 9 May 2023

DOI: 10.1002/ejp.2138

EJP European Journal of Pain

ORIGINAL ARTICLE

Testing of a predictive risk index for persistent postsurgical pain on patients undergoing total knee arthroplasty: A prospective cohort study

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Funding information
HUS Helsinki University Hospital Finnish Government Science, Grant/Award Number: TYH 2019113 and TYH 2017239; HUS Helsinki University Hospital, Grant/Award Number: Y102011095; Paulo Foundation; Finnish Medical Foundation; Research Foundation for Orthopaedics and Traumatology; Finnish Arthroplasty Society; Finnish Society of Anaesthesiologists; Finnish Medical Society Duodecim; Orion Research Foundation

Abstract

Background: We investigated whether a universal predictive risk index for persistent postsurgical pain (PPP) is applicable to patients who undergo total knee arthroplasty (TKA).

Methods: In this cohort study, 392 participants of a randomized study investigating the effects of anaesthesia methods and tourniquet use on TKA were divided into low-, moderate-, and high-risk groups for PPP, as suggested in the previous risk index study. Patients reported pain using the Oxford Knee Score pain subscale and Brief Pain Inventory–short form preoperatively and 3 and 12 months postoperatively. We compared the pain scores of the low- to moderate- and high-risk groups at respective time points and investigated changes in pain scores and the prevalence of PPP at 3 and 12 months after surgery.

Results: The high-risk group reported more pain 3 and 12 months after TKA than the low- to moderate-risk group. However, of seven variables, only a single difference reached the threshold for minimal clinical importance between the groups at 12 months. Additionally, at 12 months, the low- to moderate-risk group reported slightly worse improvements in three of seven pain variables than the high-risk group. Depending on the definition, the prevalence of PPP ranged from 2% to 29% in the low- to moderate-risk group and 4% to 41% in the high-risk group 12 months postoperatively.

Conclusions: Although the investigated risk index might predict clinically important differences in PPP between the risk groups at 3 months after TKA, it seems poorly applicable for predicting PPP at 12 months after TKA.

Significance: Although many risk factors for persistent postsurgical pain after total knee arthroplasty have been identified, predicting the risk of this pain has remained a challenge. Results of the current study suggest that accumulation of previously presented modifiable risk factors might be associated with increased postsurgical pain at 3 months, but not at 12 months after total knee arthroplasty.

1 | INTRODUCTION

Total knee arthroplasty (TKA) is an effective treatment for severe knee osteoarthritis. TKA reduces pain and improves function and health-related quality of life in the long-term (Scott et al., 2015; Shan et al., 2015). However, although most patients are satisfied with the outcome of this operation (Rantasalo et al., 2021; Scott et al., 2015; Shan et al., 2015), the prevalence of moderate to severe persistent postsurgical pain (PPP) after TKA ranges, depending considerably on the definition and timepoint of measurement, from 7% to 45% (Baker et al., 2007; Brander et al., 2003; Palanne et al., 2021; Rice et al., 2018; Singh et al., 2011; Wylde et al., 2011).

Multiple risk factors for PPP after TKA have been identified (Gungor et al., 2019; Lewis et al., 2015; Liu et al., 2012; Puolakka et al., 2010; Rice et al., 2018; Thomazeau et al., 2016). Higher preoperative pain and pain elsewhere than at the target knee area are notable predictors (Gungor et al., 2019; Lewis et al., 2015; Liu et al., 2012; Rice et al., 2018). In addition, high-intensity acute postoperative pain seems to be associated with PPP (Liu et al., 2012; Puolakka et al., 2010; Rice et al., 2018; Thomazeau et al., 2016). Other previously reported risk factors include variables such as expected pain (Rice et al., 2018), trait anxiety (Rice et al., 2018), catastrophizing (Lewis et al., 2015) and mental health (Lewis et al., 2015).

Despite the increasing data on individual risk factors, the number of clinically applicable models for predicting PPP is limited. One such model was developed by Althaus and colleagues (Althaus et al., 2012), a highly cited risk index based on a systematic literature search and multivariate analyses of 150 patients who underwent mixed elective surgery. The index consists of four preoperative and one postoperative predictors for PPP: pain in the operation area, pain elsewhere in the body, capacity overload in the past 6 months, co-morbid stress symptoms, and "considerable acute postoperative pain" (Althaus et al., 2012). Each variable is rated either absent or present. Chronic postsurgical pain was reported by 12% to 30% of patients with 0–1 risk factors, 37% of patients with 2 risk factors, and 68% to 82% of patients with 3–5 risk factors at 6 months after surgery. The authors suggested that 0–1 risk factors would correspond to low risk, 2 risk factors to moderate risk, and 3–5 risk factors to high risk for chronic postsurgical pain (Althaus et al., 2012). With the cut-off score of ≥3, the risk index had a sensitivity of 60% and specificity of 83%, and the reported area under the receiver operating characteristic (ROC) curve of the model was 0.77 (Althaus et al., 2012). Results of a study with a mixed surgery cohort supported the external validity of the risk index (Mathes et al., 2018).

A predictive risk index that is based on modifiable risk factors, such as the one presented by Althaus and colleagues (Althaus et al., 2012), could allow for targeted interventions that might reduce the risk of PPP. Additionally, it could be used for estimating the optimal time point for surgery and for informing patients more accurately on the long-term outcomes. However, before considering the implementation of the risk index for a specific patient group, its applicability to this group should be assessed.

The aim of this study was to investigate whether the risk index for PPP presented by Althaus and colleagues is applicable to patients undergoing primary TKA (Althaus et al., 2012). We compared pain scores between groups with low to moderate and high risk for PPP at 3 and 12 months after surgery. In addition, we investigated possible differences between the groups in pain reduction and in the prevalence rates for PPP at respective time points. We further studied the effect of increasing number of risk factors on the prevalence of PPP and external validity of the risk index for TKA patients. We hypothesized that the risk index is an applicable prediction model of PPP at 3 months, and more importantly, at 12 months after surgery for patients undergoing TKA.

2 | METHODS

This prospective cohort study was a secondary analysis of a randomized trial investigating the effects of anaesthesia methods and tourniquet use on TKA. The trial

was conducted at the HUS Helsinki University Hospital, Finland between October 2016 and December 2019. A separate study description and results concerning anaesthesia methods and tourniquet use have been published (Palanne et al., 2020, 2021; Rantasalo et al., 2018, 2021). The trial was registered to EudraCT (ref: 2016-002035-15) and approved by the Finnish Medicines Agency Fimea (ref: KL72/2016) and ethics committee of HUS Helsinki University Hospital, Surgery (ref: HUS1703/2016). Every participant gave written informed consent.

2.1 | Patients

Patients undergoing unilateral TKA due to Kellgren-Lawrence Grade 3 to 4 osteoarthritis were eligible for the primary trial. We excluded patients aged under 18 and over 75 years, those with a body mass index >40 kg/m^2, and/or an American Society of Anesthesiologist physical status class ≥4, and those with severe flexion or extension deficit, malalignment or prior major surgery of the target knee (Rantasalo et al., 2018). We further excluded patients with contraindications to general or spinal anaesthesia or to the study medications, ongoing usage of strong opioids, or a need for bridging anticoagulation (Rantasalo et al., 2018).

2.2 | Treatments

Patients underwent a TKA performed through a midline incision with a medial parapatellar approach (Rantasalo et al., 2018). According to randomization, patients were operated either with or without a tourniquet and under general or spinal anaesthesia (Rantasalo et al., 2018). Multimodal pain management was standardized and included local infiltration analgesia, repetitive oral ibuprofen and acetaminophen, and patient-controlled analgesia with intravenous oxycodone for the first 24 postoperative hours (Rantasalo et al., 2018). Subsequently, patients were given one extended-release oxycodone tablet and repeated immediate-release oxycodone on request. Patients received oral tramadol or a combination of codeine and acetaminophen up to three times a day from the second postoperative morning. Pregabalin and peripheral nerve blocks were used in case rescue analgesia was required. The use of analgesics after hospital discharge was not controlled.

2.3 | Data collection

Data on patient characteristics were collected at the preoperative clinic. Patient inquiries were conducted concerning the presence of the preoperative risk factors described by Althaus and colleagues: pain in the target knee area, pain elsewhere in the body, capacity overload in the past 6 months and co-morbid stress symptoms (Althaus et al., 2012). "Considerable acute postoperative pain" was defined as a numerical rating scale (NRS) ≥5 (0 to 10, 0 = no pain, 10 = worst imaginable pain) after walking five meters or an inability to walk because of pain 24 h after operation.

Patients reported pain using the validated and self-administered Oxford Knee Score (OKS) pain subscale and Brief Pain Inventory-short form (BPI-sf) questionnaires preoperatively and 3 and 12 months postoperatively (Cleeland, 2009; Dawson et al., 1998; Harris et al., 2013; Murray et al., 2007). OKS is specifically designed for TKA patients with questions related to knee pain and function during the past 4 weeks. The OKS pain subscale consists of seven questions concerning pain severity and interference that are rated from 0 to 4, resulting in a total pain score of 0 to 28 (scaled from 0 to 100, 0 = worst outcome, 100 = best outcome) (Dawson et al., 1998; Harris et al., 2013). BPI-sf is a universal tool for assessing pain severity and interference with questions referring to the last 24 h (Cleeland, 2009). Pain in BPI-sf is evaluated with NRS (0 = no pain/pain interference, 10 = worst imaginable pain/pain interference).

2.4 | Risk groups

Risk groups for PPP were defined as suggested by Althaus and colleagues (Althaus et al., 2012). The sum of the four preoperative and one postoperative risk factors was determinative: the low-risk group consisted of patients with 0–1 risk factors, the moderate-risk group of patients with two risk factors, and the high-risk group of those with 3–5 risk factors.

2.5 | Outcomes

The OKS pain subscale scores and BPI-sf pain scores at 3 and 12 months after TKA were the main outcomes of this secondary analysis. As pain after TKA seems to decrease up to 12 months after surgery (Brander et al., 2003; Palanne et al., 2021; Rice et al., 2018), we regarded the 12-month pain scores as the primary outcomes whereas the 3-month pain scores were considered transitory. From the BPI-sf, we included outcomes concerning pain severity (average pain, current pain, least and worst pain in the last 24 h, and the arithmetic mean of these four severity variables) and pain interference (the arithmetic mean of seven pain interference variables) as suggested in the Brief Pain

Inventory User Guide (Cleeland, 2009). Additionally, the change scores (i.e. differences between postoperative and preoperative pain scores) at 3 and 12 months were studied in a post hoc sensitivity analysis. We also explored the prevalence of significant PPP and its possible association with the number of risk factors at 3 and 12 months post hoc, using five different definitions for PPP. Multiple definitions were used so that the results could be compared with previous studies and to demonstrate the significance of the definition on the results. BPI-sf average pain (NRS) ≥3 was selected as one definition for significant PPP because of its resemblance to the definition used by Althaus and colleagues (Althaus et al., 2012). Additionally, NRS ≥4 and ≥5 have been presented as indicators of moderate to severe pain in previous studies (Gungor et al., 2019; Kapstad et al., 2008). Patient-reported moderate to severe knee pain for the OKS question concerning usual pain was selected because of its knee specificity and easy comparability with other studies (Baker et al., 2007; Palanne et al., 2021; Puolakka et al., 2010; Singh et al., 2011). Finally, the OKS pain subscale scores ≤14/28 were utilized because of a recent suggestion to use this as the cut-off for chronic postoperative pain after TKA (Pinedo-Villanueva et al., 2018). The external validity of the risk index for TKA patients at 3 and 12 months after surgery was also assessed by exploring areas under the ROC curves and by calculating sensitivity and specificity of the risk index with the cut-off score of ≥3, consistently with the risk index study (Althaus et al., 2012).

2.6 | Statistical analysis

For secondary analyses concerning BPI-sf scores, the sample size was calculated for the "average pain" with the mean NRS of 5.5 (standard deviation 2.2), using two-tailed tests with parametric methods and with an alpha of 0.05 and a power of 0.80. The sample size was further increased by 16% in order to adjust for possible nonparametric analyses. As NRS 1.0 was set as the minimal clinically important difference (MCID) between groups, the minimum sample size resulted in 90 patients per group (Rantasalo et al., 2018). For the OKS pain subscale, 10 scores on the scale of 0 to 100 was defined as MCID (Myles et al., 2017).

The analysis plan was completed after the collection of data. The low-risk group consisted of 33 patients (8%), the moderate-risk group of 100 patients (26%), and the high-risk group of 259 patients (66%). Thus, to maintain sufficient power, the low- and moderate-risk groups were analysed as one and compared to the high-risk group. Nevertheless, we explored the possible differences between the three separate risk groups in a supplementary sensitivity analysis. In addition, to assess the association between the number of risk factors and the prevalence rates for PPP, patients were grouped according to the number of risk factors.

We analysed categorical data concerning patient characteristics and comparisons of the three risk groups using the chi-square test or Fisher's exact test, and presented results as the number of patients with percentages. We used Bonferroni adjustments in pairwise comparisons when more than two groups were analysed. We performed comparisons concerning the prevalence rates for PPP between the low- to moderate-risk and high-risk groups using binary logistic regression and presented results as odds ratios (95% confidence interval [CI]).

Descriptive data concerning continuous variables were presented as means with standard deviations for normally distributed data and as medians with interquartile ranges for non-normally distributed data. However, to allow for easier comparisons, medians with interquartile ranges were presented if data of a variable were not normally distributed in both groups.

In the comparisons between two groups, continuous data with normal distributions were analysed using the independent samples *t*-test, and non-normally distributed data were analysed using the Mann–Whitney *U*-test. Results were expressed as mean differences (95% CI) and as Hodges-Lehman estimates of median differences (95% CI). In the supplementary sensitivity analyses concerning the comparisons of the three risk groups, normally distributed data were analysed using one-way analysis of variance with Tukey adjustments in further pairwise comparisons, and non-normally distributed data were analysed using the Kruskal–Wallis test with the Mann–Whitney U-test and Bonferroni adjustments in pairwise comparisons.

All tests were two-sided, and we regarded $p < 0.05$ as statistically significant. All analyses were conducted using IBM SPSS Statistics 27 for Windows (IBM Corp.).

3 | RESULTS

Only 4 of 2783 (0.14%) patients were excluded from the primary trial because of preoperative usage of strong opioids. Of the 404 patients who were randomized in the primary trial, two received a non-protocol prosthesis and two had Kellgren-Lawrence Grade 2 osteoarthritis. These patients were excluded from the analyses. Erroneously, postoperative data were not collected from one patient. Of the remaining 399 patients, pain scores after walking 5 meters 24 h postoperatively were missing from 19 patients. However, of these 19 patients, five were unable to walk because of pain and seven could be classified into the high-risk group based on the preoperative data. Thus,

baseline data were analysed from 392 patients (Table 1). Two patients cancelled their participation before the 3-month follow-up. Another three patients did not take part in the 12-month follow-up.

In the high-risk group, the mean age was lower and the body mass index higher than in the low- to moderate-risk group (Table 1). The proportions of females and patients with depression, rheumatological disease, and ASA physical status Class III were also higher in the high-risk than in the low- to moderate-risk group (Table 1).

The high-risk group reported lower (i.e. worse) OKS pain subscale scores than the low- to moderate-risk group at all time points (Table 2). Consistently, the BPI-sf pain scores were higher in the high-risk group (Table 2). However, the differences in OKS pain subscale scores between the groups did not reach the threshold (≥10 scores) for minimal clinical importance. The differences between the groups in BPI-sf pain scores reached or surpassed the border for minimal clinical importance (NRS ≥1.0) in all variables preoperatively and in all but one variable—the least pain in 24 h—at 3 months after surgery. However, at 12 months, only the difference concerning the worst pain in 24 h reached the border for minimal clinical importance (Table 2).

In the post hoc sensitivity analysis concerning the change scores at 3 months after TKA, no significant differences between the low- to moderate-risk and high-risk groups were detected (Table 3). At 12 months, the pain scores of patients in the high-risk group had improved better, concerning the least pain in the last 24 h, current pain and pain interference (Table 3). However, the differences remained below the threshold for minimal clinical importance. The prevalence rates for PPP were significantly lower in the low- to moderate-risk

TABLE 1 Patient characteristics.

Characteristics	Low to moderate risk ($n=133$)	High risk ($n=259$)	p value
Age (years)	65.3 ± 6.9	63.1 ± 7.4	0.004[a]
Sex (female)	72 (54)	177 (68)	0.006
Body mass index (kg/m^2)	29.6 ± 4.3	30.8 ± 4.3	0.009[b]
Medication for hypertension	68 (51)	146 (56)	0.324
Coronary artery disease	4 (3)	10 (4)	0.780
Diabetes mellitus	17 (13)	46 (18)	0.204
eGFR (ml/min/1.73 m^2)	87.2 ± 11.6	86.4 ± 11.9	0.560
Asthma or COPD	13 (10)	40 (15)	0.120
Current smoking	16 (12)	30 (12)	0.896
Depression	3 (2)	24 (9)	0.009
Rheumatological disease	3 (2)	27 (10)	0.004
Previous minor surgery of the target knee	51 (39)[1]	102 (40)[2]	0.841
Reason for operation			0.059
Primary osteoarthritis	130 (98)	236 (91)	
Rheumatoid or psoriatic arthritis	1 (1)	11 (4)	
Posttraumatic osteoarthritis	2 (2)	6 (2)	
Other	0 (0)	6 (2)	
ASA physical status classification			0.029[c]
I	16 (12)	19 (7)	
II	89 (67)	155 (60)	
III	28 (21)	85 (33)	

Note: Values present mean ± standard deviation or number of patients (percentage).

Abbreviations: ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

[a]Mean difference 2.2 (95% confidence interval [CI] 0.72 to 3.8).

[b]Mean difference −1.2 (95% CI −2.1 to −0.3).

[c]$p=0.045$ for the comparison concerning ASA physical status classification III, Bonferroni adjusted p value. Superscript numbers indicate the number of missing values.

TABLE 2 Pain scores in the low- to moderate-risk group and the high-risk group before and 3 and 12 months after total knee arthroplasty.

	Low to moderate risk	High risk	Difference (95% CI)	*p* value
Before operation				
n	133	259		
OKS pain subscale	52.3 ± 13.4[3]	47.3 ± 12.6[2]	5.0 (2.3 to 7.7)[a]	<0.001
BPI-sf average pain	3.8 ± 2.1[2]	4.9 ± 1.8[3]	−1.0 (−1.5 to −0.6)[a]	<0.001
BPI-sf worst pain in the last 24 h	5.1 ± 2.5[2]	6.1 ± 1.9[2]	−1.0 (−1.5 to −0.5)[a]	<0.001
BPI-sf least pain in the last 24 h	1.0 [0.0–2.0][2]	2.0 [1.0–3.0][3]	−1.0 (−1.0 to 0.0)[b]	<0.001
BPI-sf current pain	2.0 [0.0–3.0][2]	3.0 [2.0–5.0][3]	−1.0 (−2.0 to −1.0)[b]	<0.001
BPI-sf pain severity	3.2 ± 1.9[2]	4.2 ± 1.6[3]	−1.0 (−1.4 to −0.6)[a]	<0.001
BPI-sf pain interference	3.4 ± 2.0[3]	4.9 ± 2.1[5]	−1.5 (−1.9 to −1.0)[a]	<0.001
3 months after operation				
n	132	258		
OKS pain subscale	76.1 ± 16.4	69.8 ± 17.5[2]	6.3 (2.7 to 9.9)[a]	<0.001
BPI-sf average pain	1.0 [0.0–3.0][1]	3.0 [1.0–4.0][4]	−1.0 (−2.0 to −1.0)[b]	<0.001
BPI-sf worst pain in the last 24 h	2.7 ± 2.4	4.2 ± 2.6[3]	−1.5 (−2.0 to −1.0)[a]	<0.001
BPI-sf least pain in the last 24 h	0.0 [0.0 − 1.0]	1.0 [0.0–2.0][3]	0.0 (0.0 to 0.0)[b]	<0.001
BPI-sf current pain	0.0 [0.0–1.8]	1.0 [0.0–3.0][5]	−1.0 (−1.0 to 0.0)[b]	<0.001
BPI-sf pain severity	1.3 [0.3–2.4]	2.3 [1.0–3.8][3]	−1.0 (−1.3 to −0.8)[b]	<0.001
BPI-sf pain interference	0.7 [0.04–2.2]	2.4 [0.9–4.6][4]	−1.3 (−1.7 to −0.7)[b]	<0.001
12 months after operation				
n	131	256		
OKS pain subscale	92.8 [85.7–100.0][1]	89.3 [78.5–96.4][3]	3.6 (0.0 to 3.6)[b]	0.027
BPI-sf average pain	1.0 [0.0–3.0][2]	2.0 [0.0–4.0][2]	0.0 (−1.0 to 0.0)[b]	0.002
BPI-sf worst pain in the last 24 h	2.0 [0.0–4.0][1]	3.0 [0.0–5.0][2]	−1.0 (−1.0 to 0.0)[b]	0.003
BPI-sf least pain in the last 24 h	0.0 [0.0–1.0][1]	0.0 [0.0–1.3][2]	0.0 (0.0 to 0.0)[b]	0.056
BPI-sf current pain	0.0 [0.0–2.0][1]	0.0 [0.0–2.0][2]	0.0 (0.0 to 0.0)[b]	0.006
BPI-sf pain severity	0.8 [0.0–2.5][1]	1.6 [0.0–3.3][2]	−0.5 (−0.8 to 0.0)[b]	0.002
BPI-sf pain interference	0.2 [0.0–1.6][1]	1.1 [0.0–3.0][3]	−0.3 (−0.7 to 0.0)[b]	<0.001

Note: Values are presented as mean ± standard deviation or median [interquartile range]. Risk groups were defined based on the number of risk factors for persistent post-surgical pain (including preoperative pain in the area of operation, preoperative pain elsewhere in the body, capacity overload in the past 6 months, co-morbid stress symptoms, and significant acute postoperative pain). Low to moderate risk = 0–2 risk factors, high risk = 3–5 risk factors.

Abbreviations: BPI-sf, Brief Pain Inventory–short form, patients assessed pain and pain interference using a numerical rating scale (0–10, 0 = no pain/interference, 10 = worst pain/interference); CI, confidence interval; OKS, Oxford Knee Score (subscale standardized to 0–100, 0 = worst pain, 100 = least pain).

[a]Mean difference.

[b]Hodges-Lehman estimate for median difference. Superscript numbers indicate the number of missing values.

than in the high-risk group at 3 months after surgery (Table 4). Yet, at 12 months, the low- to moderate-risk group had significantly lower prevalence of PPP only when this pain was defined as BPI-sf average pain ≥3 (Table 4).

Patient characteristics of the three separate risk groups that were investigated in the supplementary sensitivity analysis are presented in Table S1. In the results, patients in the low- and moderate-risk groups reported less pain than patients in the high-risk group at 3 and 12 months after TKA (Table S2). However, the change scores did not differ significantly at 3 months, and only the variable concerning pain interference differed significantly between the low- and high-risk groups at 12 months (Table S3). The prevalence rates for PPP of the low-, moderate-, and high-risk groups are presented in Table S4. The differences between the low- and moderate-risk groups were not significant in any comparisons (Tables S2–S4).

The associations between the number of risk factors and the prevalence rates for PPP are presented in Figure 1. Sensitivity and specificity of the risk index according to five different definitions of PPP at 3 and 12 months after

TABLE 3 Change scores 3 and 12 months after total knee arthroplasty in the low- to moderate-risk group and the high-risk group, a sensitivity analysis.

	Low to moderate risk	High risk	Mean difference (95% CI)	*p* value
Change in pain scores 3 months after operation				
n	132	258		
OKS pain subscale	23.7 ± 18.3^{3}	22.4 ± 20.4^{4}	1.4 (−2.8 to 5.6)	0.520
BPI-sf average pain	-2.1 ± 2.3^{3}	-1.9 ± 2.3^{7}	−0.2 (−0.7 to 0.3)	0.453
BPI-sf worst pain in 24 h	-2.4 ± 3.1^{2}	-1.9 ± 2.7^{5}	−0.5 (−1.1 to 0.1)	0.112
BPI-sf least pain in 24 h	-0.9 ± 1.5^{2}	-1.0 ± 1.9^{6}	0.1 (−0.3 to 0.5)	0.550
BPI-sf current pain	-1.4 ± 2.3^{2}	-1.6 ± 2.5^{8}	0.2 (−0.3 to 0.7)	0.508
BPI-sf pain severity	-1.7 ± 2.0^{2}	-1.6 ± 1.9^{6}	−0.1 (−0.5 to 0.3)	0.635
BPI-sf pain interference	-1.9 ± 2.5^{3}	-2.0 ± 2.7^{9}	0.1 (−0.4 to 0.7)	0.677
Change in pain scores 12 months after operation				
n	131	256		
OKS pain subscale	36.6 ± 18.0^{4}	38.7 ± 18.4^{5}	−2.1 (−6.0 to 1.8)	0.291
BPI-sf average pain	-2.2 ± 2.6^{4}	-2.6 ± 2.5^{5}	0.4 (−0.1 to 0.9)	0.151
BPI-sf worst pain in 24 h	-2.7 ± 3.0^{3}	-2.9 ± 3.0^{4}	0.2 (−0.4 to 0.9)	0.469
BPI-sf least pain in 24 h	-0.9 ± 1.7^{3}	-1.3 ± 2.0^{5}	0.5 (0.06 to 0.9)	0.025
BPI-sf current pain	-1.4 ± 2.5^{3}	-2.0 ± 2.6^{5}	0.6 (0.1 to 1.2)	0.025
BPI-sf pain severity	-1.8 ± 2.2^{3}	-2.2 ± 2.1^{5}	0.4 (−0.04 to 0.9)	0.071
BPI-sf pain interference	-2.4 ± 2.3^{4}	-3.0 ± 2.6^{8}	0.7 (0.1 to 1.2)	0.013

Note: Values are presented as mean ± standard deviation. Risk groups were defined based on the number of risk factors for persistent post-surgical pain (including preoperative pain in the area of operation, preoperative pain elsewhere in the body, capacity overload in the past 6 months, co-morbid stress symptoms, and significant acute postoperative pain). Low to moderate risk = 0–2 risk factors, high risk = 3–5 risk factors. Superscript numbers indicate the number of missing values.

Abbreviations: BPI-sf, Brief Pain Inventory–short form, patients assessed pain and pain interference using a numerical rating scale (0–10, 0 = no pain/interference, 10 = worst pain/interference); CI, confidence interval; OKS, Oxford Knee Score (subscale standardized to 0–100, 0 = worst pain, 100 = least pain).

TKA are presented in Table 5. The ROC curves and areas under these curves are displayed in Figure 2.

4 | DISCUSSION

In this study, we investigated whether a previously presented predictive risk index for PPP is applicable to patients undergoing TKA (Althaus et al., 2012). In our results, patients in the low- to moderate-risk group reported less pain than patients in the high-risk group 3 and 12 months after TKA. This was consistent with the findings presented in the risk index study (Althaus et al., 2012). However, at 12 months, the threshold for MCID between the groups was reached only in 1 of 7 reported pain variables. Moreover, pain scores differed already at the baseline and improved more in the high-risk than in the low- to moderate-risk group during the 12-month follow-up. Yet, none of the differences in the improvements seemed clinically important.

The prevalence rates for PPP in the current study were significantly lower in the low- to moderate-risk group than in the high-risk group at 3 months after TKA, regardless the definition of PPP. However, at 12 months, only 1 of 5 definitions (average pain of NRS ≥3) resulted to a statistically significant difference in the prevalence of PPP between the low- to moderate-risk group (29%) and high-risk group (41%). With other definitions the prevalence rates ranged from 2% to 19% and 4% to 27%, respectively. In comparison, Althaus and colleagues reported prevalence of 12% to 37% in the low- to moderate-risk group and 68% to 82% in the high-risk group at 6 months (Althaus et al., 2012).

The results from the supplementary sensitivity analysis were consistent with the main analysis. The low- and moderate-risk groups reported less pain 3 and 12 months after TKA than the high-risk group, but only one change score variable at the respective time points reached the MCID: pain interference scores had decreased more in the high-risk than in the low-risk group during the 12 months.

TABLE 4 Prevalence of persistent postsurgical pain in the low- to moderate-risk and high-risk groups according to five different definitions 3 and 12 months after total knee arthroplasty.

	Low to moderate risk	High risk	OR (95% CI)	*p* value
3 months after operation				
OKS pain subscale scores ≤14/28	11/132 (8.3)	41/256 (16.0)	0.48 (0.24 to 0.96)	0.039
Knee pain usually moderate to severe within the last 4 weeks	17/132 (12.9)	75/254 (29.5)	0.35 (0.20 to 0.63)	<0.001
BPI-sf average pain ≥3	36/131 (27.5)	139/254 (54.7)	0.31 (0.20 to 0.49)	<0.001
BPI-sf average pain ≥4	18/131 (13.7)	89/254 (35.0)	0.30 (0.17 to 0.52)	<0.001
BPI-sf average pain ≥5	9/131 (6.9)	62/254 (24.4)	0.23 (0.11 to 0.48)	<0.001
12 months after operation				
OKS pain subscale scores ≤14/28	2/130 (1.5)	11/253 (4.3)	0.34 (0.08 to 1.57)	0.169
Knee pain usually moderate to severe within the last 4 weeks	7/130 (5.4)	19/254 (7.5)	0.70 (0.29 to 1.72)	0.441
BPI-sf average pain ≥3	37/129 (28.7)	104/254 (40.9)	0.58 (0.37 to 0.92)	0.019
BPI-sf average pain ≥4	24/129 (18.6)	68/254 (26.8)	0.63 (0.37 to 1.05)	0.079
BPI-sf average pain ≥5	18/129 (14.0)	39/254 (15.4)	0.89 (0.49 to 1.63)	0.716

Note: Values are presented as number of patients/total (%). Risk groups were defined based on the number of risk factors for persistent post-surgical pain (including preoperative pain in the area of operation, preoperative pain elsewhere in the body, capacity overload in the past 6 months, co-morbid stress symptoms, and significant acute postoperative pain). Low to moderate risk = 0–2 risk factors, high risk = 3–5 risk factors.

Abbreviations: BPI-sf, Brief Pain Inventory–short form, patients assessed pain and pain interference using a numerical rating scale (0–10, 0 = no pain, 10 = worst pain); CI, confidence interval; OKS, Oxford Knee Score (subscale 0–28, 0 = worst pain, 28 = least pain); OR, odds ratio.

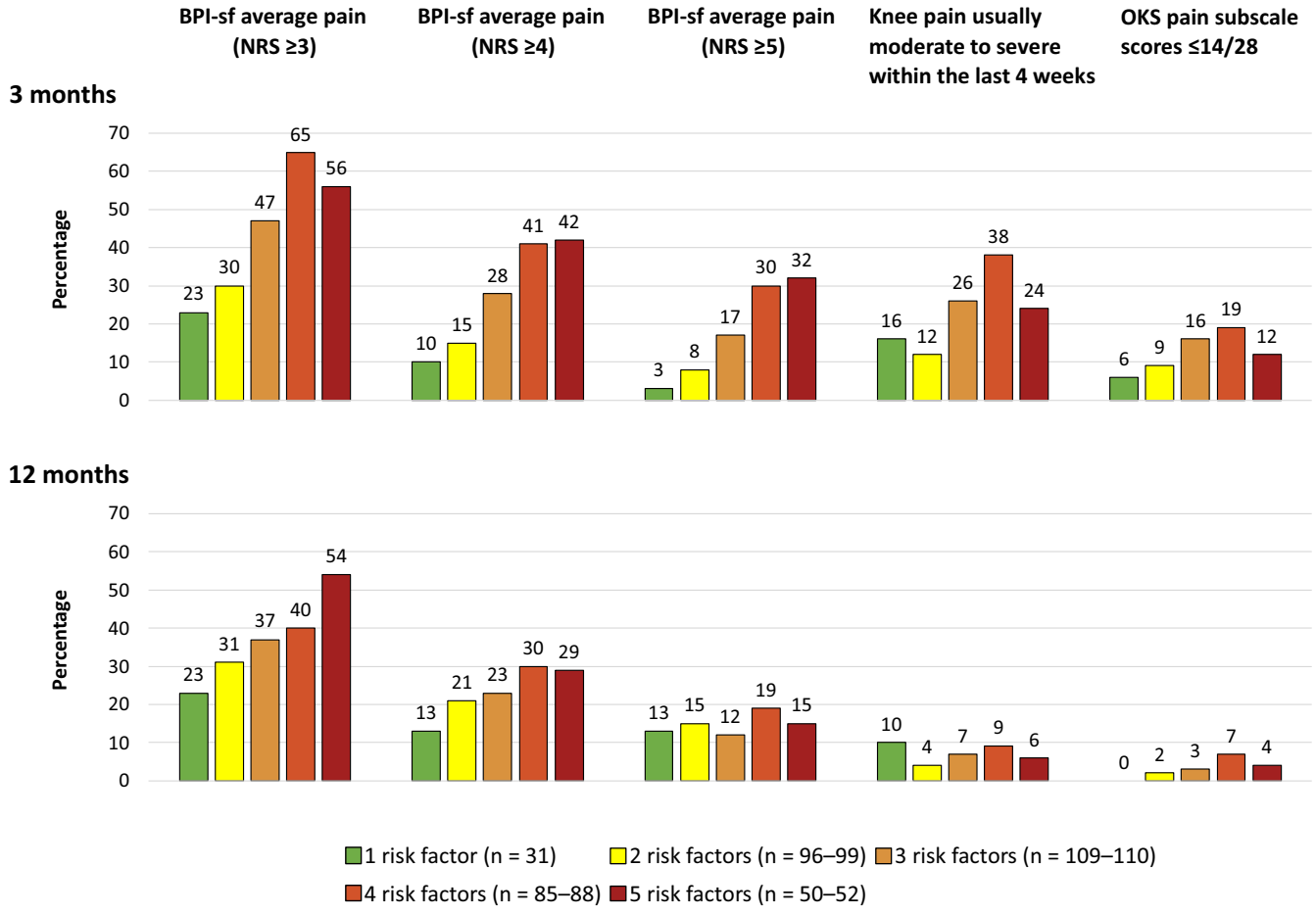

FIGURE 1 The association between the number of risk factors and the prevalence of persistent postsurgical pain after total knee arthroplasty. Results with five different definitions for persistent postsurgical pain are presented. Two patients reported no risk factors (data not shown). Patients with 0–1 risk factors, two risk factors, and 3–5 risk factors were considered to have a low, moderate or high risk for persistent postsurgical pain, respectively.

TABLE 5 Sensitivity and specificity of the risk index for persistent postsurgical pain according to five different definitions, 3 and 12 months after total knee arthroplasty.

	n	Sensitivity (%)	Specificity (%)
3 months after operation			
BPI-sf average pain ≥3	378	79	46
BPI-sf average pain ≥4	378	83	41
BPI-sf average pain ≥5	378	87	39
Knee pain usually moderate to severe within the last 4 weeks	379	81	40
OKS pain subscale scores ≤14/28	381	79	37
12 months after operation			
BPI-sf average pain ≥3	376	73	39
BPI-sf average pain ≥4	376	73	37
BPI-sf average pain ≥5	376	67	35
Knee pain usually moderate to severe within the last 4 weeks	377	73	35
OKS pain subscale scores ≤14/28	376	85	35

Note: The number of risk factors for persistent post-surgical pain (including preoperative pain in the area of operation, preoperative pain elsewhere in the body, capacity overload in the past 6 months, co-morbid stress symptoms, and significant acute postoperative pain) ranged from 0 to 5. Sensitivity and specificity are reported for the cut-off score of ≥3.

Abbreviations: BPI-sf, Brief Pain Inventory–short form, patients assessed pain and pain interference using a numerical rating scale (0–10, 0 = no pain, 10 = worst pain); OKS, Oxford Knee Score (subscale 0–28, 0 = worst pain, 28 = least pain).

The prevalence rates for PPP did not differ significantly in any pairwise comparison of the three risk groups at 12 months. No significant differences in pain scores between the low- and moderate-risk groups were detected at 3 or 12 months after surgery.

The prevalence rates for PPP according to the number of risk factors in the study by Althaus and colleagues and in the subsequent external validation study were higher than in our results, regardless of the definition of PPP (Althaus et al., 2012; Mathes et al., 2018). Similarly, areas under the ROC curves were larger in these previous studies (0.77 and 0.77) than in the current study (0.53–0.69). This is indicative of lower accuracy of the risk index on TKA patients compared to mixed surgery cohorts. However, differences between the studies in the definitions of PPP and time points of the measurements are limitations of our investigation. In the study by Althaus and colleagues, PPP was defined as the average pain intensity NRS ≥3 during the last 3 months, and it was measured 6 months after surgery (Althaus et al., 2012). We used multiple definitions which were derived from widely utilized pain questionnaires and applied a 1-year follow-up time which is sufficient for assessing long-term patient-reported outcomes after TKA (Beard et al., 2019; Ramkumar et al., 2018; Scott et al., 2015; Shan et al., 2015), whereas 6 months appears too short (Brander et al., 2003; Clement et al., 2020; Rice et al., 2018).

Our study has also other limitations that should be noted. The generalizability of our results is limited by the single-centre design of the study and especially by the exclusion criteria of the primary randomized trial (Palanne et al., 2020; Rantasalo et al., 2018). In addition, the number of patients in the low-risk group was not sufficient for adequately powered analyses containing all three risk groups separately. Thus, the results concerning the supplementary sensitivity analysis should be considered at most as indicative. Furthermore, some of the BPI-sf derived results might be biased because this questionnaire does not focus on the site of surgery. Thus, it allows patients to also refer to pain other than that of the operated knee area.

The strengths of this study include its prospective design. The patients were operated and treated according to standardized study and fast-track protocols, which reduces the effects of confounding factors. In addition, the sample size in our study was more than twofold larger than the sample size of the mixed surgery cohort presented by Althaus and colleagues (Althaus et al., 2012). Furthermore, the drop-out rate in our study was very low.

Inconsistency in defining PPP and measuring it at different time points causes challenges when different studies are compared. To reduce the risk of biased results and facilitate comparisons in the future, we suggest the use of knee-specific questionnaires, such as OKS, as primary tools for measuring pain-related outcomes on TKA patients. In addition, we suggest using at least a 1-year follow-up time because pain seems to decrease at least up to this point after TKA (Brander et al., 2003; Clement et al., 2020; Rice et al., 2018). Furthermore, the words "persistent," "long-term," and "chronic" are often used to refer to the same postsurgical pain modality. However, the use of these terms could be more accurate. Based on the recent definition for chronic postsurgical pain which refers to pain that increases in intensity or develops after surgery (Schug et al., 2019), we suggest using the term "persistent postsurgical pain" or "long-term postsurgical pain" if the residual pain from the time before surgery cannot be distinguished from the pain caused by the surgery.

5 | CONCLUSIONS

In conclusion, our results suggest that although the risk index presented by Althaus and colleagues may predict

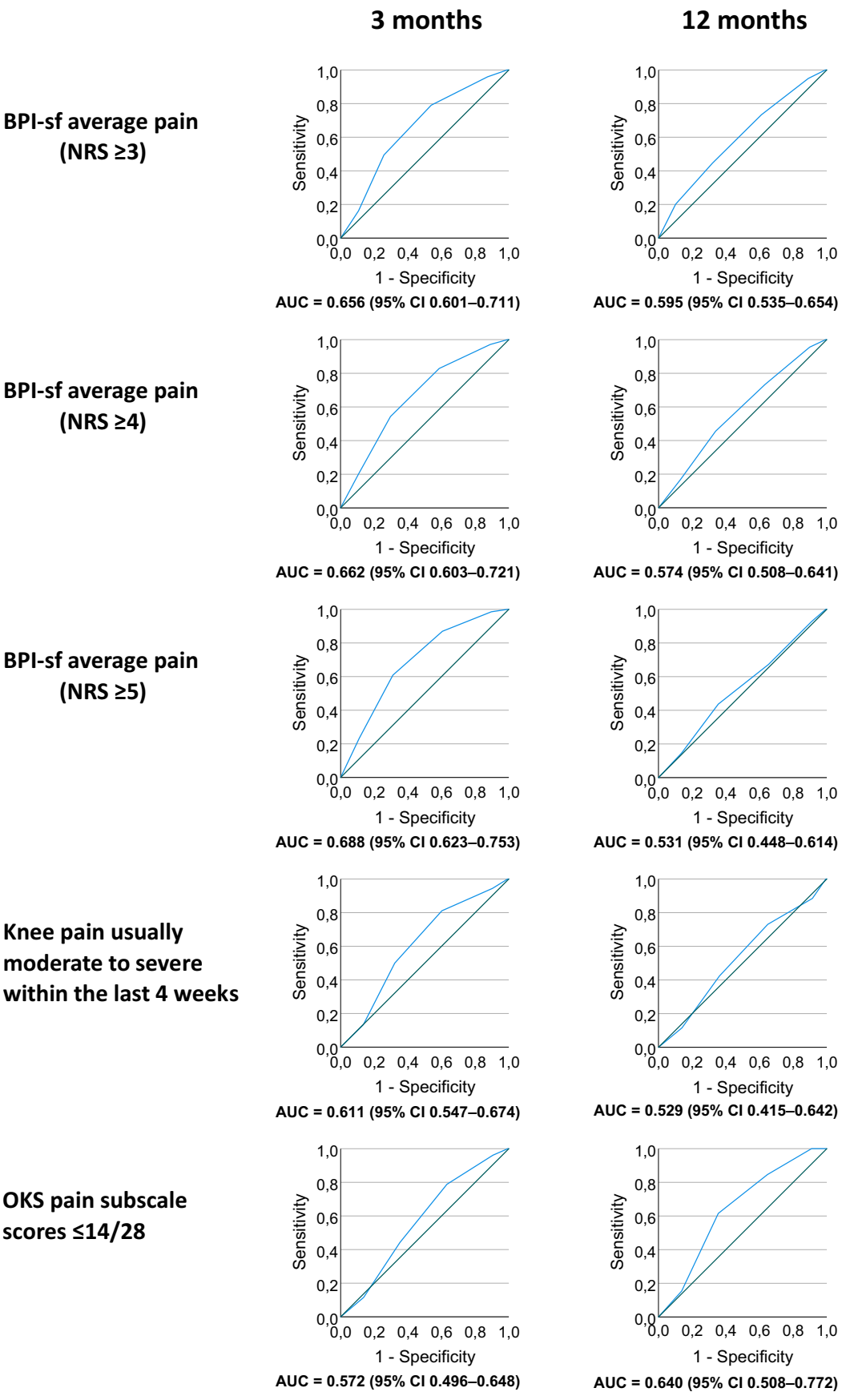

FIGURE 2 Receiver operator characteristic curves of the predictive risk index for persistent postsurgical pain according to five different definitions at 3 and 12 months after total knee arthroplasty.

clinically relevant differences between the risk groups in postsurgical pain at 3 months after TKA, it is a poorly applicable model for predicting PPP at 12 months after this surgery.

AUTHOR CONTRIBUTIONS

All authors participated in designing the study. Anne Vakkuri, Klaus T. Olkkola and Noora Skants executed project administration and supervision. Riku Palanne, Mikko Rantasalo and Noora Skants collected data. Riku Palanne and Tero Vahlberg conducted statistical analyses. Riku Palanne wrote the original draft. All authors discussed the results and reviewed the manuscript and accepted its final version.

ACKNOWLEDGEMENTS

We thank Elina Reponen, MD, PhD; Rita Linko, MD, PhD; and Rami Madanat, MD, PhD for their contribution to the study design. Additionally, we thank Arja Mäkinen, RN, and Katarina Lahtinen, MD, for their crucial work in data collection.

FUNDING INFORMATION

This study was funded by HUS Helsinki University Hospital Finnish Government Science grants (TYH 2017239 and TYH 2019113) and a HUS Helsinki University Hospital grant (Y102011095). Dr. Palanne has also received personal grants from the Paulo Foundation, Finnish Medical Foundation, Research Foundation for Orthopaedics and Traumatology, Finnish Arthroplasty Society, Finnish Society of Anaesthesiologists, Finnish Medical Society Duodecim, and Orion Research Foundation sr. The funders have had no role in the study design, data collection, data analysis, data interpretation, writing of the manuscript or decision to submit the article for publication.

CONFLICT OF INTEREST STATEMENT

Dr. Rantasalo reports research support from Zimmer Biomet and Smith & Nephew. Other authors state no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Palanne, R., Rantasalo, M., Vakkuri, A., Olkkola, K. T., Vahlberg, T., & Skants, N. (2023). Testing of a predictive risk index for persistent postsurgical pain on patients undergoing total knee arthroplasty: A prospective cohort study. *European Journal of Pain*, *00*, 1–12. https://doi.org/10.1002/ejp.2138