



## Original article

# Predictive factors for satisfaction after contemporary unicompartmental knee arthroplasty and high tibial osteotomy in isolated medial femorotibial osteoarthritis



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## ABSTRACT

**Introduction:** Both high tibial osteotomy (HTO) and unicompartmental knee arthroplasty (UKA) are viable treatment options for early osteoarthritis (OA). Although a substantial proportion of the patient selection criteria for HTO and UKA are now shared, the factors related to satisfaction following each procedure remain unclear.

**Hypothesis:** We hypothesized that patient factors associated with satisfaction following contemporary HTO and UKA would be different.

**Material and methods:** We retrospectively reviewed the records of consecutively enrolled medial opening-wedge HTOs ( $n = 123$ ) and Oxford mobile-bearing UKAs ( $n = 118$ ) with satisfactory postoperative alignment. Preoperative demographics, physical activity levels, varus deformity status, and degree of OA were recorded. Postoperative radiographs, frequency of combined procedures and patient-reported outcomes (PROs) including pain, Western Ontario and McMaster Universities Osteoarthritis Index score, and patient satisfaction were assessed.

**Results:** Severe OA ( $p < 0.01$ ) was associated with an increased risk of dissatisfaction following HTO, whereas young age ( $p < 0.01$ ) and severe varus deformity ( $p = 0.045$ ) were related to dissatisfaction after UKA. In addition, patient satisfaction following UKA was higher than that following HTO in individuals with highly physically demanding activity. All UKA PROs were superior to those of the HTO group, except pain level.

**Conclusion:** Despite the shared patient selection criteria for contemporary HTO and UKA, severe OA was associated with dissatisfaction following HTO, whereas young age and varus deformity were associated with dissatisfaction following UKA. Age, varus deformity and OA severity should be considered when deciding whether to perform HTO or UKA.

**Type of study and level of proof:** Retrospective cohort study, Level III.

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## 1. Introduction

Changes in demographics and physical activities of the younger population have increased the number of patients with medial unicompartmental knee osteoarthritis (OA) requiring surgical intervention [1,2]. Despite fundamental differences in surgical principles, both medial opening-wedge high tibial osteotomy

(HTO) and medial Oxford mobile-bearing unicompartmental knee arthroplasty (UKA) are established treatment options in this clinical scenario, and the use of both procedures are steadily increasing [3,4]. Traditionally, elderly patients with OA and lower levels of physically demanding activity have been indicated for UKA, while HTO is indicated for young, active patients with varus knee deformity [5–8]. However, advances in technology and understanding of the surgical techniques involved in both HTO and UKA have improved clinical outcomes and longevity [9–13]. Therefore, the patient selection criteria for both procedures have expanded [5–7], with a significant proportion of the patient selection criteria being shared between the two procedures [6,8,9]. However, deciding

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whether to perform HTO or UKA still remains challenging, especially in patients who do not completely fit the ideal patient selection criteria for either procedure.

Numerous studies have reported comparable clinical results following HTO and UKA in patients with similar demographic characteristics [5,6,14–16]. However, most previous studies have tended to focus on physician-assessed objective clinical outcomes and longevity. Therefore, there is a paucity of data regarding patient-reported outcomes (PROs) such as patient satisfaction, which are increasingly being accepted as an essential part of postoperative outcome assessment [17–19]. In addition, there is also limited data on the patient factors affecting patient satisfaction after each procedure. Moreover, as most previous studies compared the postoperative outcomes of patients who underwent UKA or HTO using traditional implants and surgical techniques during the 1980s to 1990s [9–12], the question of whether recent improvements in technology and surgical techniques, such as the Microplasty® instrument system [20] and rigid locking plate [21], affect PROs following each procedure remains controversial.

Thus, this comparative study was performed to identify risk factors for patient dissatisfaction following HTO and UKA and to compare PROs following HTO and UKA in patients who underwent surgery using a recently updated implant and instrumentation system. We hypothesized that patient factors associated with dissatisfaction following HTO and UKA would differ and that patients PROs rating following HTO and UKA would also differ.

## 2. Materials and methods

We retrospectively reviewed the records of 131 consecutively enrolled patients who underwent medial opening-wedge HTO performed using the TomoFix® Medial High Tibial Plate (DePuy Synthes, Solothurn, Switzerland) and 118 patients who underwent medial Oxford® mobile-bearing UKA (Zimmer Biomet, Warsaw, IN, USA) from January 2013 to January 2016 from the database of our institution. After approval was granted by our Institutional Review Board, we only included those patients who underwent medial HTO or UKA for primary medial unicompartmental knee OA with preoperatively preserved range of motion (ROM) and stability, had no lateral compartmental or patellofemoral OA, and had available clinical outcomes with a minimum follow-up period of 2 years. To avoid any confounding technical factors that might have affected postoperative PROs, we excluded patients with (1) severe postoperative under-correction, 50% < weight loading line (WLL; the line connecting the hip and ankle center) ratio which was defined as percentage of a point of WLL pass-through to whole tibial width, when measured medially, or (2) over-correction,  $\geq 75\%$  WLL ratio [22]. In total, three patients who underwent HTO were excluded because of under-correction and five were excluded because of over-correction. After excluding these patients, 123 patients who underwent HTO and 118 patients who underwent UKA (202 females and 39 males) were included in the study, and all of the medical records from these patients at 2 year postoperatively were used in the final analyses. There were no major complications that required re-operation such as periprosthetic infection, bearing dislocation, early loosening, or loss of correction in either group. The mean age of the patients was  $58.4 \pm 5.7$  years (range: 40–68 years). The mean body mass index (BMI) was  $25.8 \pm 3.0$  kg/m<sup>2</sup> (range: 17.6–34.1 kg/m<sup>2</sup>). Preoperatively, several demographic factors (age, varus deformity status, and OA severity) were different between the HTO and UKA groups. HTOs were performed in younger (<60 years) patients with less severe OA (<2 Ahlbäck grade) and more severe varus deformity ( $\geq 5^\circ$  hip-knee-ankle axis angle [HKA] determined as angle between the line connecting hip and knee center and the line connecting knee and

**Table 1**

Comparison of preoperative conditions between high tibial osteotomy (HTO) and unicompartmental knee arthroplasty (UKA) groups<sup>a</sup>.

	HTO(n = 123)	UKA(n = 118)	Significance
Demographics			
Age <sup>b</sup>	56.1 (5.6)	60.8 (4.7)	< 0.01
< 60 years	85 (69)	46 (39)	< 0.01
$\geq 60$ years	38 (31)	72 (61)	
Gender (female)	104 (85)	98 (83)	0.752
Height (cm) <sup>b</sup>	157.9 (6.7)	157.6 (6.9)	0.724
Weight (kg) <sup>b</sup>	64.4 (8.6)	64.3 (9.9)	0.917
BMI (kg/m <sup>2</sup> ) <sup>b</sup>	25.8 (2.9)	25.9 (3.2)	0.978
Varus deformity <sup>b</sup>	7.7 (2.8)	4.5 (2.5)	< 0.01
< HKA 5°	19 (15)	82 (70)	< 0.01
$\geq$ HKA 5°	104 (85)	36 (30)	
Osteoarthritis degree			
< Ahlbäck grade 2	97 (79)	37 (31)	< 0.01
$\geq$ Ahlbäck grade 2	26 (21)	81 (69)	
Activity level			
< Tegner scale 4	52 (42)	46 (39)	0.641
$\geq$ Tegner scale 4	71 (58)	72 (61)	

HKA: hip-knee-ankle axis angle.

<sup>a</sup> Data are presented as number of patients (%).

<sup>b</sup> Data are presented as means (SD).

ankle center). Alternatively, UKAs were performed in older patients with severe OA with less varus deformity (Table 1).

The decision to perform HTO or UKA was at the discretion of a single surgeon (Y.I.) and was determined by comprehensive history taking, physical examination and radiographic evaluation on a case-by-case basis. All operations were performed in a standard fashion by a single surgeon (Y.I.) with patients under general anesthesia. All HTOs were performed by medial opening-wedge osteotomy method using with TomoFix® Medial High Tibial Plate [21,23]. The surgical goal of HTO was a 62% of WLL ratio. Arthroscopic procedures, including lavage, meniscectomy and/or microfracture were performed in all patients who underwent HTO. Ninety-one of 123 HTO patients (74%) received partial meniscectomy, 103 patients (84%) received microfracture, 70 patients (53%) received both microfracture and meniscectomy, and 12 patients (10%) received arthroscopic lavage during HTO. All UKAs were performed using a Phase III Oxford mobile-bearing UKA guided by the Microplasty® instrumentation system [20].

All clinical information was evaluated by single investigator (S.E.S.) using a predesigned case report form at 3, 6, and 12 months, and then annually thereafter. Clinical information included demographic data, surgical factors, and PROs. Demographic data included age, gender, height, weight, BMI, degree of varus deformity (HKA), physical activity level (Tegner activity level [24]), and severity of OA (Ahlbäck grade system [25]). Surgical factors included both intraoperative (combined meniscal surgery or articular cartilage repair surgery during HTO) and postoperative radiographic (postoperative HKA, WLL ratio, and correction amount which was determined by the difference between preoperative and postoperative HKA) factors. Radiographic images were obtained under fluoroscopic guidance, and all measurements were based on Digital Imaging and Communications in Medicine data, utilizing the ruler and protractor functions of the Picture Archiving and Communication System software (M-View™; Marotech, Seoul, Korea). PROs were measured in terms of a visual analogue scale (VAS) of knee pain, Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score, Tegner activity scale and the score on the patient satisfaction subsection of the new Knee Society scoring system (KSS; 5 categories and maximum total score of 40 points) [19]. In addition, all PROs between preoperative and postoperative 2 year follow up were compared.

**Table 2**  
Comparisons of preoperative conditions and surgical factors by patients satisfaction in HTO and UKA groups<sup>a</sup>.

	HTO (n = 123)				UKA (n = 118)			
	Satisfied (n = 66)	Neutral (n = 30)	Dissatisfied (n = 27)	Significance	Satisfied (n = 66)	Neutral (n = 40)	Dissatisfied (n = 12)	Significance
<b>Patient factors</b>								
Age <sup>b</sup>	56.0 (6.3)	55.8 (5.1)	56.5 (3.9)	0.883	62.3 (4.6)	58.7 (3.5)	57.9 (6.0)	<0.01
< 60 years	42 (64)	24 (80)	19 (70)	0.271	18 (27)	21 (53)	8 (67)	<0.01
≥ 60 years	24 (36)	6 (20)	8 (30)		48 (73)	19 (47)	4 (33)	
BMI (kg/m <sup>2</sup> ) <sup>b</sup>	26.3 (2.9)	25.0 (3.1)	26.6 (2.7)	0.11	26.0 (3.1)	25.7 (3.4)	25.9 (3.2)	0.870
Varus deformity	7.6 (2.8)	7.5 (2.8)	8.2 (2.8)	0.537	4.4 (2.7)	4.1 (1.6)	6.9 (2.3)	<0.01
< 5°	11 (17)	6 (20)	2 (7)	0.389	48 (73)	32 (79)	3 (25)	<0.01
≥ 5°	55 (83)	24 (80)	25 (93)		18 (27)	8 (21)	9 (75)	
<b>Activity level</b>								
< Tegner scale 4	30 (46)	11 (37)	11 (41)	0.710	32 (48)	12 (29)	3 (25)	0.122
≥ Tegner scale 4	36 (54)	19 (63)	16 (59)		34 (52)	28 (71)	9 (75)	
<b>OA degree</b>								
< Ahlbäck grade 2	61 (92)	24 (80)	12 (44)	<0.01	22 (34)	13 (32)	3 (25)	0.370
≥ Ahlbäck grade 2	5 (8)	6 (20)	15 (56)		44 (66)	27 (68)	9 (75)	
<b>Surgical factors</b>								
WLL ratio <sup>c</sup>	61.1 (7.6)	60.5 (10.6)	60.4 (8.9)	0.912				
Correction amount <sup>d</sup>	10.1 (2.8)	10.4 (2.8)	10.4 (4.6)	0.906				
Postoperative HKA	-2.4 (2.1)	-2.9 (2.8)	-2.3 (3.0)	0.565				
Combined surgery	60 (91)	25 (83)	26 (96)	0.249				
Microfracture	56 (85)	24 (80)	23 (85)	0.815				
Meniscus surgery	48 (73)	20 (66)	23 (85)	0.127				

WLL: weight loading line; HKA: hip-knee-ankle axis angle.

<sup>a</sup> Data are presented as number of patients (%).

<sup>b</sup> Data are presented as means (SD).

<sup>c</sup> WLL ratio was defined as percentage of a point of weight loading line pass-through to whole tibial width, when measured from medial.

<sup>d</sup> Correction amount which was determined by the difference between preoperative and postoperative hip-knee-ankle axis angle.

### 2.1. Statistical analysis

Demographic factors, surgical factors, and PROs were compared between the HTO and UKA groups. Student's *t*-test or the Wilcoxon signed-rank test were used to analyze continuous variables and Chi-square or Fisher's exact tests were used to determine differences in categorical variables, respectively. To determine the factors associated with patient dissatisfaction, patient satisfaction was categorised into three groups: satisfied (KSS satisfaction score of ≥ 30), neutral (KSS satisfaction score of 20–29), and dissatisfied (KSS satisfaction score of < 20). In addition, age, varus deformity, activity level and OA severity were categorised into two groups: age, < 60 and ≥ 60 years; degree of varus deformity, HKA of < 5° and ≥ 5°; activity level, Tegner activity score of < 4 and ≥ 4; and severity of OA, Ahlbäck grade of < 2 and ≥ 2. Differences in demographic and surgical factors among the three satisfaction groups were compared using the chi-square test or one-way analysis of variance. To identify risk factors for patient dissatisfaction, multivariate linear regression analysis was performed and 95% confidence intervals (CIs) were calculated for dissatisfaction. A power analysis showed that this study had 80% power to detect a 2-point difference in KSS satisfaction and 80% power to detect a 10% difference from the baseline score for the WOMAC score using a two-sided hypothesis test at an alpha level of 0.05, respectively. In addition, this study had 87% power to detect a 1-point VAS difference in the pain level between groups. All computations relied on standard software (SPSS v21.0 for Windows; IBM Corp, Armonk, NY, USA), setting statistical significance at *p* < 0.05.

### 3. Results

Univariate comparisons revealed a few patient factors that differed among satisfied, neutral and dissatisfied groups in each procedure group. However, there were no among-group differences in surgical factors including WLL ratio, correction amount, combined surgery, microfracture and meniscectomy (Table 2). The dissatisfied patients in the HTO group contained a higher

proportion of advanced OA (8% in satisfied vs. 56% in dissatisfied group, *p* < 0.01). Meanwhile, the satisfied patients in the UKA group had a higher proportion of elderly patients (73% vs. 33%, *p* < 0.01) with less varus deformity (27% vs. 75%, *p* < 0.01). Multivariate regression analyses revealed that young age < 60 years and varus deformity ≥ 5° HKA were risk factors for dissatisfaction following UKA, while severe OA ≥ Ahlbäck grade 2 was a predictor of dissatisfaction after HTO (Table 3). There was no association between dissatisfaction following HTO and age, BMI, or surgical factors such as postoperative alignment and concomitant surgeries (*p* > 0.1 in all univariate comparisons).

PROs in terms of WOMAC score, Tegner activity level and satisfaction as well as improvement in PROs following surgery, were superior for UKA compared with HTO. In addition, more patients in the UKA group were satisfied than in the HTO group (*p* < 0.05 in all comparisons) (Table 4). There were no between-group differences in pain level and satisfaction during light daily activities such as sitting, lying in bed, or getting out of bed (*p* > 0.1 in all comparisons). However, satisfaction in the UKA group was higher than in the HTO group for more physically demanding activities such as household duties and recreational/leisure activities (*p* < 0.01) (Fig. 1).

### 4. Discussion

Although most of the patient selection criteria for HTO and UKA are similar in both procedures, the patient factors predicting dissatisfaction following HTO and UKA are different. In this study, severe OA was identified as a risk factor for dissatisfaction following HTO, whereas young age and severe varus deformity were predictors of dissatisfaction following UKA. These findings are in agreement with previous reports, in which the ideal indications for UKA are older age (elderly) and less severe varus deformity [5,6,26,27]. Several previous studies have also showed that unfavourable clinical outcomes following HTO were associated with severe articular destruction [11,28,29]. The data from the present study, together with those of previous studies, suggest that although recent improvements in clinical outcomes and longevity

**Table 3**  
Factors associated with patient satisfaction according to multivariate linear regression analysis in HTO and UKA group.

Factors	HTO (n = 123)					UKA (n = 118)					
	$\beta$ -Coefficient	R <sup>2</sup>	Significance	95% Confidence interval		$\beta$ -Coefficient	R <sup>2</sup>	Significance	95% Confidence interval		
OA degree <sup>a</sup>	-8.328	0.432	<b>&lt;0.01</b>	-11.454	-5.201	Age <sup>a</sup>	0.598	0.414	<b>&lt;0.01</b>	0.35	0.845
Meniscectomy	-0.143	0.021	0.145	-6.448	0.962	Varus deformity <sup>a</sup>	-0.521	0.189	<b>0.045</b>	-1.03	-0.011
Activity lever	-0.119	0.014	0.189	-2.298	0.459	OA degree	-0.099	0.01	0.298	-2.633	0.815
Postop HKA	0.12	0.014	0.186	-0.187	0.951	BMI	0.046	0.002	0.632	-0.309	0.506
BMI	0.081	0.002	0.217	-0.115	0.504	Activity level	-0.028	-0.013	0.906	-2.267	2.012
Varus deformity	-0.077	0.006	0.397	-0.719	0.287						
WLL	-0.006	0.006	0.947	-0.17	0.159						
Correction amount	-0.064	0.004	0.483	-0.596	0.283						
Microfracture	0.034	0.001	0.709	-30111	4.557						
Age	-0.025	0.001	0.784	-0.291	0.22						
Combined surgery	-0.023	0.001	0.797	-5.391	4.148						

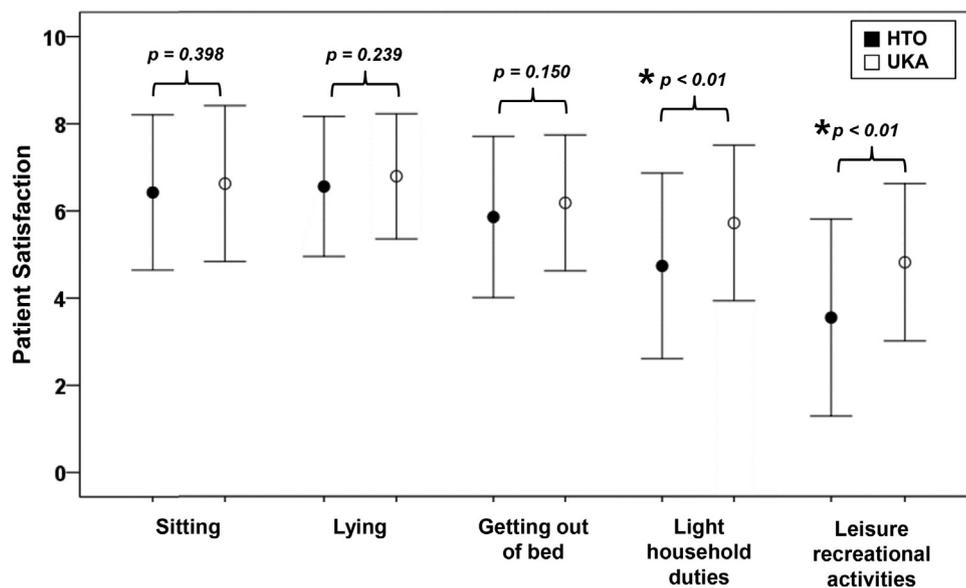
HKA: hip-knee-ankle axis angle; BMI: body mass index; WLL: weight loading line. Values with a statistical significance ( $p < 0.05$ ) are presented in bold.

<sup>a</sup> Factors with a  $p$ -value of  $< 0.05$ .

**Table 4**Comparisons of patient-reporting outcome measures between HTO and UKA at postoperative 2 year follow up and changes after surgery<sup>a</sup>.

	Postoperative 2 years			Changes after surgery		
	HTO(n = 123)	UKA(n = 118)	Significance	HTO(n = 123)	UKA(n = 118)	Significance
Pain VAS	2.6 (1.3)	2.2 (1.6)	0.098	5.2 (1.5)	5.8 (2.1)	0.018
WOMAC						
Pain	4.3 (2.6)	2.0 (1.9)	<0.01	6.0 (4.6)	9.5 (4.1)	<0.01
Stiffness	1.9 (1.1)	1.3 (1.8)	<0.01	2.4 (2.7)	2.8 (2.3)	0.151
Function	16.2 (4.8)	10.6 (9.1)	<0.01	21.8 (12.8)	31.8 (11.6)	<0.01
Total	24.2 (11.4)	13.9 (6.4)	<0.01	26.3 (18.0)	43.6 (17.0)	<0.01
Activity level <sup>24b</sup>						
< Tegner scale 4	73 (59)	39 (33)	<0.01	79 (64) <sup>c</sup>	32 (27) <sup>c</sup>	<0.01
≥ Tegner scale 4	50 (41)	79 (67)		44 (36) <sup>d</sup>	86 (73) <sup>d</sup>	
Satisfaction	27.1 (7.9)	30.0 (6.9)	<0.01	n/a		

VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index score; n/a: not applicable due to no preoperative data.

<sup>a</sup> Data are presented as means (SD).<sup>b</sup> Data are presented as number of patients (%).<sup>c</sup> Data are presented as number of patients whose Tegner activity level was worsened compared with preoperative value (%).<sup>d</sup> Data are presented as number of patients whose Tegner activity level was same or improved compared with preoperative value (%).**Fig. 1.** The graph shows comparisons of patient satisfaction between UKA and HTO at postoperative two year. Although no between-group differences were observed during daily activities, but satisfaction in the UKA group was higher than in the HTO group for highly physically demanding activities. Values with a significant difference ( $p < 0.05$ ) are marked with an asterisk.

have expanded the patient selection criteria for both HTO and UKA, patients perceive that there are inherent, procedure-specific limitations according to surgical principles, namely replacement (intra-articular procedure) and realignment (extra-articular procedure) [16]. Surgeons should recognize that there are different predictors of dissatisfaction for each procedure and take them into account when deciding whether to perform HTO or UKA, especially in patients who do not completely fit the ideal indications for either type of surgery.

In regards to PROs, patients who underwent UKA had superior PROs compared to patients in the HTO group, specifically in terms of WOMAC score, activity level and satisfaction. In addition, UKA provided greater improvement of PROs compared with preoperative status. However, patient satisfaction in the UKA group was higher only in the context of performing highly physically demanding activities such as leisure/recreational activities. The results of this study are in agreement with numerous previous reports of physician-assessed clinical outcomes, such as the KSS [30], following UKA compared with HTO [6,7,31–34]. The findings of this study, together with those of previous studies, suggest that UKA is superior to HTO not only in terms of objective clinical outcomes, but

also with respect to the PROs of patients who underwent surgeries with recently updated technologies and techniques. Patients who underwent HTO may be satisfied with their light daily activities, but not highly physically demanding activities. Considering that HTO is generally indicated for young patients whose lives demand higher levels of activity, surgeons should discuss these issues preoperatively with any patient scheduled to undergo HTO to ensure realistic expectations of outcome.

This study had several limitations. First, because we evaluated only Korean patients, the demographic and lifestyle characteristics of our study population should be considered before extrapolating these findings to other populations. In this respect, certain salient differences should be highlighted, such as the predominance of female patients undergoing knee arthroplasty [3,35,36], more frequent varus deformity [37,38], frequent squatting and kneeling in daily activities in the Korean population [39,40], and fewer obese patients among the Korean population (in the present study, only 10% of patients had a BMI of  $> 30.0 \text{ kg/m}^2$ ). Thus, our findings may not be widely generalizable because demographic and lifestyle factors may affect clinical outcomes. Second, the present study was a retrospective review based on the patient database of our

institute; thus, some data might have been omitted. However, as all patients consecutively received surgery during the study period and this data set consisted of all the procedures performed during the study period that met the mentioned inclusion criteria. Third, 37 of 118 UKA patients (31%) had Ahlbäck grade <2 osteoarthritis, which has been documented to be associated with poor clinical outcomes following UKA. This should be considered before extrapolating our findings to other study cohorts. However, recent studies comparing clinical outcomes between UKA and HTO included 37 to 40% Ahlbäck grade <2 osteoarthritis patients who underwent UKA [14,32]. Fourth, the small sample size should be considered when interpreting the results. Although the sample was powered to detect reasonable differences in each PRO at an alpha level of 0.05 (two-sided), the study was underpowered and subject to a type II error with respect to detecting differences between the UKA and HTO groups for any other variable. In this study, there was 87% power to detect a 1-point VAS difference in the pain level between groups, but it remains unclear how much of a difference in VAS scale is clinically relevant when comparing between HTO and UKA. We believe 1-point VAS scale is clinically meaningful because 2-point VAS is widely used in multiple recent orthopaedic ambulatory surgeries [41–43]. Finally, we assessed final outcomes at 2 year postoperatively, which is a relatively short period for evaluating postoperative outcomes. However, as we mainly focused on PROs, not on clinical outcomes or longevity, we believe that 2 years is sufficient to assess patient satisfaction. In addition, we sought to compare PROs between patients who underwent UKA and HTO procedures that adopted the most up-to-date implant and instrumentation systems. All UKAs in this study were performed using Microplasty®, the most advanced Oxford mobile-bearing UKA instrumentation system that was introduced in recent years. Despite these limitations, our study provides valuable information with respect to the decision to perform HTO or UKA and importance of understanding patient expectations before surgery, especially in patients who do not ideally fit the recently expanded indications for both procedures.

## 5. Conclusions

The results of this study support our hypothesis that different patient factors would be associated with satisfaction following HTO and UKA. Severe OA was a risk factor for dissatisfaction after HTO, whereas young age and severe varus deformity were associated with an increased risk of dissatisfaction after UKA. Therefore, surgeons should take these factors into account when deciding whether to perform HTO or UKA and advise patients scheduled to undergo either procedure to ensure realistic expectations of outcomes.

## Disclosure of interest

The authors declare that they have no competing interest.

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## Authors' contribution

All authors have made substantive intellectual contributions to this study. IY participated in the design of the study and performed the surgery. KMS, SS, SKY and CNY collected the subjects' data. KIJ wrote the manuscript and performed the statistical analysis. All authors have read and approved the final manuscript.

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