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Responders to Medial Opening Wedge High Tibial Osteotomy for Knee Osteoarthritis

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ABSTRACT. ***Objective.*** Medial opening wedge high tibial osteotomy (HTO) aims to improve symptoms for patients with knee osteoarthritis (OA) and varus alignment, yet the likelihood of achieving a minimum clinical threshold of response and the factors predictive of response are unclear. We evaluated the proportion of patients meeting responder criteria based on the Outcome Measures in Rheumatology–Osteoarthritis Research Society International consensus 2 years after medial opening wedge HTO and investigated predictors of response.

Methods. Patients in a prospective cohort with symptomatic knee OA and varus alignment completed the Knee Injury and Osteoarthritis Outcome Score questionnaire < 3 months before and 2 years after HTO. For our primary analysis, we calculated the proportion of responders with ≥ 20% relative improvement and an absolute change of ≥ 10 points in pain and function from baseline. We performed logistic regression to evaluate the association of predictors with response and completed sex-disaggregated analyses.

Results. At a mean of 20.3 (SD 6.2) months post-HTO, 406 patients (78%) met the responder criteria. Older age, higher BMI, and larger postoperative mechanical axis angles (ie, slight valgus) were associated with increased odds of achieving responder criteria, although odds ratios were small. When stratified by sex, 316/405 male patients (78%) and 90/118 female patients (76%) met the responder criteria.

Conclusion. Based on responder criteria for knee OA, 78% of patients undergoing medial opening wedge HTO were responders at 2 years postsurgery. Although patients who are younger, male, and nonobese are viewed as appropriate candidates for HTO, patients who are female, are older, and have a high BMI also achieve sizable improvements in pain and function.

Key Indexing Terms: function, high tibial osteotomy, knee osteoarthritis, pain, responder criteria

Realignment surgeries for patients with knee osteoarthritis (OA) symptoms aim to improve pain and function by shifting mechanical loads away from the joint's most affected region.[1] However, the likelihood of achieving a minimum clinical threshold of response and the factors predictive of response are not known. Such information is critical for clinical decision making and for the design of future clinical trials.

Knee OA is the most common form of arthritis and is a leading cause of pain and disability that creates tremendous personal and economic burden worldwide.[2] Exercise, education, weight loss, and pain medications are mainstays of treatment for knee OA, yet many patients continue to experience substantial pain and reduced function for many years—on average of 13.3 years—while exhausting these treatments.[3] An estimated 30% of patients also eventually receive a total knee replacement (TKR).[4] In the USA alone, there are more than 700,000 TKRs performed annually.[5]

Lower limb alignment has a large influence on knee loading,[6] and varus alignment is a strong risk factor for OA progression.[7] Medial opening wedge high tibial osteotomy (HTO) is a limb

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realignment surgery for patients with varus alignment and medial-dominant knee OA.[8-13] The procedure may be considered when adequate symptom relief is not achieved with therapeutic and pharmacological treatments, and when preserving the native joint is preferred over TKR because of earlier-stage disease, younger age, and greater physical demands. Although it is a longstanding treatment for knee OA, HTO is relatively uncommon for this highly prevalent disease. HTO use rates are low and declining, whereas TKR use is high and rising.[14-16] HTO is often not included in clinical guidelines.[17,18]

The Outcome Measures in Rheumatology–Osteoarthritis Research Society International (OMERACT-OARSI) responder criteria provide a composite summary measure for improvements in pain and function after intervention by evaluating changes in patient-reported outcomes from baseline.[19] OMERACT-OARSI criteria are often used in rheumatology to evaluate the effect of pharmacological interventions.[20-25] Recent studies have also used the OMERACT-OARSI responder criteria to evaluate TKR.[26-28] Despite its goal of improving pain and function, response to HTO has not been evaluated using the OMERACT-OARSI responder criteria. Therefore, the objectives of this study were to (1) evaluate the proportion of patients meeting various modified OMERACT-OARSI responder criteria following medial opening wedge HTO, and (2) investigate potential predictors of response in a longstanding cohort of patients.

METHODS

Study design. We used data from an ongoing, prospective cohort study evaluating patients undergoing medial opening wedge HTO for symptomatic knee OA, primarily affecting the medial compartment of the knee, and with varus alignment. Participants had been referred to the Fowler Kennedy Sport Medicine Clinic in London, Ontario, Canada, between 2002 and 2014 by primary care physicians or orthopedic surgeons. Specifically, participants were referred for the management of unresolved knee pain and/or decreased function, and dissatisfaction with the degree of symptom relief from rehabilitation and/or pharmacological therapies. In total, 4 surgeons with international fellowship training in orthopedic sports medicine and lower limb realignment surgery participated.

Patients eligible for HTO had radiographic evidence of knee damage that was greatest in the medial tibiofemoral compartment, had varus alignment of the lower limb, and were not satisfied with the level of improvement achieved with previously completed rehabilitation and medical treatments. Patients met the American College of Rheumatology criteria[29] and had varus alignment (ie, mechanical axis angle [MAA] < 0°) assessed on full limb standing anteroposterior hip-to-ankle radiographs. Clinical suitability for HTO was assessed based on a combination of radiographic disease severity (eg, medial joint space narrowing) and medial-dominant knee symptoms during walking, while factoring in perioperative risks and patients' treatment preferences. Patients with radiographic joint space narrowing in the lateral and/or patellofemoral compartments were also considered eligible for HTO if medial joint space narrowing and medial knee pain, identified through history and physical exam, were more severe. Patients with complete radiographic joint space loss in ≥ 2 knee compartments were not deemed to be suitable HTO candidates and were referred for potential arthroplasty.

For patients who underwent staged bilateral HTO, we included only follow-up data pertaining to a patient's first limb, which was assessed before the contralateral limb HTO was performed. We excluded patients who underwent different HTO procedures (eg, lateral closing wedge), patients who underwent a different procedure on the study or contralateral limb (eg, TKR) or contralateral HTO before follow-up at 12 months after primary HTO, and patients without 12-month or 24-month data.

We asked patients to complete the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire[30,31] within 3 months prior to their HTO surgery and at subsequent follow-up visits, including at 12 and 24 months postoperatively. Patients also completed radiographic assessments, including full limb standing anteroposterior (ie, hip-to-ankle) views to assess lower limb alignment through the MAA[32,33] and radiographic disease severity using Kellgren-Lawrence (KL) grading.[34] The MAA was evaluated by one reviewer using a customized digital software program designed to measure alignment (HTO Pro, Wolf Orthopedic Biomechanics Laboratory, Western University), which has been shown to have excellent intra- and interrater reliability (intraclass correlation coefficient range 0.96-0.99).[32] We also assessed disease stage using the OARSI Radiographic Atlas for Osteoarthritis.[29] The MAA and KL grading were evaluated by a single reader (KML) using the standing anteroposterior radiographs. The OARSI grades were completed by a separate reader (CAP) using both the standing anteroposterior radiographs and the semiflexed posteroanterior radiographs. KL grades and OARSI grades were used to describe the sample. The KL grades were included as covariates in regression models, as described below. We also completed direct measurements of participant mass (in kg) and height (in cm) at the clinic. The study was approved by Western University's Research Ethics Board (REB) for Health Sciences Research Involving Human Subjects (REB no. 1187). All patients provided written and informed consent prior to participation in any study-related activities.

Responder criteria. We identified responders to HTO based on a modified version of the responder criteria reported in the OMERACT-OARSI consensus.[19] We evaluated response using KOOS scores at baseline and 24 months. If the 24-month follow-up was missing (eg, participants who underwent a second HTO before 24 months), we carried forward the 12-month visit data for the study limb, as previous studies suggest little change occurs from 12 to 24 months after HTO.[9,10] We defined a responder as having experienced a relative improvement ≥ 20% with an absolute change ≥ 10 points in both the pain and function in daily living (ie, function) subscales of the KOOS from pre- to post-HTO.[19] As secondary analyses, we also defined thresholds of improvement of ≥ 50% and ≥ 70%—instead of 20%—for both pain and function subscales. OMERACT-OARSI criteria have previously been used to evaluate response to interventions using scales where lower scores indicate better outcome and where larger scores indicate poorer outcome. Therefore, we reversed the KOOS scales (ie, 0 = best and 100 = worst) to calculate responder criteria only. For individuals where an absolute improvement ≥ 10 points in the KOOS was not achievable (eg, baseline KOOS pain and/or function was > 90 points), only relative improvements ≥ 20% were used as a response criterion.

Statistical analysis. We described demographics and clinical characteristics using means and frequencies. We first calculated the percentage of responders, then fitted a multivariate logistic regression model to evaluate the association of potential predictors with achieving responder status, reported as odds ratios (ORs) with 95% CIs. We selected potential predictors a priori, based on previous studies reporting their association with HTO outcome,[8,11-13,35,36] in order to minimize the risk of model overfitting.[37] Specific variables included radiographic stage of disease (KL grade ≤ 2 vs KL grade 3 or 4), alignment achieved with surgery (MAA), baseline knee pain (KOOS pain per 20 points), sex, age (per 10 yrs), and BMI (calculated as weight in kilograms divided by height in meters squared; per BMI of 5). As a covariate, KOOS pain remained on a scale of 0 (worst) to 100 (best) for ease of interpretation. As HTOs were performed by 4 different surgeons, we adjusted the variance for clustering at the surgeon level with robust sandwich estimators. We tested the assumptions for logistic regression models, and the assumptions were met. We did not include the KOOS function subscale in our model because of multicollinearity with the pain subscale (variance inflation factor of 5).

Following the Sex and Gender Equity in Research guidelines,[38] we also completed sex-stratified analyses and compared baseline characteristics in males and females using independent *t* tests and chi-square tests (Supplementary Table S1, available with the online version of this article). We also repeated analyses for males and females separately, then with an interaction term between sex and baseline knee pain—centered to the study mean—from the main analysis. We used the lincom function from Stata/IC 16 (StataCorp LLC) to estimate linear combinations of regression parameters. We also completed additional analyses including a disaggregated analysis by radiographic stage of disease (KL grade ≤ 2 vs KL grade 3 or 4), substituting the continuous postoperative MAA variable for a categorical variable (< 0°, varus; 0° to 3°, neutral; or > 3°, valgus), substituting postoperative MAA for change in MAA (postoperative minus preoperative MAA), removing MAA variables from the analysis, and excluding patients whose 12-month visit was carried forward to 24 months. We also completed sensitivity analyses removing patients who had a contralateral HTO between 12 and 24 months after the initial HTO (n = 40), and again when removing participants whose baseline KOOS pain and/or function score was > 90 points at baseline. All analyses were completed using Stata/IC 16 statistical software using a 2-sided *P* value < 0.05 to indicate statistical significance.

RESULTS

A total of 523 patients completed the study (Figure 1). Most patients were male, were middle-aged, had a higher BMI, had varus alignment, and had radiographic features of OA primarily located in the medial compartment (Table 1). Data are also presented by responders and nonresponders at different relative improvement thresholds (≥ 20%, ≥ 50%, and ≥ 70%; Table 1). At a mean follow-up of 20.3 (SD 6.2) months after HTO, 78% (n = 406) of patients met the responder criteria (Figure 2). The final endpoint for 394 patients (75%) was 24 months, and the endpoint for 129 patients (25%) was 12 months where no 24-month data were available. When using a relative improvement threshold of ≥ 50% and ≥ 70%, the percentage of responders was 32% (n = 166) and 20% (n = 103), respectively (Figure 2). In total, 40 participants (8%) underwent contralateral HTO between 12 and 24 months after the first surgery.

A larger postoperative MAA (valgus) achieved with surgery (OR 1.04, 95% CI 1.01-1.07), older age (OR 1.34, 95% CI 1.28-1.40; per 10 yrs), and a higher BMI (OR 1.21, 95% CI 1.09-1.33; per BMI of 5) were associated with increased odds of achieving the responder criteria (Table 2), although the ORs were small. At an improvement threshold of ≥ 50%, postoperative MAA and BMI were no longer predictors of response; however, baseline knee pain was a strong predictor. Results indicated that a higher baseline KOOS pain score (ie, less baseline knee pain) reduced the odds (OR 0.17, 95% CI 0.13-0.21; per 20 points) of meeting responder criteria at 24 months (Table 2). At an improvement threshold of ≥ 70%, late-stage radiographic disease (OR 0.82, 95% CI 0.67-0.99), a higher (ie, better)

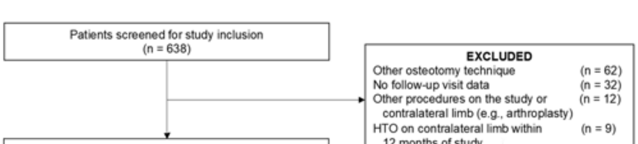

Figure 1. Patient flow diagram. HTO: high tibial osteotomy.

baseline KOOS pain score (OR 0.11, 95% CI 0.10-0.13; per 20 points), and a higher BMI (OR 0.89, 95% CI 0.82-0.95; per BMI of 5) were associated with reduced odds of achieving the responder criteria, whereas female sex (OR 1.33, 95% CI 1.05-1.69) and older age (OR 1.26, 95% CI 1.03-1.55; per 10 yrs) were associated with increased odds (Table 2). Results were similar for additional analyses and are presented in Supplementary Tables S2 to S6 (available with the online version of this article). The percentage of responders was similar after removing patients with a contralateral HTO. Responder rates were 77%, 30%, and 18% at relative improvement thresholds of ≥ 20%, ≥ 50%, and ≥ 70%, respectively.

Sex-stratified analyses. Female patients were slightly younger, had less varus malalignment, and had worse baseline knee pain and function than males at baseline (Supplementary Table S1, available with the online version of this article). When stratified by sex, 316/405 male patients (78%) and 90/118 female patients (76%) met the responder criteria (Figure 2). When using relative improvement thresholds of ≥ 50% and ≥ 70%, the percentages of responders were 31% (n = 124) and 18% (n = 73) for males and 35% (n = 42) and 25% (n = 30) for females (Figure 2). In the logistic regression models, results were similar to the primary analysis for males (Table 3). For females, later-stage radiographic disease (OR 0.46, 95% CI 0.31-0.69) was associated with reduced odds of achieving the responder criteria after HTO, and older age increased the odds (Table 3). Contrary to males, a higher BMI (OR 0.83, 95% CI 0.70-0.97; per BMI of 5) was associated with reduced odds of achieving responder criteria for females.

Sex and pain. There was a significant interaction between sex and baseline knee pain (OR 0.66, 95% CI 0.52-0.85; Table 4), suggesting that less baseline knee pain was associated with increased odds of achieving responder criteria for females (OR 1.25, 95% CI 1.02-1.52) but not for males (OR 0.86, 95% CI 0.67-1.09). The overall effects of other variables were similar to those found in the primary analysis, except that later-stage radiographic disease was now also associated with reduced odds of meeting responder criteria (OR 0.76, 95% CI 0.58-0.99).

DISCUSSION

A total of 78% of patients met responder criteria 24 months after undergoing medial opening wedge HTO. When using more stringent criteria (ie, higher relative improvement thresholds), 32% of patients improved by 50% or greater in both pain and function, and 20% of patients improved by 70% or greater. With the understanding that surgical interventions for knee OA should provide sizable benefits and may include placebo effects, these results are encouraging. Studies evaluating responders after pharmacological interventions report response rates between 60% and 89% at 6 months[20,22,24] and between 57% and 73% at 12 months.[20,21,25] For example, a recent randomized trial[24] found that 77% of patients responded to tanezumab at 24 weeks, whereas placebo response rates were 65%. In another trial,[25] response rates between 69% and 73% for varying dosages of lutikizumab were found at 12 months, whereas the placebo group response rate was 71% and not significantly different (mean differences

Table 1. Baseline demographics and clinical characteristics of patients[a].

	Total, N = 523	Relative Threshold ≥ 20%		Relative Threshold ≥ 50%		Relative Threshold ≥ 70%	
		Responder, n = 406	Non-responder, n = 117	Responder, n = 166	Non-responder, n = 357	Responder, n = 103	Non-responder, n = 420
Age, yrs, mean (SD)	46.6 (9.1)	47.1 (9.1)	44.7 (8.8)	48.4 (8.5)	45.8 (9.3)	48.4 (8.6)	46.2 (9.2)
Sex, male	405 (77.4)	316 (77.8)	89 (76.1)	281 (78.7)	124 (74.7)	332 (79.1)	73 (70.9)
BMI[b], mean (SD)	29.6 (5.0)	29.8 (4.8)	29.0 (5.5)	30.5 (5.3)	29.2 (4.8)	30.4 (5.4)	29.4 (4.9)
Preoperative mechanical axis angle, degrees[c], mean (SD)	−7.8 (3.7)	−7.9 (3.7)	−7.6 (4.0)	−8.2 (3.9)	−7.7 (3.6)	−7.8 (3.8)	−7.9 (3.7)
Postoperative mechanical axis angle, degrees[c,d], mean (SD)	0.9 (2.6)	1.0 (2.6)	0.8 (2.6)	1.0 (2.8)	0.9 (2.5)	0.9 (3.0)	0.9 (2.5)
KOOS pain subscale score (0-100)[e], mean (SD)	50.3 (17.7)	49.9 (17.0)	51.8 (19.8)	37.2 (11.5)	56.4 (16.7)	33.3 (10.9)	54.5 (16.5)
KOOS function in daily living subscale (0-100)[e], mean (SD)	59.1 (19.9)	58.9 (19.4)	59.7 (21.6)	43.9 (13.1)	66.2 (18.5)	38.5 (12.2)	64.2 (18.1)
Kellgren-Lawrence grade[f]							
0	3 (0.6)	3 (0.7)	–	–	3 (0.8)	–	3 (0.7)
1	50 (9.6)	35 (8.6)	15 (12.8)	12 (7.2)	38 (10.6)	6 (5.8)	44 (10.5)
2	151 (28.9)	122 (30.1)	29 (24.5)	45 (27.1)	106 (29.7)	30 (29.1)	121 (28.8)
3	196 (37.5)	144 (35.5)	52 (44.4)	58 (34.9)	138 (38.7)	38 (36.9)	158 (37.6)
4	123 (23.5)	102 (25.1)	21 (18)	51 (30.7)	72 (20.2)	29 (28.2)	94 (22.4)
OARSI joint space narrowing grade[g]							
Medial tibiofemoral compartment							
0	12 (2.4)	9 (2.3)	3 (2.7)	2 (1.2)	10 (2.9)	–	12 (3)
1	156 (30.8)	123 (31.1)	33 (29.7)	44 (27)	112 (32.7)	26 (25.7)	130 (32.1)
2	206 (40.7)	159 (40.3)	47 (42.3)	68 (41.7)	138 (40.2)	45 (44.6)	161 (39.8)
3	132 (26.1)	104 (26.3)	28 (25.2)	49 (30.1)	83 (24.2)	30 (29.7)	102 (25.2)
Lateral tibiofemoral compartment							
0	425 (84)	329 (83.3)	96 (86.5)	134 (82.2)	291 (84.8)	81 (80.2)	344 (84.9)
1	75 (14.8)	61 (15.4)	14 (12.6)	26 (16)	49 (14.3)	18 (17.8)	57 (14.1)
2	6 (1.2)	5 (1.3)	1 (0.9)	3 (1.8)	3 (0.9)	2 (2)	4 (1)
3	–	–	–	–	–	–	–

Data are in n (%) unless otherwise indicated. [a] All patients had a clinical diagnosis of knee OA according to the American College of Rheumatology criteria as described by Altman.[29] Clinical knee OA is defined as knee pain and 3 of the 6 following criteria: morning stiffness < 30 mins, age > 50 yrs, crepitus, bony tenderness, bony enlargement, and/or no palpable warmth. [b] BMI is calculated as weight in kilograms divided by height in meters squared. [c] A negative angle indicates varus alignment; a positive angle indicates valgus alignment. [d] Correction achieved during surgery, measured from postoperative visit. [e] A KOOS of 0 indicates extreme knee symptoms and 100 indicates no knee symptoms. [f] The Kellgren-Lawrence grade evaluates the degree of radiographic OA severity. Grade 0 indicates a normal knee; grade 1 indicates doubtful joint space narrowing and possible osteophytic lipping; grade 2 indicates possible joint space narrowing and definite osteophytes; grade 3 indicates definite joint space narrowing, multiple moderate osteophytes, some sclerosis, and possible deformity of the bone contour; and grade 4 indicates marked joint space narrowing, large osteophytes, severe sclerosis, and definite deformity of bone contour. [g] The OARSI Radiographic Atlas for Osteoarthritis is a semiquantitative scoring system that includes compartment-specific joint space narrowing grades on a scale of 0 (normal joint space) to 3 (total loss of joint space). OARSI grading was available for 506 of the total 523 knees. KOOS: Knee Injury and Osteoarthritis Outcome Score; OA: osteoarthritis; OARSI: Osteoarthritis Research Society International.

−1.3 to 2.1). Response rates between 64% and 91% have been reported at 6 months,[26] between 86% and 87% at 12 months,[27] and between 69% and 83% at 24 months after TKR.[28]

The time required to achieve the maximum effects of treatment is also important to consider and is faster for pharmacological vs surgical interventions. After HTO, patients undergo an extended period of recovery and postoperative rehabilitation, and pain and function experience slower improvement over several months following surgery.[9] Although the rate of serious adverse events with HTO is low,[39] it has risks (eg, deep vein thrombosis, infection, and delayed union), and the procedure requires a prolonged period of time with limited weight-bearing after surgery. These factors need to be considered by patients and clinicians when considering treatment options.

Interestingly, the effect of BMI on the odds of meeting responder criteria were opposite depending on the relative improvement threshold evaluated. At an improvement threshold of 20% or greater, older age, and a higher BMI were associated with increased odds of achieving responder criteria at 24 months after HTO, while controlling for covariates. The latter is consistent with an interaction between varus alignment and BMI on medial knee joint load.[40,41] Changes in alignment of similar magnitude may provide a greater reduction in the magnitude of mechanical knee loading for individuals with a greater BMI, which may lead to a greater reduction of symptoms. Interestingly, at higher improvement thresholds (ie, ≥ 70%) for responders, a lower BMI was predictive of responding. Collectively, these results suggest that although individuals with a lower BMI may

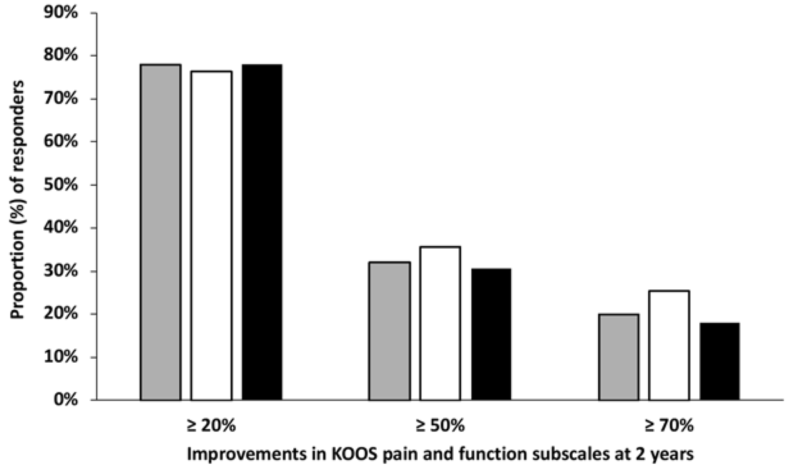

Figure 2. Proportion of all study patients (gray bars; N = 523), females (white bars; 118/523), and males (black bars; 405/523) achieving at least 20%, 50%, and 70% relative improvements with an absolute change of at least 10 points in the scores for the KOOS pain and function (ie, activities of daily living) subscales at 2 years following HTO. HTO: high tibial osteotomy; KOOS: Knee Injury and Osteoarthritis Outcome Score.

Table 2. Multivariate logistic regression estimates for achieving responder criteria by 24 months after HTO defined as a relative improvement of ≥ 20%, ≥ 50%, or ≥ 70% with an absolute change ≥ 10 points in pain and function outcomes (N = 523).

Predictor	OR (95% CI)[a]		
	Relative Threshold ≥ 20%	Relative Threshold ≥ 50%	Relative Threshold ≥ 70%
Radiographic stage (Kellgren-Lawrence grade)			
Mild to moderate[b]	Ref	Ref	Ref
Moderate to severe[b]	0.76 (0.58-1.01)	0.85 (0.71-1.02)	**0.82 (0.67-0.99)**
Postoperative alignment (mechanical axis angle, degrees)	**1.04 (1.01-1.07)**	1.06 (0.99-1.15)	1.04 (0.92-1.18)
KOOS pain subscale score (per 20 points)[c]	0.93 (0.75-1.17)	**0.17 (0.13-0.21)**	**0.11 (0.10-0.13)**
Sex			
Male	Ref	Ref	Ref
Female	0.93 (0.69-1.25)	0.98 (0.75-1.31)	**1.33 (1.05-1.69)**
Age (per 10 yrs)	**1.34 (1.28-1.40)**	**1.35 (1.03-1.77)**	**1.26 (1.03-1.55)**
BMI (per BMI of 5)[d]	**1.21 (1.09-1.33)**	1.06 (0.98-1.14)	**0.89 (0.82-0.95)**

Bolded estimates represent statistically significant associations at the 5% level. [a] The variance was adjusted for surgeon using robust sandwich estimators. [b] Mild to moderate represents a Kellgren-Lawrence grade ≤ 2; moderate to severe represents a Kellgren-Lawrence grade of 3 or 4. [c] A KOOS of 0 indicates extreme knee symptoms and 100 indicates no knee symptoms. [d] BMI is calculated as weight in kilograms divided by height in meters squared. HTO: high tibial osteotomy; KOOS: Knee Injury and Osteoarthritis Outcome Score; OR: odds ratio.

experience improvements of greater magnitude in pain and function, individuals with a higher BMI can also achieve meaningful improvements after HTO. Although patients who are younger, with lower BMI, and with earlier-stage radiographic disease have traditionally been considered better candidates for HTO, results from this study suggest that older patients and those with a higher BMI may also experience substantial pain and function benefits from the surgery.

The effects of pain and radiographic stage can vary considerably for different knee OA interventions. In the present data, less baseline knee pain (ie, higher KOOS pain scores) reduced the odds of achieving responder criteria at both 50% or greater and 70% or greater thresholds (ORs < 0.18). Early-stage radiographic disease (KL grade ≤ 2) and female sex were associated with increased odds of meeting responder criteria at a 70% or greater threshold, although the reported ORs were small. Larger postoperative MAAs were also associated with increased odds of achieving responder criteria at a threshold of 20% or greater, but the OR was small. When taken together, these findings suggest that patients with worse pain, with earlier-stage disease, and requiring larger MAA corrections may be the best candidates for selecting HTO.

This study also investigated the influence of sex on outcomes after HTO. Sex-stratified response rates were similar for males and females (78% and 76%, respectively), and were higher in females compared to males (25% vs 18%) at an improvement threshold of 70% or greater. In females only, earlier radiographic disease severity and a lower BMI increased the odds of meeting responder criteria. The latter supports research suggesting that BMI is a potentially modifiable risk factor affecting females to a larger extent than males with knee OA.[42] Results showed that less baseline knee pain was more strongly associated with meeting

Table 3. Sex-stratified multivariate logistic regression estimates for achieving responder criteria by 24 months after HTO for males (n = 405) and females (n = 118).

Predictor	OR (95% CI)[a]
Males	
Radiographic stage (Kellgren-Lawrence grade)	
Mild to moderate[b]	Ref
Moderate to severe[b]	0.81 (0.57-1.16)
Postoperative alignment (mechanical axis angle, degrees)	**1.05 (1.00-1.10)**
KOOS pain subscale score (per 20 points)[c]	0.89 (0.70-1.13)
Age (per 10 yrs)	**1.33 (1.22-1.45)**
BMI (per BMI of 5)[d]	**1.56 (1.39-1.74)**
Females	
Radiographic stage (Kellgren-Lawrence grade)	
Mild to moderate[b]	Ref
Moderate to severe[b]	**0.46 (0.31-0.69)**
Postoperative alignment (mechanical axis angle, degrees)	0.96 (0.86-1.08)
KOOS pain subscale score (per 20 points)[c]	1.08 (0.89-1.31)
Age (per 10 yrs)	**1.59 (1.31-1.93)**
BMI (per BMI of 5)[d]	**0.83 (0.70-0.97)**

Bolded estimates represent statistically significant associations at the 5% level. [a] The variance was adjusted for surgeon using robust sandwich estimators. [b] Mild to moderate represents a Kellgren-Lawrence grade ≤ 2; moderate to severe represents a Kellgren-Lawrence grade of 3 or 4. [c] A KOOS of 0 indicates extreme knee symptoms and 100 indicates no knee symptoms. [d] BMI is calculated as weight in kilograms divided by height in meters squared. HTO: high tibial osteotomy; KOOS: Knee Injury and Osteoarthritis Outcome Score; OR: odds ratio.

Table 4. Multivariate logistic regression estimates for achieving responder criteria by 24 months after HTO exploring the interaction between sex and baseline knee pain (N = 523).

Predictor	OR (95% CI)[a]
Radiographic stage (Kellgren-Lawrence grade)	
Mild to moderate[b]	Ref
Moderate to severe[b]	**0.76 (0.58-0.99)**
Postoperative alignment (mechanical axis angle, degrees)	**1.04 (1.01-1.07)**
KOOS pain subscale score (per 20 points)[c]	1.29 (1.03-1.62)
Sex	
Male	Ref
Female	0.97 (0.74-1.25)
Age (per 10 yrs)	**1.35 (1.28-1.42)**
BMI (per BMI of 5)[d]	**1.23 (1.11-1.35)**
Interaction between sex and KOOS pain subscale score	
Male	**0.66 (0.52-0.85)**
Female	Ref

Bolded estimates represent statistically significant associations at the 5% level. [a] The variance was adjusted for surgeon using robust sandwich estimators. [b] Mild to moderate represents a Kellgren-Lawrence grade ≤ 2; moderate to severe represents a Kellgren-Lawrence grade of 3 or 4. [c] A KOOS of 0 indicates extreme knee symptoms and 100 indicates no knee symptoms. [d] BMI is calculated as weight in kilograms divided by height in meters squared. HTO: high tibial osteotomy; KOOS: Knee Injury and Osteoarthritis Outcome Score; OR: odds ratio.

responder criteria in females than for males. These results support studies suggesting that there are differences in pain perception between males and females.[43] To our knowledge, this is the first study to evaluate sex differences in pain response after HTO through responder criteria. However, there were fewer females in this study; therefore, results from the sex-disaggregated analyses and interaction effects are exploratory. Although the study may lack sufficient power for sex-disaggregated analyses, our results provide a compelling rationale for larger studies to evaluate potential sex differences,[44] and they provide early evidence that males and females can be offered HTO and expect similar response rates. This is important, as females are much less likely to be offered HTO surgery for reasons that are not currently clear.

Some of the present results may also seem counterintuitive; for example, how less baseline knee pain may be associated with poorer outcomes. It is important to acknowledge the potential for ceiling effects, as both absolute and relative improvements were evaluated for both pain and function to meet the responder criteria. Patients with less knee pain and better function at baseline have a smaller window for improvement, as evidenced by our analyses at thresholds of 50% or greater and 70% or greater. However, this also suggests that our overall group estimates for responder status may be more conservative in nature. Similarly, surgery has its own associated morbidity; therefore, larger improvements are needed to overcome the effects of surgery. Individuals with less knee pain at baseline may not be able to improve enough to experience noticeable changes beyond the effects of the surgery/recovery. Further, the patient global assessment (PtGA) may also be included in the assessment of OMERACT-OARSI responder criteria, where response can be defined as achieving an improvement of at least 20% in 2 out of 3 criteria (ie, pain, function, and/or PtGA). Since PtGA was not collected in our study, our results likely represent more conservative or underestimated HTO responder rates.

To our knowledge, this is the largest sample size of a study evaluating 24-month pain and function data in patients who underwent HTO. This study also provides important data for HTO in a North American population, as many HTO studies have been reported in Europe and Asia. Given that the data provided are from patient participants, vs administrative data, it improves the translatability, generalizability, and contextualization of study results.

Several limitations in this study should be acknowledged. We do not know the number of patients who were eligible but declined to undergo HTO or study participation, as patients were recruited for the study after the orthopedic surgeon deemed them to be eligible candidates for HTO; these patients were subsequently referred to our lab for study participation. This observational cohort study had no control group; therefore, potential for biases related to regression to the mean, self-inclusion bias, natural variation in symptoms, and placebo effects, among others, are possible. Selection bias is possible, as patients were most often referred by other primary care physicians or orthopedic surgeons with knowledge of HTO. It is possible that previous knee trauma or knee surgeries could have influenced the present results but were not evaluated. We also did not include contralateral limb data for those patients who underwent staged bilateral HTO, as we suggest that it is a conservative approach to the present question. Also, the HTO surgeries were performed at a single tertiary care center by 1 of 4 orthopedic surgeons with specialized training in HTO, which may introduce expert bias and limit generalizability of the findings to similar centers. The present participants may represent the best candidates for HTO or those willing to participate in studies, rather than all patients eligible for the procedure.

In conclusion, the present study suggests that 78% of patients with medial-dominant knee OA and varus alignment undergoing HTO meet the modified pain and function responder criteria 24 months after surgery. Although patients who are younger, are male, and have a low BMI have been proposed to have better outcomes post-HTO, our results suggest that patients who are older and have a higher BMI can also experience sizable pain and function responses from HTO surgery; in addition, males and females can expect similar response rates at 24 months. There may also be underlying sex differences in individuals' pain-related responses to HTO surgery that require further exploration. Overall, these findings support the hypothesis that load-altering interventions may be effective for managing knee OA, which underscores the importance of conducting prospective controlled trials to better assess the effect size.

DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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