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Clinical Phenotype Classifications Based on Static Varus Alignment and Varus Thrust in Japanese Patients With Medial Knee Osteoarthritis

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Objective. **To investigate the association between knee pain during gait and 4 clinical phenotypes based on static varus alignment and varus thrust in patients with medial knee osteoarthritis (OA).**

Methods. **Patients in an orthopedic clinic (n = 266) diagnosed as having knee OA (Kellgren/Lawrence [K/L] grade ≥1) were divided into 4 phenotype groups according to the presence or absence of static varus alignment and varus thrust (dynamic varus): no varus (n = 173), dynamic varus (n = 17), static varus (n = 50), and static varus + dynamic varus (n = 26). The knee range of motion, spatiotemporal gait parameters, visual analog scale scores for knee pain, and scores on the Japanese Knee Osteoarthritis Measure were used to assess clinical outcomes. Multiple logistic regression analyses identified the relationship between knee pain during gait and the 4 phenotypes, adjusted for possible risk factors, including age, sex, body mass index, K/L grade, and gait velocity.**

Results. **Multiple logistic regression analysis showed that varus thrust without varus alignment was associated with knee pain during gait (odds ratio [OR] 3.30, 95% confidence interval [95% CI] 1.08–12.4), and that varus thrust combined with varus alignment was strongly associated with knee pain during gait (OR 17.1, 95% CI 3.19–320.0). Sensitivity analyses applying alternative cutoff values for defining static varus alignment showed comparable results.**

Conclusion. **Varus thrust with or without static varus alignment was associated with the occurrence of knee pain during gait. Tailored interventions based on individual malalignment phenotypes may improve clinical outcomes in patients with knee OA.**

Knee osteoarthritis (OA) is a major public health issue and a prominent cause of chronic pain and disability, particularly during gait (1,2). Knee OA is a multifactorial disease, and the population of knee OA patients is heterogeneous (3). Therefore, patients with knee OA may be classified into different subgroups, or phenotypes (4,5).

The identification of different knee OA phenotypes may be highly relevant to disease treatment, and isolating these phenotypes may be critical to the development of effective treatment and disease prevention strategies (6,7). In identifying applicable phenotypes, knee malalignment is a key factor (6) because sufficiently malaligned knees progress to more severe disease in the absence of other known risk factors such as obesity (8).

Static varus alignment, evaluated with radiography, is a risk factor for increasing the load on the medial compartment and the progression of medial compartment knee OA (9). Similarly, varus thrust, which has been defined as the dynamic worsening or abrupt onset of varus alignment in the stance phase (dynamic varus), with a return to less varus alignment in the swing phase during gait (10), is a risk factor for the progression of medial compartment knee OA. Presence of varus thrust

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increases the odds of radiographic disease progression 4-fold (11), demonstrating the deleterious effect of dynamic varus knee alignment. In addition, varus thrust is strongly associated with weight-bearing pain and might represent a specific knee OA phenotype; patients with this phenotype may selectively respond to biomechanical gait modification (12).

Interestingly, in a study by Barrios et al, the dynamic varus angle in the knees of healthy individuals during gait enhanced the prediction of static measures, explaining the external knee adduction moment (KAM) (13). In addition, Chang and colleagues showed that varus thrust increases the likelihood of OA progression beyond the risk conferred by static varus alignment (11). Therefore, there are potentially several types of malalignment phenotypes based on the presence or absence of static varus alignment and varus thrust. Moreover, dynamic varus alignment combined with static varus alignment may be a malalignment phenotype that is better predictive of clinical outcomes, particularly knee pain during gait, compared with either varus thrust or static varus alignment alone.

As pain in patients with knee OA is generally characterized as pain that occurs during weight bearing, evaluating the presence of pain during weight bearing is potentially a good strategy to confirm malalignment phenotypes. Varus thrust is a measure of dynamic malalignment during gait. Therefore, questions that assess pain during gait are considered to represent proper clinical outcomes.

In the present study, we divided patients with medial knee OA into 4 novel malalignment phenotypes according to the presence or absence of static varus alignment and varus thrust. The groups comprised no varus, dynamic varus, static varus, and static varus + dynamic varus. Each of these phenotypes was assessed for associations with knee pain during gait, as measured using self-reported questionnaires. The purpose of this study was to investigate the relative impact of static varus alignment and varus thrust on the clinical outcomes, particularly knee pain during gait, by comparing the 4 phenotypes that can be easily assessed in clinical practice. We hypothesized that the 4 medial compartment knee OA phenotypes would show different clinical outcomes, that varus thrust without static varus alignment would be associated with knee pain during gait, and that varus thrust combined with static varus alignment would be more strongly associated with knee pain during gait than would no varus thrust without static varus alignment.

PATIENTS AND METHODS

Patients. This cross-sectional study was approved by the ethics committee of Kyoto University. All patients who agreed to participate provided written informed consent before study enrollment. All patients had a diagnosis of knee OA and had visited a community orthopedics clinic for conservative management in January 2014. The inclusion criteria for the present study were as follows: 1) age >50 years, 2) presence of radiographic OA in the medial knee compartment and a Kellgren/Lawrence (K/L) grade (14) of ≥1 in one or both knees, as evaluated on weight-bearing anteroposterior radiographs of the tibiofemoral joint, and 3) ability to independently walk on a flat surface. Patients were excluded if they had a prior knee surgery, inflammatory arthritis, a history of periarticular fractures, present neurologic problems such as hemiplegia, or lateral compartment knee OA. Lateral compartment knee OA was diagnosed if the K/L grade in the lateral compartment was greater than that in the medial compartment of the tibiofemoral joint (15).

Gait observation for varus thrust. Patients were recorded while walking 10 meters away from and toward a stationary camera (HDR-CX550V; Sony), at a self-selected speed, with their pants rolled up to expose the knees. The gait of each subject was examined from the recorded movies for the presence of varus thrust, with examinations performed by 2 independent, trained examiners (HI and NF) without knowledge of each patient's clinical status. The examiners identified the affected limb according to a validated method (12), to evaluate whether varus thrust was present. The affected limb in each individual was defined as the limb with symptoms or the limb with more symptoms than the contralateral (unaffected) limb. If the patient had no symptoms in either knee during the evaluation, the affected limb was defined as the limb that had previously had more symptoms than the contralateral limb.

The presence of varus thrust was defined as the dynamic worsening of varus alignment as the limb accepted weight. To enhance the reliability of identifying varus thrust, varus thrust was classified as being definitely present, possibly present, or definitely absent. We then categorized patients into those with definite varus thrust (only those with varus thrust being definitely present) and those without definite varus thrust (those with varus thrust being possibly present or definitely absent), as has been described previously by Lo et al (12). Any disagreements between the 2 examiners were resolved by a consensus reached by discussion. If no consensus was reached, a third person without knowledge of each patient's clinical status decided whether the patients had varus thrust.

In addition, to determine the intra- and interrater reliability of the assessment, the 2 evaluators (HI and NF) performed another gait assessment of all patients more than 1 week after the first assessment. The intrarater agreement values for varus thrust were excellent ($\kappa = 0.92$ and $\kappa = 0.81$ for NF and HI, respectively), and the interrater reliability between the 2 evaluators was also good ($\kappa = 0.73$).

Radiographic evaluation of the stage of progression and static varus alignment of the knee. Anteroposterior radiographs of the affected knees in the weight-bearing position were obtained within 3 months of enrollment. The radiographic severity of knee OA was assessed using K/L grades (scale 0–4), with assessments performed by an experienced researcher (TA). To assess intrarater reliability, 100 randomly selected radiographs were scored again by the same examiner (TA) more than 1 week after the first assessment. The intrarater agreement for K/L grade determination was excellent ($\kappa = 0.90$).

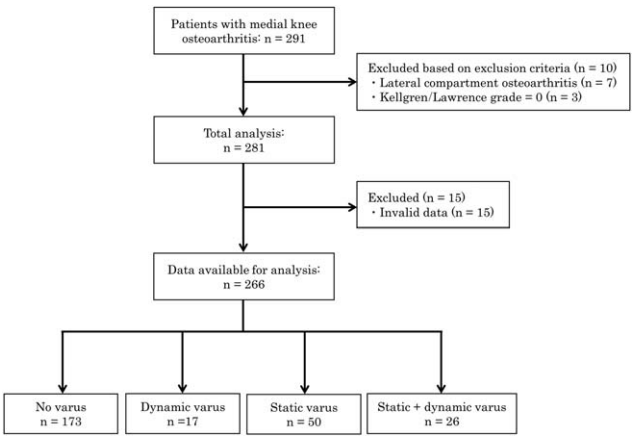

Figure 1. Flow chart describing the distribution of study patients with medial knee osteoarthritis.

The static knee alignment angle of the affected knee was measured according to a validated method (16), by a trained examiner (HI). The anatomic axis angle (AAA) was defined as the internal angle formed by the intersection of 2 lines originating from points bisecting the femur and tibia and converging at the center of the tibial spine tips (17). To better reflect mechanical alignment, knees with an AAA of $<181°$ in women or $<183°$ in men were defined as having static varus alignment (12,18), which was based on values obtained using the sex-specific regression equations as described by Kraus et al (16). In addition, knees with an AAA of $\geq 181°$ but $<185°$ in women or $\geq 183°$ but $<187°$ in men were defined as having neutral alignment, while those with an AAA of $\geq 185°$ in women or $\geq 187°$ in men were defined as having valgus alignment. To assess intrarater reliability, 100 randomly selected radiographs were scored again by the same examiner (HI) more than 1 week after the first assessment. The intrarater agreement for evaluating AAA was excellent (intraclass correlation coefficient of 0.98).

Phenotype identification based on static and dynamic varus alignment. All patients were allocated to 1 of 4 phenotypes on the basis of their static varus alignment and varus thrust during gait: no varus (no static varus [neutral or valgus] alignment + no varus thrust), dynamic varus (no static varus [neutral or valgus] alignment + varus thrust), static varus (static varus alignment + no varus thrust), and static + dynamic varus (static varus alignment + varus thrust).

Clinical outcome variables. To compare clinical outcomes among the 4 phenotype groups, the following outcomes were evaluated: range of motion (ROM) of both knees, knee pain, spatiotemporal gait parameters, and the Japanese Knee Osteoarthritis Measure (JKOM) (19). The ROM of the knee joint was measured passively by physical therapists. We measured the amount of time and the number of steps required to walk a distance of 10 meters. For measurement of spatiotemporal gait, the following spatiotemporal gait parameters were calculated: velocity (expressed in meters/second), cadence (expressed in steps/minute), and step length normalized to body height (expressed as a percentage of body height).

The JKOM is a patient-based, self-answered evaluation score that includes 4 subcategories, assessing 1) pain and stiffness (8 questions, range 0–32 points), 2) activities of daily living (10 questions, range 0–40 points), 3) participation in social activities (5 questions, range 0–20 points), and 4) general health conditions (2 questions, range 0–8 points) (19), with 100 points set as the maximum score. For each subcategory, higher scores indicate a worse condition. The JKOM has also been shown to have reliability and validity, as determined using statistical evaluation and comparison with the Western Ontario and McMaster Universities Osteoarthritis Index and the Medical Outcomes Study Short Form 36 health survey (19).

Knee pain was evaluated with the use of a visual analog scale (VAS; range 0–100 mm) and the pain and stiffness subscale of the JKOM, as person-specific assessments. Furthermore, to specifically evaluate pain during gait, the following question was asked: "Do you have pain in your knees when you walk on a flat surface?", with the response provided on a Likert scale (score range 0–4 points; where 0 indicates no pain and 4 represents extreme pain). This question is also one of the questions on the JKOM pain and stiffness subscale.

Statistical analysis. Data analyses were performed using JMP version 11 (SAS Institute) or the R statistical software package (R Foundation for Statistical Computing). The normality of continuous variables for each phenotype group was assessed using the Shapiro-Wilk test. The homogeneity of the variances between groups for all parametric continuous variables was confirmed using Levene's test. We statistically analyzed the differences among the 4 phenotypes using analysis of variance (ANOVA) with a subsequent post hoc Tukey-Kramer test for parametric continuous variables, Kruskal-Wallis test with subsequent post hoc Steel-Dwass test for nonparametric continuous variables, and Fisher's exact test for categorical variables. Descriptive statistics were calculated as the mean and SD for continuous variables and as counts and percentages for categorical variables.

Furthermore, to clarify the associations between knee pain during gait and the phenotype classifications, odds ratios (ORs) and their 95% confidence intervals (95% CIs) were calculated using 2 cumulative models of multiple logistic regression analyses. Model 1 was performed with inclusion of 1 item from the JKOM, pain with walking on a flat surface, as an objective variable, for which the scores of 0, 1, 2, 3, and 4 were dichotomized into 2 categories: normal (0 points) and mild/moderate/severe/extreme pain (1–4 points) for the logistic regression models (0 = no pain, 1 = pain). Each risk factor was

Table 1. Demographic and clinical characteristics of the study patients (n = 266)*

Age, years	72.7 ± 6.94
Height, meters	1.54 ± 0.07
Weight, kg	57.3 ± 9.93
BMI, kg/m^2	24.1 ± 3.57
Sex, % female	77.8
K/L grade, no. (%)	
1	94 (35.3)
2	115 (43.2)
3	37 (13.9)
4	20 (7.5)
Anatomic axis angle, degrees	181.9 ± 4.00
Static varus alignment, no. (%)	76 (28.6)
Varus thrust, no. (%)	43 (16.2)

* Except where indicated otherwise, values are the mean ± SD. BMI = body mass index; K/L = Kellgren/Lawrence.

Table 2. Demographic characteristics of and clinical outcomes in the patients according to knee malalignment phenotype*

Variable	No varus (n = 173)	Dynamic varus (n = 17)	Static varus (n = 50)	Static + dynamic varus (n = 26)	*P* for trend
Age, years	72.2 ± 6.58	72.5 ± 8.63	73.9 ± 7.74	74.2 ± 6.42	0.32
BMI, kg/m^2	23.5 ± 3.55	25.7 ± 2.63†	24.6 ± 3.56	25.5 ± 3.54†	<0.01
Anatomic axis angle, degrees	183.8 ± 1.87	183.4 ± 1.67	178.1 ± 3.83‡	176.0 ± 4.80‡	<0.01
Static varus alignment, no. (%)	0 (0)	0 (0)	50 (100)	26 (100)	
Varus thrust, no. (%)	0 (0)	17 (100)	0 (0)	26 (100)	
K/L grade, no. (%)					
1	70 (40.5)	6 (35.3)	15 (30.0)	3 (11.5)	<0.01
2	87 (50.3)	9 (52.9)	14 (28.0)	5 (19.2)	
3	13 (7.5)	1 (5.9)	13 (26.0)	10 (38.5)	
4	3 (1.7)	1 (5.9)	8 (16.0)	8 (30.8)	
Range of motion, degrees					
Affected knee					
Flexion	143.4 ± 8.48	143.2 ± 8.40	136.7 ± 14.7	132.3 ± 11.6‡	<0.01
Extension§	−4.05 ± 6.34	−4.00 ± 3.92	−4.44 ± 5.02	−6.62 ± 6.07	0.22
Total range	139.3 ± 11.6	139.2 ± 9.53	132.3 ± 17.9	125.7 ± 16.1‡	<0.01
Unaffected knee					
Flexion	144.4 ± 7.89	143.8 ± 9.23	139.6 ± 12.3	135.8 ± 9.67‡	<0.01
Extension§	−3.35 ± 5.76	−4.29 ± 4.31	−4.34 ± 5.47	−4.46 ± 5.25	0.33
Total range	141.0 ± 10.5	139.5 ± 11.1	135.3 ± 15.8	131.3 ± 12.8‡	<0.01
Gait parameters					
Gait velocity, meters/second	1.24 ± 0.23	1.22 ± 0.19	1.12 ± 0.22†	1.05 ± 0.14‡	<0.01
Step length, %BH	37.4 ± 4.73	37.9 ± 4.62	35.1 ± 6.14†	33.9 ± 3.82‡	<0.01
Cadence, steps/minute	129.2 ± 15.4	126.8 ± 12.5	121.4 ± 11.6†	121.4 ± 17.4†	<0.01
VAS score for pain, mm	24.8 ± 25.8	39.8 ± 27.9	35.8 ± 27.6	49.5 ± 28.8†	<0.01
JKOM					
Pain and stiffness	6.11 ± 5.44	11.3 ± 7.28†	9.48 ± 6.23†	12.7 ± 5.64†	<0.01
Activities of daily living	4.78 ± 5.30	11.1 ± 7.89†	9.30 ± 7.46†	10.7 ± 8.12†	<0.01
Participation in social activities	3.05 ± 3.32	4.82 ± 4.68	3.98 ± 4.34	3.73 ± 3.08	0.25
General health conditions	2.47 ± 1.56	3.29 ± 2.02	3.10 ± 1.67	3.31 ± 1.67	0.05
Total score	16.4 ± 13.6	30.5 ± 19.9†	25.9 ± 16.1†	30.4 ± 16.5†	<0.01

* Except where indicated otherwise, values are the mean ± SD. *P* values are based on unadjusted analyses (analysis of variance, Kruskal-Wallis test, or Fisher's exact test) comparing the 4 phenotypes. BMI = body mass index; K/L = Kellgren/Lawrence; %BH = percentage of body height; VAS = visual analog scale (0–100 mm); JKOM = Japanese Knee Osteoarthritis Measure.
† Significantly worse compared with the no varus group.
‡ Significantly worse compared with the no varus and dynamic varus groups.
§ A negative value for knee extension range of motion means that the knee was flexed.

expressed as a dichotomous variable, such as the no varus group (reference), dynamic varus group (0 = no, 1 = yes), static varus group (0 = no, 1 = yes), static + dynamic group (0 = no, 1 = yes), and sex (0 = male, 1 = female), or expressed as a continuous variable, such as age, body mass index (BMI), and K/L grade. Model 2 was performed with inclusion of the same objective variable and risk factors as in model 1. In addition, gait velocity (a continuous variable), which potentially affects the incidence of knee pain during walking, was included in model 2.

To address the possibility that the cutoff value for AAA of <181° in women or <183° in men for defining static varus alignment is optimal, a sensitivity analysis evaluating alternative cutoff points was also performed. *P* values less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics of the patients. A flow chart of the present study is shown in Figure 1. Although 291 patients were initially enrolled, 10 patients (3.4%) were excluded on the basis of the exclusion criteria; the remaining 281 patients were included in the data analysis. Among these 281 patients, 15 patients (5.2% of the initial cohort) were excluded because of invalid data (due to incomplete clinical evaluation scores). Thus, a total of 266 patients (91.4% of the initial cohort) were included in the final analysis.

The patients' characteristics are shown in Table 1. In the no varus group (n = 173) and dynamic varus group (n = 17), 51 patients (29.5%) and 4 patients (23.5%), respectively, had a valgus alignment, and the remaining patients had a neutral alignment. Valgus thrust was not identified by means of gait observation in any of the patients.

Differences in clinical outcomes, according to phenotype classification. Table 2 shows the clinical outcome variables for each of the 4 phenotypes, with the results being the values from unadjusted statistical analyses (ANOVA, Kruskal-Wallis, or Fisher's exact

Table 3. Associations with pain with walking according to knee malalignment phenotype and patients' demographic and clinical characteristics*

Variable	Presence of pain, no. (%)		Odds ratio (95% confidence interval)		
	No	Yes	Crude model	Model 1	Model 2
Phenotype					
No varus (reference)	93 (53.8)	80 (46.2)	–	–	–
Dynamic varus (0 = no, 1 = yes)	4 (23.5)	13 (76.5)	3.66 (1.24–13.4)†	3.21 (1.06–11.9)†	3.30 (1.08–12.4)†
Static varus (0 = no, 1 = yes)	15 (30.0)	35 (70.0)	2.63 (1.36–5.28)‡	1.78 (0.85–3.84)	1.67 (0.78–3.62)
Static + dynamic varus (0 = no, 1 = yes)	1 (3.8)	25 (96.2)	28.1 (5.76–507.8)‡	19.7 (3.70–366.0)‡	17.1 (3.19–320.0)‡
Sex (0 = male, 1 = female)	–	–	0.48 (0.25–0.89)†	0.53 (0.26–1.06)	0.56 (0.27–1.14)
Age (years)	–	–	1.03 (0.99–1.06)	1.02 (0.98–1.06)	1.00 (0.96–1.05)
BMI	–	–	1.13 (1.04–1.22)‡	1.10 (1.01–1.20)†	1.08 (0.99–1.18)
K/L grade	–	–	1.57 (1.17–2.13)‡	1.11 (0.77–1.62)	1.06 (0.72–1.55)

* Pain with walking was determined using the pain and stiffness subscale of the Japanese Knee Osteoarthritis Measure, with the question "Do you have pain in your knees when you walk on a flat surface?", in which a "no" response represents absence of knee pain and a "yes" response represents presence of knee pain (mild to extreme) during gait. Model 1 includes values derived from multiple binary logistic regression models with phenotypes based on static and dynamic varus alignment, adjusted for sex, age, body mass index (BMI), and Kellgren/Lawrence (K/L) grade, entered simultaneously as predictors. Model 2 includes the same variables as in model 1, as well as adjustment for gait velocity.
† $P < 0.05$.
‡ $P < 0.01$.

test). No differences in age existed among these 4 phenotypes ($P = 0.32$). Patients in the dynamic varus and the static + dynamic varus groups had significantly higher BMI than those in the no varus group ($P < 0.05$). Among patients in the static + dynamic varus group, 18 (69.2%) of 26 patients had severe tibiofemoral disease (K/L grade ≥3), which was a higher proportion than that in the no varus (9.2%), dynamic varus (11.8%), and static varus (42.0%) groups.

More patients had restricted knee flexion ROM and restricted total ROM in both the affected and unaffected knees in the static + dynamic varus group than in the no varus group ($P < 0.01$) and dynamic varus group ($P < 0.05$). Furthermore, lower gait velocity and shorter step length were noted in the static + dynamic varus group than in the dynamic varus group ($P < 0.05$). In the static + dynamic varus group and static varus group, all 3 spatiotemporal gait parameters were significantly worse compared with those in the no varus group ($P < 0.01$ and $P < 0.05$, respectively). Person-specific knee pain evaluated by the VAS was significantly higher in the static + dynamic varus group than in the no varus group ($P < 0.01$).

In addition, scores on the pain and stiffness and activities of daily living subcategories of the JKOM were significantly lower in the no varus group than in the 3 other groups ($P < 0.01$), indicating that patients in the no varus group experienced less knee pain and disability, but there were no significant differences among the dynamic varus, static varus, and static + dynamic varus groups. The total JKOM score was also significantly lower in the no varus group than in the 3 other groups ($P < 0.01$), indicating that patients in the no varus group had the highest quality of life among the 4 phenotypes. However, there were no significant differences in the scores for the JKOM subcategories of participation in social activities and general health conditions among the 4 phenotypes. In addition, no significant differences were identified between the dynamic varus and static varus groups, or between the static varus and static + dynamic varus groups, for any clinical outcome except AAA.

Factors associated with knee pain during gait. To investigate whether varus alignment and varus thrust in the 4 phenotypes were associated with knee pain, we performed multiple logistic regression analysis to determine the difference in knee pain among the 4 groups (Table 3). The static + dynamic varus group was most frequently associated with knee pain during gait ($P < 0.01$). The dynamic varus group was also associated with knee pain during gait ($P < 0.05$). Age, sex, and K/L grade were not associated with knee pain in the adjusted models; however, BMI was significantly associated with knee pain during gait in the adjusted analyses with model 1 ($P < 0.05$).

We performed a sensitivity analysis with alternative cutoff values for defining static varus alignment (Table 4). When using any of the 3 alternative cutoff points, no associations were found between the static varus group and knee pain during gait, whereas the dynamic varus and static + dynamic varus groups remained associated with knee pain during gait. These results demonstrated that varus thrust could be strongly associated with pain during gait, regardless of varus alignment status, a notion that was supported by the higher OR for reporting knee pain during gait in patients with dynamic varus alignment, as determined in analyses adjusted for age, sex, BMI, K/L grade, and varus alignment (OR 4.72, 95% CI 1.85–14.6).

Table 4. Sensitivity analyses of associations between pain with walking and each knee malalignment phenotype, using different cutoff points of anatomic axis angle (AAA) for defining static varus alignment*

Cutoff for defining static varus alignment	Presence of pain, no. (%)		Odds ratio (95% confidence interval)		
	No	Yes	Crude model	Model 1	Model 2
AAA <182° in women and <184° in men					
No varus (reference)	85 (54.5)	71 (45.5)	–	–	–
Dynamic varus (0 = no, 1 = yes)	3 (18.8)	13 (81.2)	5.00 (1.54–22.5)†	4.28 (1.28–19.5)‡	4.50 (1.33–20.6)‡
Static varus (0 = no, 1 = yes)	23 (34.3)	44 (65.7)	2.21 (1.23–4.06)†	1.55 (0.79–3.08)	1.51 (0.76–3.02)
Static + dynamic varus (0 = no, 1 = yes)	2 (7.4)	25 (92.6)	14.4 (4.10–91.6)†	9.72 (2.50–65.0)†	8.49 (2.16–57.1)†
AAA <180° in women and <182° in men					
No varus (reference)	99 (51.3)	94 (48.7)	–	–	–
Dynamic varus (0 = no, 1 = yes)	4 (19.0)	17 (81.0)	4.34 (1.54–15.5)†	3.84 (1.32–13.6)‡	3.89 (1.34–14.2)‡
Static varus (0 = no, 1 = yes)	9 (30.0)	21 (70.0)	2.38 (1.07–5.73)‡	1.68 (0.67–4.40)	1.53 (0.61–4.04)
Static + dynamic varus (0 = no, 1 = yes)	1 (4.5)	21 (95.5)	21.4 (4.35–388.1)†	15.9 (2.86–301.4)†	13.7 (2.41–259.4)†
AAA <179° in women and <181° in men					
No varus (reference)	101 (51.3)	96 (48.7)	–	–	–
Dynamic varus (0 = no, 1 = yes)	4 (16.0)	21 (84.0)	5.36 (1.95–18.9)†	4.62 (1.63–16.6)†	4.62 (1.62–16.6)†
Static varus (0 = no, 1 = yes)	7 (26.9)	19 (73.1)	2.77 (1.16–7.37)‡	2.07 (0.77–5.96)	1.88 (0.69–5.45)
Static + dynamic varus (0 = no, 1 = yes)	1 (5.6)	17 (94.4)	17.4 (3.46–315.6)†	13.4 (2.31–257.9)†	11.5 (1.94–220.1)†

* Pain with walking was determined using the pain and stiffness subscale of the Japanese Knee Osteoarthritis Measure, with the question "Do you have pain in your knees when you walk on a flat surface?", in which a "no" response represents absence of knee pain and a "yes" response represents presence of knee pain (mild to extreme) during gait. Model 1 includes values derived from multiple binary logistic regression models with phenotypes based on static and dynamic varus alignment, adjusted for sex, age, body mass index, and Kellgren/Lawrence grade, entered simultaneously as predictors. Model 2 includes the same variables as in model 1, as well as adjustment for gait velocity.
† $P < 0.01$.
‡ $P < 0.05$.

In addition, we evaluated whether the association between knee pain and the 4 phenotypes changed when the subsample of patients with a K/L grade of ≥2 was included. We found that the effect estimates were attenuated, and only the associations with the static + dynamic varus group were significant (results available upon request from the corresponding author).

DISCUSSION

The present study investigated the relative impact of static varus alignment and varus thrust on clinical outcomes, such as knee ROM, gait parameters, VAS scores, and JKOM measures (Table 2), in patients with medial compartment knee OA. A trend was observed in which patients in the static + dynamic varus group with severe tibiofemoral disease had relatively more severe clinical outcomes than did patients in the other 3 phenotype groups, particularly the no varus group. Furthermore, we found that varus thrust combined with static varus alignment increased the likelihood of knee pain 17-fold compared with no varus (Table 3). Previous studies have shown that varus thrust is associated with a 3-fold increase in the likelihood of knee OA progression in patients with static varus knees (12), indicating that a varus thrust adds mechanical loading to the already degenerated medial compartment of varus knees, resulting in the progression of symptomatic knee OA.

Differences in phenotype-related clinical outcomes may be attributed, in part, to the extreme mechanical loading of the medial compartment and the degenerated condition of the knee. In the present study, static varus alignment was more pronounced in the degenerated knee, as evaluated using the K/L grade (Table 2), which is consistent with previous results (20). Degenerated knees, such as those in advanced OA (K/L grades of 3 or 4), are potentially susceptible to mechanical loading, resulting in more destructive changes (21,22) and greater functional declines (23). Therefore, the clinical outcomes in the static varus group were worse than those in the no varus group. In addition, multiple logistic regression analysis showed that adding K/L grade to the models attenuated the OR for the association between pain during gait and the static varus and static + dynamic varus groups (Table 3). These findings indicate that some of the association between phenotype and pain was attributable to severity of medial knee OA.

Visually identified varus thrust is associated with a high peak knee varus during the stance phase of gait (10,24), which is associated with external KAM (11,24,25). Previous studies showed that external KAM is associated with knee pain (26,27) and with the presence of bone marrow lesions (28) in patients with knee OA. Thus, in the dynamic varus group, which had more mild medial knee OA, there was an association with knee pain during gait even after adjustment for K/L grade. This was not the

case for patients with static varus alignment, who tended to have more severe medial knee OA. These observations were consistent with previous results showing that varus thrust is more closely associated with knee pain than is varus alignment (12). Although we cannot draw any conclusions about causation, identifying potential interventions that will modify the effects of varus thrust on mild medial knee OA may be a potentially useful strategy for preventing the progression of knee OA.

A sensitivity analysis showed that the static + dynamic varus group was strongly associated with knee pain during walking, regardless of the cutoff value applied for defining static varus AAA (Table 4). Moreover, although the eligibility criteria of our study included presence of medial knee OA with a K/L grade of 1, we confirmed that the trends were almost the same as those when the eligibility criteria were confined to patients with a K/L grade of ≥2 (results available upon request from the corresponding author). The relationship between static + dynamic varus and knee pain during walking is robust, and dynamic varus alignment combined with static varus alignment might be a malalignment phenotype that is a better predictor of knee pain during gait. Although the static + dynamic varus group had the highest OR among the 4 phenotypes, its 95% CI was extremely wide. The major reason for this result is the limited number of outcomes data in the static + dynamic varus group (n = 26), in which almost all patients had knee pain, and only 1 patient had absence of knee pain. Therefore, the effect estimate should be interpreted with caution and future work should include a large sample size to provide a more precise OR in the static + dynamic varus group.

Our classification of patients into 4 malalignment phenotypes may have clinical significance in categorizing heterogeneous patients with knee OA according to their ROM, gait capacity, and knee pain. These phenotypes may be used as clinical indices for predicting the effects of biomechanical modifications designed to improve clinical outcomes. The presence of a varus thrust during gait may represent knee frontal plane dynamic instability and malalignment (10), which might be improved through knee bracing (29–31), gait modification (32,33), and neuromuscular training (34,35). Therefore, patients with the dynamic varus phenotype could be transformed to a phenotype of no varus, and those with static + dynamic varus alignment could be transformed to a static varus alignment using these therapies. In patients with these phenotypes, the differences in knee pain are particularly relevant (Table 2). On the basis of a minimum clinically important difference (36), the treatment of varus thrust could lead to improvement in patients' functional decline and the progression of knee OA through symptom improvement (37).

A previous study identified obesity, which could be modified through weight loss (4), as a phenotype that may result in decreased tibiofemoral force (38). However, most patients in our study were classified as nonobese (Table 1), consistent with a previous study that recruited Japanese patients (39). Furthermore, we showed that BMI was not strongly associated with knee pain while walking (Table 3). These data indicate that the effects of weight loss programs on pain during gait may be limited, particularly in patients with static varus knee alignment (8). Biomechanical modification programs should be chosen according to the malalignment phenotype, particularly in patients with varus thrust (40,41).

This study has several limitations. First, the sample sizes of the groups were small, except in the no varus group, because the total number of patients was only 266, and only 76 patients (28.6%) demonstrated static varus alignment and only 43 patients (16.2%) demonstrated varus thrust. Therefore, larger sample sizes are needed to detect a significant difference among all 4 phenotypes.

Second, we demonstrated 4 malalignment phenotypes on the basis of our data set involving nonobese Japanese patients. In previous studies, more than 80% of the included patients were overweight or obese (8). In addition, female patients in our study were less likely to have knee pain during walking (Table 3), which conflicts with the observations in a previous study in a large Japanese cohort (42). Therefore, the results of the present study might be community specific; other data sets will be needed to replicate our findings.

Third, we used corrected AAA to measure static varus alignment, as opposed to the gold-standard mechanical alignment axis angle. Therefore, static varus alignment based on true mechanical alignment could be more reflective of knee pain during gait.

Fourth, we could not evaluate the disease severity of the tibiofemoral joints in the contralateral (unaffected) limb; whether bilateral knee OA affects the relative impact of static varus alignment and varus thrust on the clinical outcomes, particularly knee pain during gait, could not be determined. We found that restricted knee flexion ROM of the unaffected knee in the static + dynamic varus group possibly indicated the presence of knee OA in the unaffected knee in this group, due to the association between osteophyte reaction and restriction of knee flexion ROM (43). Muraki et al showed that bilateral knee OA is common in the Japanese population (44), accounting for ~50% of cases of knee OA with a K/L grade of ≥2. Therefore, individuals with bilateral knee OA could be included in the present study, which may have affected the

clinical outcomes, particularly person-specific assessment results, such as the VAS score and JKOM.

Fifth, the varus thrust assessment performed by the 2 examiners was subjective. Although we confirmed the reliability of identifying varus thrust and the robustness of the results using sensitivity analyses, the possibility remains that quantitative assessment with such a 3-dimensional motion analysis system could yield a stronger association between varus thrust and knee pain during gait.

Finally, this was a cross-sectional study. Therefore, we could not comment on the causal relationships between phenotype characteristics and clinical outcomes, particularly knee pain.

In conclusion, 4 phenotype classifications based on static varus alignment and varus thrust were found to be partly associated with clinical outcomes in patients with medial compartment knee OA. A multiple logistic regression analysis showed that dynamic varus malalignment was associated with knee pain during gait, and, combined with static varus alignment, was strongly associated with knee pain. These results suggest that dynamic malalignment, in addition to static varus alignment, might enhance the explanation of clinical outcomes such as knee pain. Tailored interventions such as biomechanical modifications, based on these phenotypes, might be needed to improve clinical outcomes.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Aoyama had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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