

The inverse OARSI-OMERACT criteria is a valid indicator of the clinical worsening of knee osteoarthritis: data from the Osteoarthritis Initiative

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RUNNING HEAD: Defining Osteoarthritis Worsening

ABSTRACT

Objective: We assessed if the inverse OARSI-OMERACT criteria relate to concurrent radiographic knee osteoarthritis (KOA) progression and decline in walking speed as well as future knee replacement.

Methods: We conducted knee-based analyses of data from the Osteoarthritis Initiative. All knees had symptomatic osteoarthritis: at least doubtful radiographic KOA (Kellgren-Lawrence Grade \geq 1) and knee pain \geq 10/100 (WOMAC pain) at the 12-month visit. The inverse of the OARSI-OMERACT responder criteria depended on knee pain and function, and global assessment of knee impact. We used generalized linear mixed models to assess the relationship of the inverse OARSI-OMERACT criteria over 2 years (i.e., 12 and 36-month visits) with worsening radiographic severity (any increase in Kellgren-Lawrence Grade from 12- to 36-months) and decline in self-selected 20-m walking speed of \geq 0.1m/s (from 12- to 36-months). We used a Cox model to assess time to knee replacement during the 6 years after the 36-month visit as an outcome.

Results: Among the 1,746 analyzed, 19% met the inverse OARSI-OMERACT criteria. Meeting the inverse OARSI-OMERACT criteria was associated with almost double the odds of experiencing concurrent worsening in radiographic KOA severity (odds ratio [OR]=1.89 (95% confidence interval [CI]=1.32 to 2.70)) or decline in walking speed (OR=1.82 (95%CI=1.37 to 2.40)). A knee meeting the inverse OARSI-OMERACT criteria was more likely to receive a knee replacement after the 36-month visit (23%) compared with a non-responder (10%; hazard ratio=2.54, 95%CI=1.89 to 3.41).

Conclusion: The inverse OARSI-OMERACT criteria for worsening among people with KOA had good construct validity in relation to clinically relevant outcomes.

The mandate to focus on patient-reported outcomes and individual-specific outcomes requires a strategy to define clinically meaningful improvement and worsening of osteoarthritis. While there exist validated methods to indicate clinically meaningful improvement, such as the OARSI-OMERACT responder criteria set(1), no complementary strategy to indicate worsening is widely accepted for research applications(2-7). One possibility is to apply the inverse of the OARSI-OMERACT responder criteria to assess clinically meaningful worsening; however, this approach has not been validated in relation to clinically relevant worsening outcomes in people with knee osteoarthritis.

In this brief report we describe our efforts to assess if the inverse OARSI-OMERACT criteria for clinical worsening relates to concurrent radiographic knee osteoarthritis progression and slowed walking speed as well as future knee replacement. Since the OARSI-OMERACT criteria is considered a gold standard for defining clinical improvement of osteoarthritis, our goal is to demonstrate the construct validity of the inverse OARSI-OMERACT criteria as an indicator of clinical worsening osteoarthritis.

MATERIALS AND METHODS

Study design

We conducted knee-based analyses of data from the Osteoarthritis Initiative (OAI). We assessed the inverse OARSI-OMERACT criteria, worsening radiographic knee osteoarthritis severity, and a decline in walking speed over 2 years (between the 12-

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and 36-month visits). We also assessed if someone received a knee replacement during the 6 years after the 36-month visit.

The OAI is a prospective cohort study of 4,796 adults with or at risk for symptomatic knee osteoarthritis from 4 clinical sites in the United States. Study staff recruited participants between February 2004 and May 2006. OAI data and protocols are freely available online(8).

Participant selection

The selection process is summarized in Figure 1. We required all knees to have an inclusive definition of symptomatic osteoarthritis: at least doubtful osteoarthritis (Kellgren-Lawrence Grade \geq 1) and knee pain \geq 10/100 (WOMAC pain subscale) at the 12-month visit. The Kellgren-Lawrence Grade defined radiographic severity and was based on blinded central readings of bilateral weight-bearing, fixed-flexion posteroanterior knee radiographs (intrarater agreement: weighted kappa=0.70 to 0.80)(8, 9). We excluded participants who had missing data that prevented us from determining if a knee met the inverse OARSI-OMERACT criteria, worsening radiographic knee osteoarthritis severity or a decline in walking speed. Furthermore, we excluded knees that received a joint replacement between the 12- and 36-month visits.

Inverse OARSI-OMERACT criteria

The OARSI-OMERACT criteria relies on self-reported knee pain (knee-specific WOMAC pain), knee-related function (knee-specific WOMAC Function), and patient's global

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assessment of knee impact (Files: allclinical## (version 1.2.2 and 5.2.1))(1, 8, 10, 11). All scores were converted to 0 to 100, with 100 being a poorer outcome. We calculated 2-year absolute change (36-month visit data minus 12-month visit data) and percent change. We selected a 2-year observation period because 2 years is a common duration for a clinical trial for knee osteoarthritis. Figure 2 illustrates the decision rule for the inverse OARSI-OMERACT criteria. First, if a knee had worsening pain or function $\geq 50\%$ and absolute change in pain or function ≥ 20 then the knee was classified as worsening. If not, we classified a knee as worsening if it met at least 2 out of 3 criteria that relied on a $\geq 20\%$ and absolute change $\geq 10/100$ for each outcome (Figure 2). If a knee failed to meet at least 2 of the criteria then the knee had no worsening.

Worsening radiographic severity

We classified a knee with worsening radiographic severity if central readers reported any increase in Kellgren-Lawrence grade between the 12- and 36-month weight-bearing knee radiographs (File: kXR_SQ_BU##_SAS (versions 1.8 and 5.7))(8). If a knee had no increase in Kellgren-Lawrence grade then it was classified as having no radiographic severity worsening.

Decline in walking speed

Decline in walking speed was based on change in 20-meter walk speed between the 12- and 36-month visits (Files: allclinical## (versions 1.2.2 and 5.2.1))(8).. In brief, participants performed 2 trials of a 20-meter walk at their usual, comfortable walking pace(12, 13). The time needed to walk 20 meters was converted to walking speed (i.e.

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meters/second [m/s]) and averaged across the 2 trials. We defined a decline in walking speed as someone who walked at least 0.1 m/s slower at 36-months compared to 12-months(12, 14).

Knee replacement

We classified a knee with a future knee replacement if receipt of a knee replacement (partial or total) was reported or observed on radiographs in the 6 years after the timeframe used to define the inverse OARSI-OMERACT criteria (12- to 36-month visit; >98% adjudicated, 3 unadjudicated cases). Hence, a knee was classified with a knee replacement if it met 1 of 3 criteria for a knee replacement: 1) the knee replacement was centrally adjudicated (2 adjudicators reviewed medical records and a physician adjudicator was included if there was a disagreement between the first 2), 2) the knee replacement was observed on a x-ray, or 3) the knee replacement was self-reported (even if the self-reported replacement had not gone through the adjudication process) (Files: outcomes99 (version 10))(8).

Statistical Analysis

We evaluated the association of the inverse OARSI-OMERACT criteria with concurrent worsening radiographic severity and a decline in walking speed by performing 2 knee-based analyses using a logistic regression with repeated measures (generalized linear mixed model) to adjust for correlations between knees within person. The inverse OARSI-OMERACT criteria was the outcome for these analyses. To assess the association between the inverse OARSI-OMERACT criteria and time to knee

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replacement, we used a Cox model with a robust sandwich covariance matrix estimate to account for correlation between knees(15). Our models were unadjusted because we were interested in the overall association between the inverse OARSI-OMERACT criteria and the other outcomes as a means of construct validity. We performed a sensitivity analysis among people with Kellgren-Lawrence ≥ 2 . All analyses were performed with SAS Enterprise 7.15 (Cary, NC, USA) with a p-value ≤ 0.05 to define statistical significance.

Ethical standards

The OAI was approved and meets all criteria for ethical standards regarding human studies defined in the 1964 Declaration of Helsinki and all amendments made after. Institutional review boards at each clinical site and the coordinating center (University of California, San Francisco) approved the OAI study (approval number 10-00532). All participants provided informed consent prior to participation.

RESULTS

We analyzed 1,746 out of the 2,319 (75%) knees with symptomatic knee osteoarthritis at the 12-month visit (n=1,291 people; Figure 1). On average, excluded knees had more severe knee symptoms than those included in the analyses (Table 1). Overall, 19% of knees (n=335) met the inverse OARSI-OMERACT criteria for worsening. Both responders and non-responders were mostly female (62%, 61%, respectively) and

Caucasian/white (70%, 74%). Table 1 offers additional insights in the group characteristics.

A knee meeting the inverse OARSI-OMERACT criteria for worsening was approximately twice as likely to experience concurrent worsening radiographic severity (odds ratio=1.89; 95% confidence interval (CI)=1.32 to 2.70; Table 1) or a decline in walking speed (odds ratio=1.82; 95%CI=1.37 to 2.40; Table 1).

A knee meeting the inverse OARSI-OMERACT criteria for worsening was also more likely to receive a knee replacement after the 36-month visit compared with a non-responder (hazard ratio=2.54, 95%CI=1.89 to 3.41; Table 1).

The results were similar when only including knees with Kellgren-Lawrence ≥ 2 (n=1,405).

DISCUSSION

The inverse OARSI-OMERACT criteria among people with knee osteoarthritis had good construct validity in relation to worsening of clinically relevant outcomes. Furthermore, we found that 19% of knees met the criteria, which is comparable to prior reports of self-reported worsening (9 to 29%)(2, 4-6). Hence, the inverse OARSI-OMERACT responder criteria may be appropriate for use in epidemiological studies.

While other investigators have explored the minimal clinically meaningful difference in a single patient-reported outcome for worsening, this approach offers a crude strategy that fails to account for the multiple dimensions of clinical symptoms(2, 3, 5). Recently, investigators found that this inverse OARSI-OMERACT criteria performed well for specificity (0.87) but had a low sensitivity (0.22) to detect people reporting at least slight worsening after 3 months of multimodal treatment(4). Hence, the criteria are a conservative marker of clinically meaningful worsening that successfully excludes people without meaningful worsening but misses some people who perceive worsening symptoms. In the current project we also demonstrated that this criteria had good construct validity.

Unfortunately, we were unable to test the sensitivity and specificity of the criteria in this cohort because we lacked questions about transitions in symptom states. Furthermore, we relied on patient-reported outcome measures from 2005 (first 12-month visits) to 2009 (last 36-month visits) and knee replacements from 2007 to 2014, which may impact the generalizability of these findings to the current population. While the impact over time is likely minimal, future studies should monitor the validity of the inverse OARSI-OMERACT criteria as clinical practice changes. Finally, we focused on just 1 set of criteria to define clinical worsening because we believe it is valuable to adopt a definition for worsening that is comparable to one used to define improvement.

In conclusion, the inverse OARSI-OMERACT criteria to define worsening clinical outcomes among people with knee osteoarthritis had good construct validity and may be useful in longitudinal studies.

REFERENCES

1. Pham T, van der HD, Altman RD, Anderson JJ, Bellamy N, Hochberg M, et al. OMERACT-OARSI initiative: Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited¹. *Osteoarthritis Cartilage* 2004;12:389 - 99.
2. Angst F, Benz T, Lehmann S, Aeschlimann A, Angst J. Multidimensional minimal clinically important differences in knee osteoarthritis after comprehensive rehabilitation: A prospective evaluation from the bad zurzach osteoarthritis study. *RMD Open* 2018;4:e000685.
3. Mills KAG, Naylor JM, Eyles JP, Roos EM, Hunter DJ. Examining the minimal important difference of patient-reported outcome measures for individuals with knee osteoarthritis: A model using the knee injury and osteoarthritis outcome score. *J Rheumatol* 2016;43:395-404.
4. Mahler EAM, den Broeder AA, Woodworth TG, Busch V, van den Hoogen FH, Bijlsma JWJ, et al. How should worsening in osteoarthritis be defined? Development and initial validation of preliminary criteria for clinical worsening in knee and hip osteoarthritis. *Scand J Rheumatol* 2017;46:396-406.

5. Angst F, Aeschlimann A, Michel BA, Stucki G. Minimal clinically important rehabilitation effects in patients with osteoarthritis of the lower extremities. *J Rheumatol* 2002;29:131-8.
6. Eyles JP, Mills K, Lucas BR, Williams MJ, Makovey J, Teoh L, et al. Can we predict those with osteoarthritis who will worsen following a chronic disease management program? *Arthritis Care Res (Hoboken)* 2016;68:1268-77.
7. Alschuler KN, Molton IR, Jensen MP, Riddle DL. Prognostic value of coping strategies in a community-based sample of persons with chronic symptomatic knee osteoarthritis. *PAIN®* 2013;154:2775-81.
8. The osteoarthritis initiative. [cited 2019]; Available from: <https://nda.nih.gov/oai/>.
9. Felson DT, Niu J, Guermazi A, Sack B, Aliabadi P. Defining radiographic incidence and progression of knee osteoarthritis: Suggested modifications of the kellgren and lawrence scale. *Ann Rheum Dis* 2011;70:1884-6.
10. Dougados M, Leclaire P, van der Heijde D, Bloch DA, Bellamy N, Altman RD. Response criteria for clinical trials on osteoarthritis of the knee and hip: A report of the osteoarthritis research society international standing committee for clinical trials response criteria initiative. *Osteoarthritis Cartilage* 2000;8:395-403.
11. Bingham CO, 3rd, Bird SR, Smugar SS, Xu X, Tershakovec AM. Responder analysis and correlation of outcome measures: Pooled results from two identical studies comparing etoricoxib, celecoxib, and placebo in osteoarthritis. *Osteoarthritis Cartilage* 2008;16:1289-93.
12. Herzog MM, Driban JB, Cattano NM, Cameron KL, Tourville TW, Marshall SW, et al. Risk of knee osteoarthritis over 24 months in individuals who decrease walking

speed during a 12-month period: Data from the osteoarthritis initiative. *J Rheumatol* 2017;44:1265-70.

13. White DK, Niu J, Zhang Y. Is symptomatic knee osteoarthritis a risk factor for a trajectory of fast decline in gait speed? Results from a longitudinal cohort study. *Arthritis Care Res* 2013;65:187-94.

14. Motyl JM, Driban JB, McAdams E, Price LL, McAlindon TE. Test-retest reliability and sensitivity of the 20-meter walk test among patients with knee osteoarthritis. *BMC Musculoskelet Disord* 2013;14:166.

15. Lee EW, Wei LJ, Amato DA. Cox-type regression analysis for large numbers of small groups of correlated failure time observations. In: Klein JP, Goel PK, editors. *Survival analysis: State of the art*. Dordrecht, Netherlands: Kluwer Academic Publishers; 1992. p. 237-47.

FIGURE LEGENDS

Figure 1. Flow Chart for Eligibility in Analyses

Figure 2. The Inverse OARSI-OMERACT Criteria for Clinical Worsening. Δ = change.

Table 1. Participant Characteristics

	Excluded Knees with Symptomatic Osteoarthritis (with missing data) n = 573	OARSI- OMERACT Criteria No Worsening n = 1411	OARSI-OMERACT Criteria Worsening n = 335
Baseline			
Female n (%)	347 (61%)	859 (61%)	209 (62%)
Caucasian/White n (%)	374 (65%) n miss = 1	1048 (74%)	234 (70%)
Age (years)	64.0 (9.3)	62.3 (9.0)	63.4 (9.0)
Body Mass Index (kg/m ²)	30.8 (5.3) n miss = 26	29.9 (4.8)	30.4 (5.1)
WOMAC Pain (0 to 100)	31.6 (18.1)	25.7 (15.8)	22.8 (12.7)
WOMAC Function (0 to 100)	29.3 (20.0) n miss = 14	22.8 (17.0)	22.2 (15.1)
Global Impact (0 to 100)	34.6 (24.2)	27.4 (22.2)	30.5 (21.2)

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Radiographic Severity

Kellgren-Lawrence = 1	91 (16%)	288 (20%)	53 (16%)
Kellgren-Lawrence = 2	217 (38%)	603 (43%)	116 (35%)
Kellgren-Lawrence = 3	152 (27%)	389 (28%)	123 (37%)
Kellgren-Lawrence = 4	113 (20%)	131 (9%)	43 (13%)

Concurrent Worsening (12 to 36 months)

Worsening Radiographic Severity	n/d	121 (9%)	52 (16%)
Decline in Walking Speed (\leq -0.1 m/s)	n/d	289 (20%)	107 (32%)
Future Knee Replacement (after 36 months)	119 (21%)	142 (10%)	77 (23%)

Note: Radiographic severity worsening = any increase in Kellgren-Lawrence grade. Means (standard deviation) reported unless noted otherwise. n miss = number of knees with missing data for a variable. n/d = no data reported with > 340 knees missing data

Figure 1. Flow Chart for Eligibility in Analyses

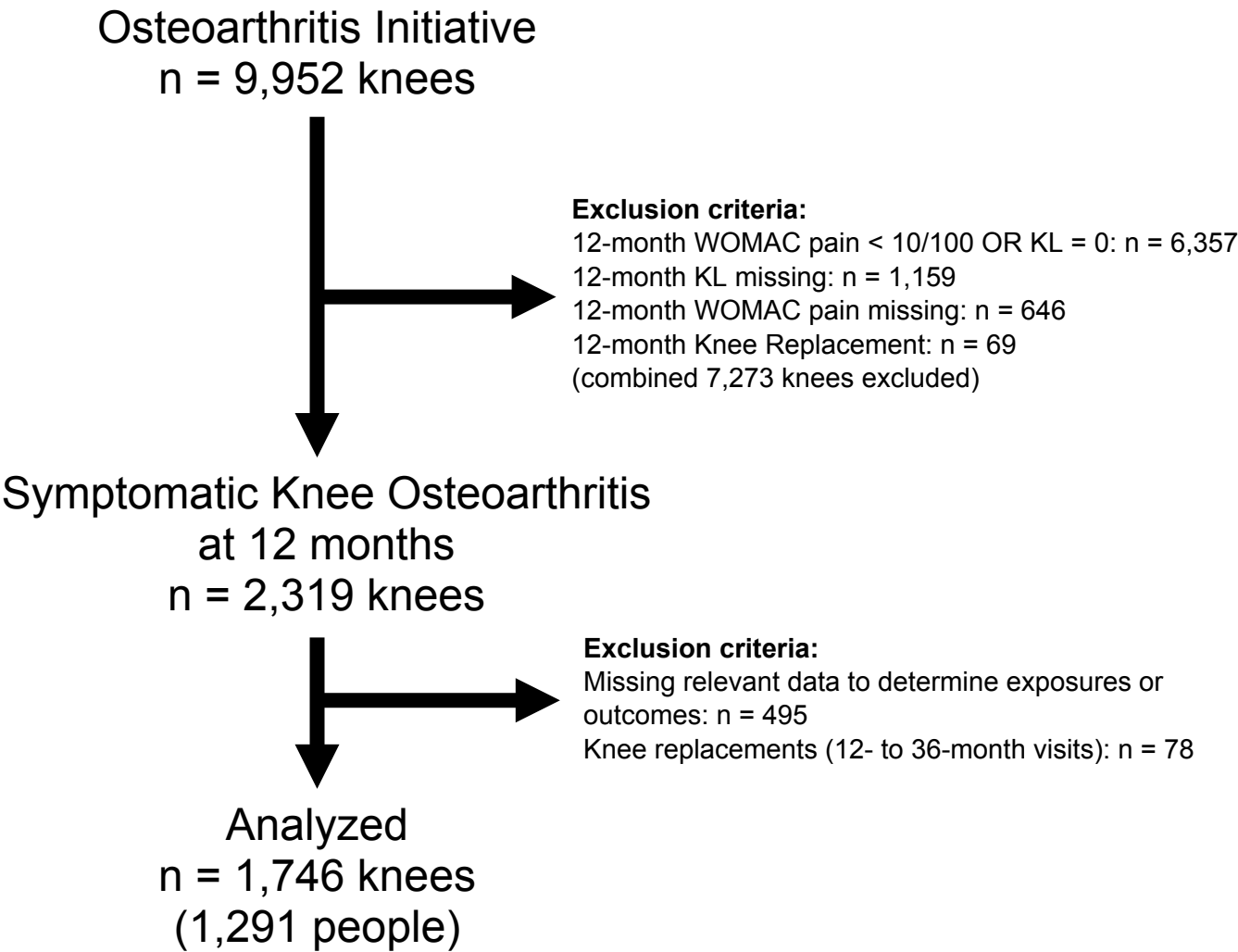


Figure 2. The Inverse OARSI-OMERACT Criteria for Clinical Worsening

