

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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ABSTRACT. *Objective.* We assessed if the inverse Osteoarthritis Research Society International (OARSI) and Outcome Measures in Rheumatology (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 OA: at least doubtful radiographic KOA (Kellgren-Lawrence grade ≥ 1) and knee pain $\geq 10/100$ (Western Ontario and McMaster Universities Osteoarthritis Index 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-month and 36-month visits) with worsening radiographic severity (any increase in Kellgren-Lawrence grade from 12 months to 36 months) and decline in self-selected 20-m walking speed of $\geq 0.1\text{m/s}$ (from 12 months 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 1746 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 (OR 1.89, 95% CI 1.32–2.70) or decline in walking speed (OR 1.82, 95% CI 1.37–2.40). 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 nonresponder (10%; HR 2.54, 95% CI 1.89–3.41).

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

Key Indexing Terms: knee, osteoarthritis, pain, patient-reported outcome measures

The mandate to focus on patient-reported outcomes (PRO) and individual-specific outcomes requires a strategy to define clinically meaningful improvement and worsening of osteoarthritis (OA). While there exist validated methods

to indicate clinically meaningful improvement, such as the Osteoarthritis Research Society International (OARSI) and Outcome Measures in Rheumatology (OMERACT) responder criteria set¹, no complementary strategy to indicate worsening is

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widely accepted for research applications^{2,3,4,5,6,7}. 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 OA (KOA).

In this brief report, we describe our efforts to assess if the inverse OARSI-OMERACT criteria for clinical worsening relates to concurrent radiographic KOA 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 OA, our goal is to demonstrate the construct validity of the inverse OARSI-OMERACT criteria as an indicator of clinical worsening OA.

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 KOA severity, and a decline in walking speed over 2 years (between the 12-month 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 4796 adults with or at risk for symptomatic KOA 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 online⁸.

Participant selection. The selection process is summarized in Figure 1. We required all knees to have an inclusive definition of symptomatic OA: at least doubtful OA [Kellgren-Lawrence (KL) grade ≥ 1] and knee pain

$\geq 10/100$ [Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale] at the 12-month visit. The KL grade defined radiographic severity and was based on blinded central readings of bilateral weight-bearing, fixed-flexion posteroanterior knee radiographs (intrarater agreement: weighted κ 0.70–0.80)^{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 KOA severity, or a decline in walking speed. Further, we excluded knees that received a joint replacement between the 12-month 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 global assessment of knee impact [Files: allclinical## (versions 1.2.2 and 5.2.1)]^{1,8,10,11}. All scores were converted to 0–100, with 100 being a poorer outcome. We calculated the 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 KOA. 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 worsening of $\geq 20\%$ and an absolute change of $\geq 10/100$ for each outcome. 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 KL grade between the 12-month 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 the KL grade, then it was classified as having no radiographic severity worsening.

Decline in walking speed. Decline in walking speed was based on change in

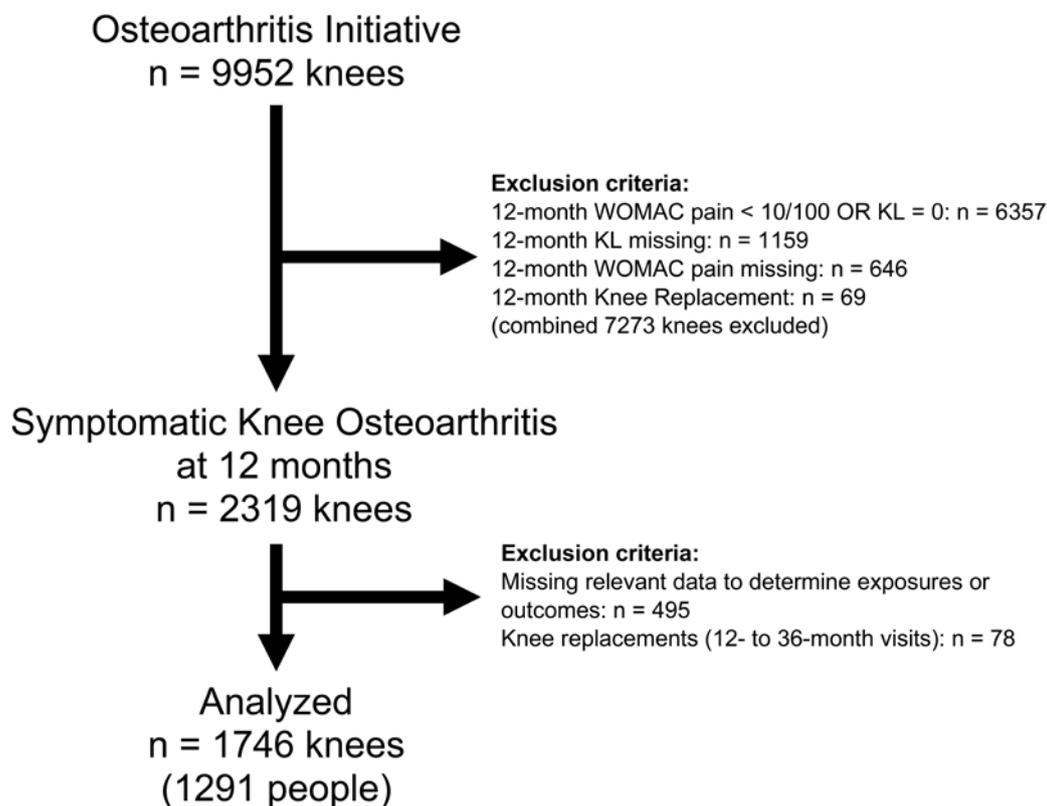


Figure 1. Flowchart for eligibility in analyses. KL: Kellgren-Lawrence arthritis grading scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

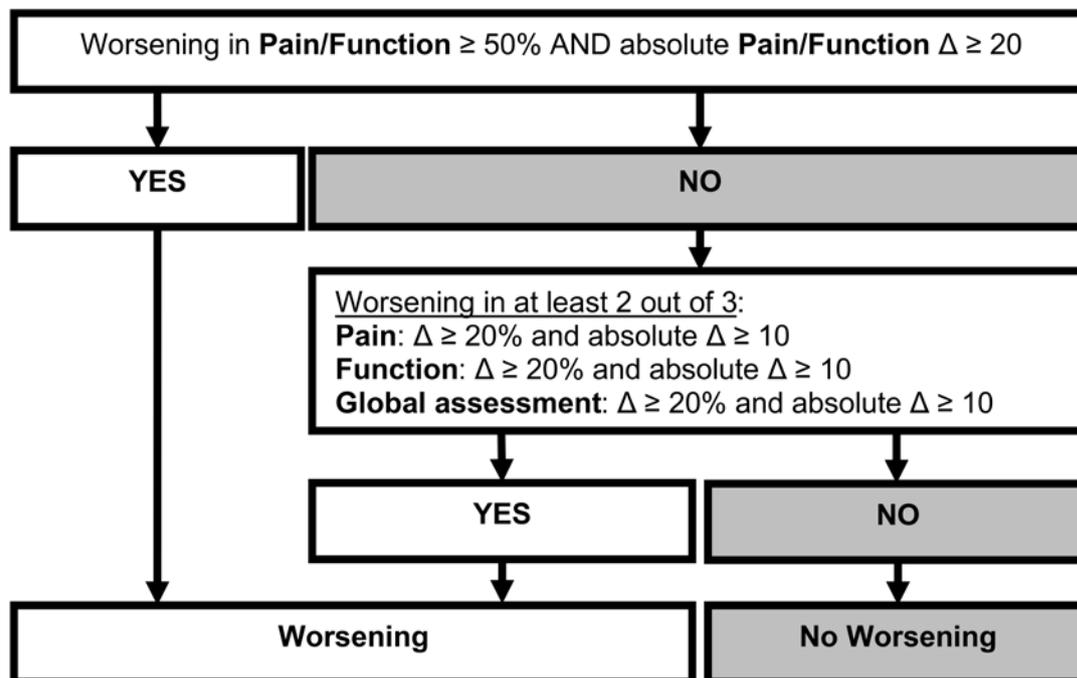


Figure 2. The inverse OARSI-OMERACT criteria for clinical worsening. Δ = Change. OARSI: Osteoarthritis Research Society International; OMERACT: Outcome Measures in Rheumatology.

the 20-meter walk speed between the 12-month 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., 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 time frame used to define the inverse OARSI-OMERACT criteria (12-month 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 radiograph; 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 replacement, we used a Cox model with a robust sandwich covariance matrix estimate to account for correlation between knees¹⁵. 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 KL ≥ 2 . All analyses were performed with SAS Enterprise 7.15 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, USA) approved the OAI study (approval number 10-00532). All participants provided informed consent prior to participation.

RESULTS

We analyzed 1746 out of the 2319 (75%) knees with symptomatic KOA at the 12-month visit ($n = 1291$ 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 nonresponders were mostly female (62% and 61%, respectively) and White (70% and 74%, respectively). Table 1 offers additional insights in the group characteristics.

A knee meeting the inverse OARSI-OMERACT criteria for worsening was about twice as likely to experience concurrent worsening radiographic severity (OR 1.89, 95% CI 1.32–2.70) or a decline in walking speed (OR 1.82, 95% CI 1.37–2.40; see Table 1 for the frequency of each outcome by group).

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 to a nonresponder (HR 2.54, 95% CI 1.89–3.41; Table 1).

The results were similar when only including knees with KL ≥ 2 ($n = 1405$).

DISCUSSION

The inverse OARSI-OMERACT criteria among people with KOA had good construct validity in relation to worsening of clinically relevant outcomes. Further, we found that 19% of knees met the criteria, which is comparable to prior reports

Table 1. Participant characteristics.

	Excluded Knees with Symptomatic OA (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)
White, n (%)	374 (65), n miss = 1	1048 (74)	234 (70)
Age, yrs	64.0 (9.3)	62.3 (9.0)	63.4 (9.0)
BMI, kg/m ²	30.8 (5.3), n miss = 26	29.9 (4.8)	30.4 (5.1)
WOMAC pain, 0–100	31.6 (18.1)	25.7 (15.8)	22.8 (12.7)
WOMAC function, 0–100	29.3 (20.0), n miss = 14	22.8 (17.0)	22.2 (15.1)
Global impact, 0–100	34.6 (24.2)	27.4 (22.2)	30.5 (21.2)
Radiographic severity, KL grade			
1	91 (16%)	288 (20%)	53 (16%)
2	217 (38%)	603 (43%)	116 (35%)
3	152 (27%)	389 (28%)	123 (37%)
4	113 (20%)	131 (9%)	43 (13%)
Concurrent worsening, 12–36 months			
Worsening radiographic severity ^a	ND	121 (9%)	52 (16%)
Decline in walking speed, ≤ 0.1 m/s	ND	289 (20%)	107 (32%)
Future knee replacement, after 36 months	119 (21%)	142 (10%)	77 (23%)

Means (SD) reported unless noted otherwise. ^a Radiographic severity worsening defined as any increase in KL grade. KL: Kellgren-Lawrence; n miss = number of knees with missing data for a variable; ND = no data reported with > 340 knees missing data. OA: osteoarthritis; OARSI: Osteoarthritis Research Society International; OMERACT: Outcome Measures in Rheumatology; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

of self-reported worsening (9–29%)^{2,4,5,6}. Hence, the inverse OARSI-OMERACT responder criteria may be appropriate for use in epidemiological studies.

While other investigators have analyzed the minimal clinically meaningful difference in a single PRO 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 treatment⁴. 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 study, we also demonstrated that these 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. Further, we relied on PRO measures from 2005 (first 12-month visits) to 2009 (last 36-month visits) and knee replacements from 2007 to 2014, which may affect the generalizability of these findings to the current population. While the effect 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 KOA had good construct validity and may be useful in longitudinal studies.

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