Knee Pain Patterns and Associations with Pain and Function in Persons with or at Risk for Symptomatic Radiographic Osteoarthritis: A Cross-sectional Analysis

Daniel L. Riddle and Mateusz Makowski

ABSTRACT. ***Objective.*** Knee pain location is routinely assessed in clinical practice. We determined the patterns of patient-reported pain locations for persons with knee osteoarthritis (OA). We also examined associations between knee pain patterns and severity of self-reported pain with activity and self-reported functional status.

Methods. The Osteoarthritis Initiative data were used to examine reports of pain location (localized, regional, or global) and type and extent of knee OA. Multivariable ANCOVA models were used to determine associations between the Knee Injury and Osteoarthritis Outcome Survey (KOOS) Pain and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Function scales and pain location after adjusting for potential confounding. We also used radar graphs to illustrate pain patterns for various locations and severity of knee OA.

Results. Radar graphs of 2696 knees indicated that pain pattern and location and extent of knee OA demonstrate substantial overlap. An interaction between race and pain location was found for WOMAC Function, but not for KOOS Pain scores. Global knee pain was associated ($p < 0.001$) with substantially worse function (by 6.5 points in African Americans) compared with pain that was localized. Knee pain reported as global was independently associated ($p < 0.001$) with clinically important lower (worse by 3.9 points) KOOS Pain scores compared with pain that was localized.

Conclusion. Pain patterns are not useful for inferring potential location or severity of knee OA in individual patients, but knee pain patterns that are global are independently associated with worse pain and function compared with localized pain, and associations differ for function based on race. (J Rheumatol First Release November 15 2015; doi:10.3899/jrheum.150545)

Key Indexing Terms:
KNEE PAIN OSTEOARTHRITIS RADIOGRAPHY ASSOCIATION

Patients are routinely asked during a clinical encounter to report the location(s) of their knee pain. Clinicians ask for this information for a variety of reasons. For example, pain over the area of the pes anserine bursa may suggest bursitis, while pain on the medial side of the knee in a middle-aged or elderly person may suggest medial compartment tibiofemoral osteoarthritis (OA). The location of knee pain may also trigger more extensive diagnostic tests. Tibiofemoral joint line pain in some persons, for example, may lead to magnetic resonance imaging to determine the presence of a meniscus tear.

From the Department of Physical Therapy, Department of Orthopaedic Surgery, Department of Biostatistics, Virginia Commonwealth University, Richmond, Virginia, USA.

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D.L. Riddle, PT, PhD, FAPTA, Departments of Physical Therapy and Orthopaedic Surgery, Virginia Commonwealth University; M. Makowski, BS, Department of Biostatistics, Virginia Commonwealth University.

Address correspondence to D.L. Riddle, Otto D. Payton Professor, Departments of Physical Therapy and Orthopaedic Surgery, Virginia Commonwealth University, Richmond, Virginia 23298-0224, USA. E-mail:dlriddle@vcu.edu

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The diagnostic use of knee pain location assessment for inferring radiographic OA status has been examined and these studies have suggested that pain location is not strongly associated with tibiofemoral OA[1,2,3]. However, these studies either examined small samples[1] or did not consider the effect of specific Kellgren-Lawrence grades (KL) or the tibiofemoral compartment involved[3].

Patterns of knee pain and associations with pain and function have also been studied[1,3]. Persons with generalized knee pain have been shown to have Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain scores that are on average more than double those of persons with pain localized over the patella[3]. This association, however, relied on bivariate statistical testing[3] or small samples[1]. Given the ubiquitous use of pain pattern assessment in clinical practice, further determination is warranted of associations between pain location and knee OA KL categories and associations between pain location and self-reported pain with activity or functional status, on a large sample of symptomatic knees.

Our study had 2 purposes. First, we determined the patterns of patient-reported pain locations for persons with

the full range of KL grades from 0 to 4 and for knees with isolated medial and isolated lateral compartment tibiofemoral radiographic OA grades from 0 to 3[4]. Second, we examined associations between knee pain patterns and severity of self-reported pain with activity and self-reported functional status after adjustment for potential confounding.

MATERIALS AND METHODS

Participants were 2696 persons from the parent Osteoarthritis Initiative (OAI) study of 4796 persons with or at risk of knee OA[5]. We selected only those who attended the in-person data collection session during the Year 2 visit of the OAI and who reported having had knee pain or aching in 1 or both knees in the previous 30 days. The Year 2 visit was used because this visit was the only session in which pain pattern was determined using knee pain maps[6]. We used the OAI-reported knee pain map data for the painful knee for subjects with unilateral pain, and randomly selected only 1 knee for subjects with bilateral knee pain, to maintain data independence. We had data from 1395 left knees and 1301 right knees in our study. We decided to include knees with no radiographic knee OA because these patients also seek clinical care and in addition, we wanted to report on the entire disease spectrum from no OA disease to endstage disease as measured with the KL and Osteoarthritis Research Society International (OARSI) systems.

All persons underwent yearly flexed knee standing radiographs. KL grades of 0 (no radiographic OA) to 4 (large osteophytes, marked narrowing of joint space, severe sclerosis, and definite deformity of bone ends) for tibiofemoral joints[7] and OARSI grades of 0 (no OA in both compartments) to 3 [67% to 100% joint space narrowing (JSN) in 1 compartment and 0 in the other compartment] for both medial and lateral tibiofemoral compartments[4] were provided by OAI investigators. An extensive adjudication process was used for KL and OARSI grades for all knees over all time periods. Two central site readers and a third adjudicator, all either a rheumatologist or a musculoskeletal radiologist with extensive training and experience with KL and OARSI grading, read the radiographs. Test-retest reliability was substantial to almost perfect with weighted κ coefficients for both KL grades ranging from 0.70 to 0.80 for 300 randomly selected knee films[8].

Assessments of knee pain location using pain maps. Trained interviewers instructed subjects to point with 1 or 2 fingers to the localized area of their knee pain, or if the pain was more diffuse, to put their hand over the area of the pain. The examination was conducted while the person was sitting. The interviewers recorded data on a knee pain map, an anatomical diagram of the knee. Pain location was coded as localized, regional, or global. Localized pain was coded as medial or lateral joint line, patellar or superior medial, superior lateral, inferior medial, or inferior lateral. Regional pain was coded as medial, lateral, patellar, or posterior knee. If a subject reported more than 4 localized pain areas or more than 2 regional areas, the data were coded as global knee pain. Subjects were asked to identify all knee pain locations over the past 30 days. Subjects could have greater than 1 pain location in a knee. Reliability for this approach ranges from $\kappa = 0.7$ to 1.0[6].

The Knee Injury and Osteoarthritis Outcome Survey (KOOS) Pain and WOMAC Function scores were used to quantify the extent of activity limiting knee pain and functional status, respectively. Both scales have been extensively validated[9,10,11,12]. The WOMAC Function Scale ranges from 0 to 68 with higher scores equating to worse function, and asks patients to rate the extent of difficulty associated with 17 daily activities. The WOMAC Function scale is identical to the KOOS Function scale, but is scored differently. The KOOS Pain scale ranges from 0 to 100 with higher scores equating to less pain. The KOOS Pain Scale was chosen over the WOMAC Pain Scale because KOOS Pain has 4 additional items, which allows for a more comprehensive assessment of the pain with activity construct. Both scales were obtained for each knee. To describe the sample and to adjust for potential confounding, we also report age, sex, body mass index (BMI), sex, race, and KL grade.

Statistical analyses: Part 1. We reported pain locations using radar graphs to illustrate the distributions for KL and OARSI scores for each of the localized, regional, and global pain locations. To reduce the total number of lines on the radar graphs to a manageable number, we collapsed some of the localized pain locations. All reports of localized medial knee pain (i.e., joint line, superior medial, and inferior medial) were reported in the radar graphs as "localized medial knee pain." The same approach was used to classify localized lateral knee pain. These 2 localized pain categories combined with localized patellar pain represented all the localized pain reports on the radar graphs. These were combined with the 4 regional pain categories, and along with global pain, represented a comprehensive summary of the localized, regional, and global pain locations.

The graphical approach allows for rapid visual assessment of the extent of overlap in pain location prevalence among pain patterns across different OA severities and locations. Given that pain location data are used by clinicians at the individual patient level, we believe this approach affords a more clinically useful interpretation of the data as compared with statistical comparisons across groups. Each spoke on the radar graph represents a pain location and the length of each spoke represents the prevalence of a pain location in the studied sample. In our study, we labeled the vertical spoke with a prevalence ranging from 0% to 40%. The overall pattern of all spokes in a radar graph allows the reader to quickly assess pain patterns for a large group of patients, and in our case, allows for a rapid comparison of pain patterns and specifically the extent of overlap across different levels of OA disease locations and severities. We chose not to conduct formal statistical testing of pain categories. Statistical tests would likely show statistical differences even for very small differences in prevalence among disease severity groups because we had very large samples for most disease categories.

Statistical analyses: Part 2. We used ANCOVA models to analyze associations between 2 self-report scales (KOOS Pain and WOMAC Function) and knee pain location. We were interested in the association between the self-reported scales and pain location after adjusting for variables commonly associated with pain intensity and knee OA[13,14,15,16], and these were BMI, age, sex, race (African American and non-African American), and KL score. For our analysis, we collapsed pain location categories into localized, regional, and global subgroups. We reasoned that localized, regional, and global pain locations identified sequentially larger areas of pain and larger areas of pain may associate with self-reported function and pain differently from smaller areas of pain. This premise has been supported in prior work[1,3].

Race was dichotomized because of the very small numbers of persons self-categorized as other non-white and Asian. We used a backward stepwise model selection procedure to build our models. The starting model included the following independent variables: BMI, age, sex, race, KL score, pain location, and 2-way interactions with pain location and the other predictors. To build the final model, variables were sequentially removed from the model until all independent variables were significant below a cutoff value of $p = 0.05$. Further, the KOOS and WOMAC scales did not follow a Gaussian distribution, so a transformation was required for statistical modeling. We used a Box-Cox transformation with $\lambda = 2$ for the KOOS Pain scale and a square root transformation for the WOMAC Function scale. The estimated group differences were then back-transformed to be reported in the original KOOS Pain and WOMAC scale points. The KOOS Pain scale was back-transformed by inverting the Box-Cox transformation formula:

$$original\ scale = \sqrt{(2 \times gm \times t)} + 1$$

"gm" is the geometric mean and "t" is the transformed value. The WOMAC Function scale was back-transformed by squaring the transformed value. Note that the use of these transformations does not result in a change of direction for differences. A Bonferroni correction was used to correct for multiple comparisons. All analyses were done using JMP Pro 11.1.1. (SAS Institute Inc.).

RESULTS

Part 1. Our sample consisted of 2696 persons; 57.3% were women, 16.9% were African American, and the mean age

was 62.7 (SD 9.1) years (Table 1). The radar graphs for the various KL and OARSI grades are illustrated in Figure 1. The radar graphs summarize the prevalence of each pain pattern (localized medial, localized lateral, localized patellar, regional lateral, regional medial, regional patellar, regional pain in the back of the knee, and global knee pain). For each radar graph, the percentage of subjects with each KL (or OARSI) grade who reported pain in each pain pattern is presented. For example, Figure 1A illustrates pain patterns across the entire KL disease spectrum. While medial knee pain is most prevalent in the sample (i.e., the vertical spokes show the highest prevalence), pain in other regions of the knee are only slightly less prevalent. In addition, pain patterns vary only slightly for KL grades from 0 to 4. These graphical data suggest that there is substantial variation in pain locations among individuals with either the same or different KL grades.

Part 2. The model used for the WOMAC Function scale included the following predictors: BMI, age, sex, race, KL score, pain location, and a pain location by race interaction. African American subjects reported significantly higher WOMAC Function scores ($p < 0.05$) across pain location categories as compared with non-African American subjects. For example, WOMAC Function scores among African Americans in the global pain group had a substantially and clinically important worse mean score compared with the localized pain group of about 7 points. For the non-African American subjects, the global pain group had a WOMAC

Table 1. Characteristics of the study sample (n = 2696). Values are n (%) unless otherwise specified.

Variable	Values
Female	1544 (57.3)
Age, yrs, mean (SD)	62.7 (9.1)
BMI, kg/m^2, mean (SD)	29.0 (5.0)
Race	
African American	456 (16.9)
White or other	2236 (83.1)
KL Score	
0	771 (29.6)
1	411 (15.8)
2	702 (27.0)
3	500 (19.2)
4	218 (8.4)
OARSI JSN, medial, lateral	
0	1409 (56.9), 1554 (83.6)
1	600 (24.2), 117 (6.3)
2	329 (13.3), 114 (6.1)
3	138 (5.6), 73 (3.9)
KOOS Pain, median (IQR)	83.3 (22.2)
WOMAC Function, median (IQR)	6.4 (15.9)

BMI: body mass index; KL: Kellgren-Lawrence arthritis grading scale; OARSI: Osteoarthritis Research Society International; JSN: joint space narrowing; KOOS: Knee injury and Osteoarthritis Outcome Score; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; IQR: interquartile range.

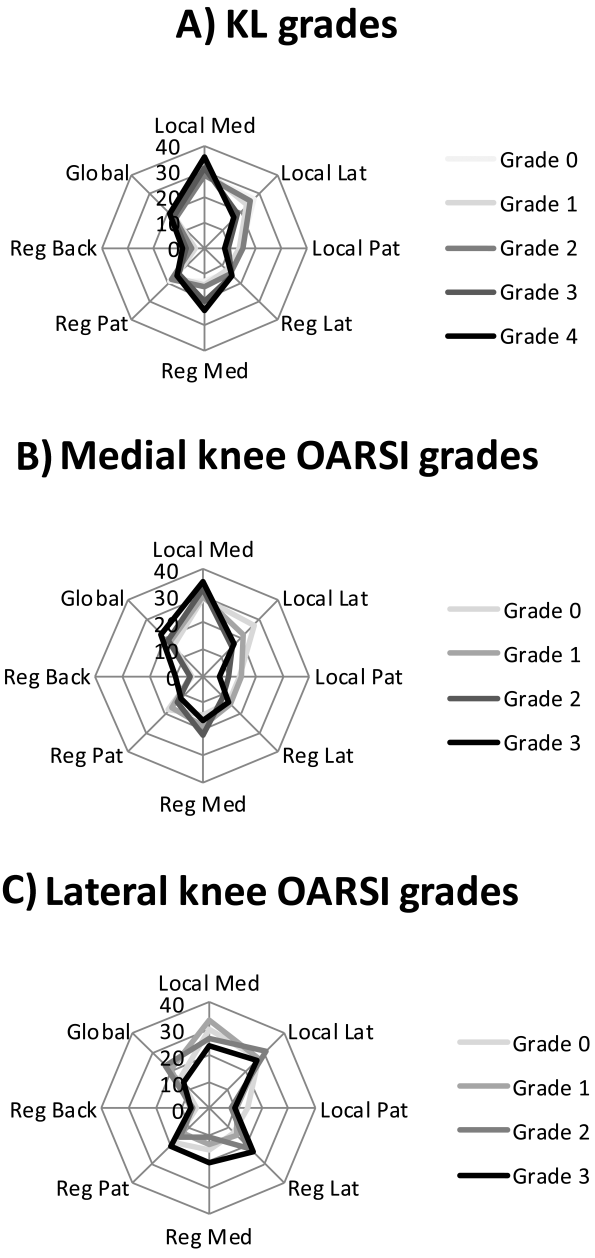

Figure 1. Radar graphs for KL and OARSI grades for the complete sample. A. Distribution of KL grades from 0 to 4. B. OARSI grades from 0 to 3 for isolated medial JSN. C. OARSI grades from 0 to 3 for isolated lateral JSN for all localized, regional, and global pain patterns. To determine the prevalence, identify the grade of interest (e.g., KL grade of 4) and then identify the point on the graph where the KL grade of 4 intersects the radar graph. In the case of localized medial pain in Panel A for a KL grade of 4, about 35.3% of persons had localized medial knee pain. KL: Kellgren-Lawrence arthritis grading scale; OARSI: Osteoarthritis Research Society International; JSN: joint space narrowing; Local Med: localized medial pain; Local Lat: localized lateral pain; Local Pat: localized patellar pain; Reg Lat: regional lateral pain; Reg Med: regional medial pain; Reg Pat: regional patellar pain; Reg Back: regional pain in the back of the knee.

Function score that was slightly less than 2 points higher than the localized pain group. The median WOMAC Function score was 20.2 [interquartile range (IQR) = 23.4] for the African American subjects with global pain while the median WOMAC Function score for the non-African American subjects with global pain was 7 (IQR = 16). Regional pain and localized combined with regional pain was also associated with worse WOMAC Function in African American (by 3 to 8 WOMAC Function points) relative to pain that was localized. Differences between regional and localized pain were not found for the non-African American subjects.

The model used for inferences with the KOOS Pain scale included the following predictors: BMI, age, sex, race, KL score, and pain location. There was no pain location by race interaction found for KOOS Pain scores. We found, for example, that patients with global pain reported significantly lower (worse) scores than patients with localized pain ($p < 0.001$) or regional pain ($p = 0.002$). Score differences were on the order of 3 to 4 KOOS Pain points higher (indicating worse pain) for regional and global pain relative to localized pain. Patients with regional only pain also had worse KOOS Pain scores than persons with only localized pain ($p = 0.035$), resulting in worse pain by about 1.5 points for regional relative to localized pain (results of both models in Table 2).

Minimal clinically important difference (MCID) estimates are frequently used to interpret group differences in clinical trials and provide a context for interpretation of the differences between groups in our study[17]. MCID for the OA outcome measures have consistently been estimated to be about 25% relative to baseline scores[18,19,20]. The better the baseline score (i.e., the larger the KOOS or the smaller the WOMAC score), the smaller the change necessary to conclude that clinically important differences exist. Our baseline scores indicated mostly mild or moderate pain and functional loss. Changes required to infer a clinically important difference between groups were generally small and on the order of 2 or 3 scale points for KOOS and WOMAC scales. Applying this threshold to our data allowed for an interpretation of the potential meaningfulness of the differences we found. For example, the global pain pattern group had clinically important and worse KOOS Pain scores relative to the localized and regional groups, and WOMAC Function differences, particularly for the African American subjects, were likely to be clinically important.

DISCUSSION

We found that pain location patterns for KL and OARSI scores showed substantial overlap across tibiofemoral OA locations and severity levels, and while persons with isolated

Table 2. ANCOVA models* for associations between pain location and KOOS Pain and WOMAC Physical Function.

Pain Group	Comparator Pain Group	Transformed Difference	Standard Error	95% CI	p	Back-transformed Difference**
KOOS Pain						
Localized	Global	3.87	0.78	1.85–5.90	< 0.001‡	3.90
Localized	Localized and regional	3.74	1.95	–1.28 to 8.75	0.056‡	3.75
Regional only	Global	2.55	0.82	0.43–4.67	0.002‡	2.59
Regional only	Localized and regional	2.41	1.97	–2.65 to 7.47	0.22‡	2.44
Localized	Regional only	1.33	0.63	–0.29 to 2.94	0.035‡	1.31
Localized and regional	Global	0.14	2.03	–5.07 to 5.35	0.94‡	0.15
WOMAC Function^ African Americans						
Localized	Global	0.88	0.21	0.46–1.30	< 0.001†	6.52
Localized	Localized and regional	1.06	0.54	0.01–2.12	0.05†	8.08
Regional only	Global	0.39	0.21	–0.03 to 0.81	0.07†	3.06
Regional only	Localized and regional	0.57	0.54	–0.49 to 1.63	0.29†	4.62
Pain localized	Regional only	0.49	0.18	0.13–0.85	0.007†	3.46
Localized and regional	Global	0.18	0.55	–0.90 to 1.26	0.74†	1.56
Others						
Localized	Global	0.34	0.10	0.14–0.55	0.001†	1.81
Localized	Localized and regional	0.16	0.25	–0.33 to 0.66	0.52†	0.84
Regional only	Global	0.27	0.11	0.05–0.48	0.01†	1.44
Regional only	Localized and regional	0.09	0.26	–0.41 to 0.60	0.73†	0.47
Localized	Regional only	0.07	0.08	–0.08 to 0.23	0.36†	0.37
Localized and regional	Global	0.18	0.27	–0.34 to 0.70	0.50†	0.97

* Models are adjusted for Kellgren-Lawrence arthritis grading score, age, sex, body mass index, and race. ** The back-transformed difference represents the difference among pain groups in the units of interest. These differences are interpreted so that the value indicates the magnitude of difference between the 2 pain locations. For example, for KOOS Pain, the difference between the global and the localized group is 3.9 KOOS Pain points. This indicates that after adjustment for other covariates in the model, the global pain group had a KOOS Pain score that was 3.9 points lower (indicating worse pain) as compared with the local pain group. ^ The comparisons are reported separately for African American subjects and for all other subjects. ‡ Student t test p values compared with Bonferroni cutoff value of 0.008. † Student t test p values compared with Bonferroni cutoff value of 0.004. KOOS: Knee injury and Osteoarthritis Outcome Score; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

medial JSN demonstrated a tendency toward more medial knee pain (and vice versa for lateral JSN), there was still a substantial percentage who reported pain in a variety of knee locations, even when OA was isolated to either the medial or lateral tibiofemoral compartment. These descriptive data suggest that knee pain location does not inform decisions regarding likely location(s) of tibiofemoral OA or severity of radiographic tibiofemoral OA when considering an individual patient. The variability and degree of overlap among disease severity categories is simply too great, in our opinion, to provide initial diagnostic information.

Independent associations between pain location and self-reported KOOS Pain suggest that global pain is associated with more severe pain with activity than localized or regional pain. This difference is on the order of 2 to 4 KOOS Pain points. For WOMAC Function scores, African American subjects demonstrated substantial differences of about 7 points when pain was reported as global versus local. Among all other subjects of which 97% were white, differences were also found among those with global versus those with localized pain, but these differences were small, about 2 WOMAC Function points. No other statistically significant differences were found among the other pain locations.

When applying the MCID to interpretation of the differences we found, some clinically important differences are likely. For example, KOOS Pain scores for persons with global knee pain relative to those with either localized or regional pain are likely to be important. Patients with global knee pain consistently had worse KOOS Pain scores. For WOMAC Function, application of MCID estimates of 2 or 3 WOMAC Function points for persons with mild or moderate functional loss indicate that all statistically significant differences we found for African American subjects are likely to be clinically important. Regional and global pain patterns are associated with clinically important reduced function relative to localized pain groups. However, for non-African American subjects, the only statistically significant and clinically important difference was for the global relative to the localized pain group.

Reasons for the race by pain location interaction for WOMAC Function, but not for KOOS Pain, was a surprising finding. African Americans have been found to have significantly worse pain and function scores after controlling for radiographic severity and age, and these higher scores have been shown to be associated with higher BMI and worse mental health[21]. WOMAC Function scores quantify the difficulty during functional tasks while KOOS Pain scores quantify the extent of pain during functional tasks. These measures are strongly correlated for persons with OA[22], but in our study the race by pain location interaction was found only for WOMAC Function. We suspect 2 reasons for this finding. Pain location may simply have a greater effect on functional status difficulty than pain during function for African Americans compared with non-African American subjects. The other possibility is that WOMAC Function consists of 17 items while KOOS Pain contains only 9 items and it may be that WOMAC Function is a more psychometrically sound measure of the construct of interest particularly when considering pain location. Our study supports the need for more research in this area.

In an *a posteriori* analysis, we examined the diagnostic validity for pain location assessments by determining the sensitivity, specificity, and likelihood ratios when considering knees with isolated medial JSN and no lateral JSN (n = 1066) and knees with isolated lateral JSN and no medial JSN (n = 273). We used the OARSI JSN measurements in the OAI to identify persons with isolated medial or isolated lateral JSN. We considered this analysis a best-case scenario diagnostic test approach because the knees of interest only had unicompartmental disease. We tested whether pain location (either medial or lateral) could "diagnose" either isolated medial or isolated lateral knee OA with JSN. If a person reported any medial knee pain and had isolated medial knee joint disease, this was considered a diagnostically positive test and vice versa for the lateral compartment. Table 3 summarizes the findings. Briefly, the sensitivity and specificity were all 0.7 or less and all likelihood ratios were between 0.5 and 2.0, which indicate that even considering the best-case scenario of isolated medial or lateral knee compartment disease and no other OA combinations, pain location is not diagnostically accurate enough for routine clinical use.

Our findings are consistent with others in that global pain has been reported to be associated with worse self-reported pain and function compared with other pain patterns[1,3]. However, our work builds on this past evidence by examining a very large sample, accounting for OA severity and location

Table 3. Diagnostic test validity indices for identifying persons with either isolated medial compartment knee OA (n = 1066) or isolated lateral compartment knee OA (n = 273).

Knee Pain Location Test Result	Knee OA Status	Sensitivity (95% CI)	Specificity (95% CI)	+ Likelihood Ratio (95% CI)	– Likelihood Ratio (95% CI)
Any medial knee pain	Isolated medial compartment disease	0.51 (0.48–0.54)	0.63 (0.57–0.69)	1.35 (1.15–1.60)	0.79 (0.71–0.88)
Any lateral knee pain	Isolated lateral compartment disease	0.48 (0.42–0.54)	0.70 (0.67–0.73)	1.60 (1.37–1.87)	0.74 (0.66–0.84)

OA: osteoarthritis.

and adjusting for potential confounders. Our study is limited because we did not have patellofemoral OA data and our analysis was restricted to cross-sectional associations.

Our radar graph data suggest that pain pattern and extent or location of tibiofemoral radiographic OA are only weakly related if at all and that the extent of pain overlap among OA disease severity subgroups is likely too great for individual patient application. Knee pain reported to be global has a clinically important association with self-reported KOOS Pain scores. Global pain and regional pain patterns also have a strong association with worse functional status relative to localized pain reports and this is particularly true for African Americans relative to non-African Americans. We encourage clinicians to use reports of pain location and particularly reports of global and regional pain because these reports are independently associated with activity-related pain and function. Pain location does not appear to be helpful for inferring radiographic OA location or severity.

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