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Diagnostic performance of knee physical exam and participant-reported symptoms for MRI-detected effusion-synovitis among participants with early or late stage knee osteoarthritis: data from the Osteoarthritis Initiative

A. Berlinberg †, E.L. Ashbeck ‡, F.W. Roemer § ||, A. Guermazi ||, D.J. Hunter ¶, J. Westra ‡ #, J. Trost †, C.K. Kwoh † ‡ *

† *Department of Medicine, University of Arizona, Tucson, AZ, USA*
‡ *Arizona Arthritis Center, University of Arizona, Tucson, AZ, USA*
§ *Department of Radiology, University of Erlangen-Nuremberg, Erlangen, Germany*
|| *Quantitative Imaging Center (QIC), Department of Radiology, Boston University School of Medicine, Boston, MA, USA*
¶ *Department of Rheumatology, Royal North Shore Hospital, Institute of Bone and Joint Research, Kolling Institute, University of Sydney, Sydney, New South Wales, Australia*
# *Department of Epidemiology and Biostatistics, Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ, USA*

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SUMMARY

Objective: Evaluate the diagnostic performance of knee physical exam findings and participant-reported symptoms for MRI-detected effusion-synovitis (ES) among knees with early and late-stage osteoarthritis (OA).

Design: The Osteoarthritis Initiative (OAI) is a longitudinal study of participants with or at risk for knee OA. Two samples with MRI readings were available: 344 knees with early OA (312 participants) and 216 with late-stage OA (186 participants). Trained examiners performed bulge sign (BS) and patellar tap (PT) exams, and participants reported on knee swelling and pain with leg straightening. Effusion-synovitis on 3T non-contrast MRI was scored using the MRI Osteoarthritis Knee Score (MOAKS). Diagnostic performance of physical exam findings and symptoms was estimated with bootstrapped confidence intervals.

Results: For the early OA sample, the highest sensitivity for medium/large effusion-synovitis was achieved with a positive finding for any of the physical exam maneuvers and/or participant-reported symptoms (81.0 [95% CI: 70.0, 91.3]). Both knee symptoms in combination had a prevalence of 11.7% and yielded the highest estimated positive predictive value (PPV) (50.0 [95% CI: 34.2, 66.7]) and likelihood ratio positive (LR+) (5.2 [95% CI: 2.9, 9.7]). In late-stage OA knees, exam findings and symptoms provided minimal information beyond the prevalence.

Conclusion: Patient report of both symptoms, or at least one positive exam finding and at least one symptom, could be used to identify knees at increased risk of effusion-synovitis in knees with early stage OA, either for screening purposes in clinical evaluation, or for study sample enrichment with an inflammatory phenotype; diagnostic performance was not sufficiently high for clinical diagnostic purposes.

Introduction

Knee osteoarthritis (OA) is a common, complex and debilitating progressive joint disease that affects nearly 27 million Americans and causes structural damage and chronic pain[1]. Although OA was traditionally thought to be a non-inflammatory process, recent findings have demonstrated an inflammatory component, involving immune cell infiltration and cytokine secretion[2,3].

* Address correspondence and reprint requests to: C. Kent Kwoh, Medicine and Medical Imaging, Division of Rheumatology, University of Arizona Arthritis Center, 1501 N. Campbell Avenue, Room 8303, 85724-5093, Tucson, AZ, USA. Tel.: 1-520-626-6399; Fax: 1-520-626 5018.
E-mail address: Kwoh@arthritis.arizona.edu (C.K. Kwoh).

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Ultrasound or radiography has typically been used to assess knee inflammation as manifested by synovitis and effusion[4–7], given the cost and lack of access to MRI. Clinical exam findings of knee swelling had low sensitivity but high specificity for findings of effusion-synovitis on non-contrast MRI[8], and patient-reported swelling had high sensitivity for the detection of effusion-synovitis on non-contrast MRI[9] in previous reports.

Clinicians are routinely taught to perform the BS and PT maneuvers to detect the presence of knee effusions in clinical practice. Further, identification of joint effusion as a manifestation of inflammation by physical examination is inexpensive and common in clinical settings. Patients are routinely asked about the presence of knee swelling in clinical practice and standardized questions to elicit patient-reported knee symptoms such as swelling have been developed[10–12]. In addition, patient-reported symptoms such as pain, stiffness or swelling have been associated with the presence of effusion-synovitis on non-contrast MRIs[9,12–14]. Fluctuation of knee pain has been associated with fluctuation of MRI-detected effusion-synovitis, supporting the relationship between MRI-detected inflammation and symptoms[15]. Authors of a recent systematic review examined the feasibility of physical exam maneuvers to identify knee effusion in OA and concluded that there is insufficient evidence to recommend a single test for identifying knee inflammation and that a combination of physical exam maneuvers improved performance[16]. The performance characteristics of physical exam maneuvers in combination with patient-reported symptoms for MRI-detected knee inflammation have not been established.

Different knee OA phenotypes have been identified, including an inflammatory phenotype that can be identified through findings on MRI[17,18]. The presence of effusion-synovitis on non-contrast MRI has been associated with a higher risk of developing incident radiographic knee OA, rapid cartilage loss and progression to knee replacement[19–21]. If clinical evaluation involving a combination of physical exam and patient-reported symptoms of swelling were able to predict the presence of effusion-synovitis on MRI, this diagnostic tool could then be used to identify an inflammatory phenotype of knee OA, facilitating targeted treatment in a clinical setting or to enrich clinical trials of drugs targeting inflammation in knee OA[22], without requiring further imaging. Our objective was to evaluate the diagnostic performance of physical exam findings, including BS and PT, and participant-reported symptoms of swelling for the presence of MRI-detected effusion-synovitis in two convenient samples: knees with early OA and knees with late-stage OA that subsequently underwent knee replacement.

Methods

Study design, setting, and participants

The Osteoarthritis Initiative (OAI) is a multi-center, longitudinal, prospective observational study of knee OA. Study overview, objectives, protocol, and data are available online (https://oai.epi-ucsf.org/datarelease/About.asp). Briefly, 4796 men and women with or at risk for knee OA ages 45–79 enrolled between February 2004 and May 2006 from the following sites: Ohio State University (Columbus, OH), University of Maryland School of Medicine and Johns Hopkins University School of Medicine (Baltimore, MD), University of Pittsburgh School of Medicine (Pittsburgh, PA), Brown University School of Medicine and Memorial Hospital of Rhode Island (Pawtucket, RI). The study was approved by the Institutional Review Board (IRB) of the OAI Coordinating Center at the University of California, San Francisco and the IRBs of each site.

Participants who developed incident radiographic knee osteoarthritis (ROA) within 4 years of baseline, including 355 knees from 323 individuals[19] (i.e., 'early OA' sample), and those who underwent knee replacement (KR) within 5 years of baseline, including 225 knees from 195 individuals[20] (i.e., 'late stage OA' sample), were identified from two previous studies in Pivotal Osteoarthritis MRI Analyses (POMA). MRI readings were available from the clinic visits leading up to the first visit following first radiographic detection of knee OA, as well as the clinic visits prior to KR. Knees with early OA and knees with late stage OA provided two samples across the spectrum of disease severity with available MRI readings.

Knee physical exam

Physical exams were conducted at baseline, 2-year, and 4-year follow-up OAI visits. Physical exam maneuvers used to identify knee swelling included the BS and PT, described briefly below. The detailed knee exam operations manual is available online[23].

The BS test is intended to detect effusions, potentially even small effusions, by attempting to move swelling from one part of the joint to another. Briefly, the examiner used the flat of the hand to sweep upwards from the lower medial side of the knee with sustained moderate pressure, and then swept the hand downwards on the lateral side of the knee. The examiner recorded whether a bulge appeared in the medial recess. The PT test is also intended to detect effusions, particularly large effusions. The fluid in the supra-patellar pouch was pushed into the knee joint and held with sustained hand pressure. The test was considered positive if the patella was felt to abruptly stop as it contacted the underlying femoral condyles, and recorded accordingly[24].

Knee exam experts trained the clinical examiners, facilitated examiner certification, and continued quality assurance with training sessions that included blinded parallel exam.

Participant-reported symptoms of swelling

Participant-reported symptoms were assessed as part of the Other Knee Symptoms subscale of the Knee injury and Osteoarthritis Outcome Score (KOOS) instrument[25] administered at annual clinic visits. The KOOS questions were knee-specific, that is, separate questions were asked for the right knee and the left knee. Two items that address potential inflammation include "Do you have swelling in your right/left knee?" and "How much pain have you had [when] straightening [your] right/left knee fully?", both anchored to "during the last 7 days". Potential responses to the question about swelling in the knee included "Never", "Rarely", "Sometimes", "Often", and "Always". Potential responses to the question about pain when straightening the knee fully included "None", "Mild", "Moderate", "Severe", and "Extreme".

Knee MRI acquisition and assessment

Non-contrast MRIs were obtained on 3T Trio systems (Siemens Healthcare, Erlangen, Germany) and acquired with a dedicated quadrature transmit/receive knee coil using a coronal intermediate-weighted (IW) 2-dimensional turbo spin-echo sequence, a sagittal 3-dimensional dual-echo steady-state (DESS) sequence, and a sagittal IW fat-suppressed turbo spin-echo sequence. The complete pulse sequence protocol and sequence parameters have been described previously[26].

MRI readings were selected from OAI baseline, year 2 and year 4 follow-up, as those clinic visits included a physical exam of the knee. Knee inflammation was evaluated using the MRI Osteoarthritis Knee Score (MOAKS), a semi-quantitative scoring instrument[27]. Effusion-synovitis represents a combination of joint effusion and synovial thickening on fluid-sensitive sequences and is scored as a physiologic amount (0), small (1), medium (2), or large

(3) according to the amount of distension of the joint capsule (Fig. 1). Hoffa-synovitis represents diffuse hyperintense signal on T2/Proton density/IW-weighted fat suppressed sequences within the intercondylar region of the Hoffa fat pad, and is scored as normal (0), mild (1), moderate (2), and severe (3). Reliability for MOAKS readings of effusion-synovitis and Hoffa-synovitis has been reported, with inter-rater reliability weighted kappa 0.72 and 0.70, respectively, and intra-rater reliability 0.90 and 0.42 respectively[27].

Demographic and clinical characteristics

Age, sex, and race were self-reported. Participant height and weight were measured by trained clinic staff at each clinic visit, and body mass index (BMI) was calculated and categorized based on the World Health Organization definition.

Baseline OA severity was assessed on knee radiographs centrally read by two expert readers with over 50 years of total experience, and graded according to the Kellgren–Lawrence (KL) system[28]. Briefly, bilateral posteroanterior fixed-flexion weight-bearing radiographic views were obtained using a SynaFlexerTM frame (Synarc, Newark, CA, USA). The detailed Radiographic Procedure Manual is available online[29].

Statistical methods

The BS and PT are both considered present or absent, though the participant-reported symptoms were reported using ordinal scales, as described above. Initially we plotted discrete receiver operating characteristic (ROC) curves for effusion-synovitis, and identified the dichotomization that achieved the minimum distance between the ROC curve and the point (0,1), representing 100% sensitivity and 100% specificity. Diagnostic performance of the two physical examination maneuvers and participant-reported swelling and pain when straightening the knee fully were evaluated by estimating sensitivity, specificity, PPV, negative predictive value (NPV), LR+, and likelihood ratio negative (LR−) using MRI-detected moderate/severe effusion-synovitis as the gold standard. We selected effusion-synovitis graded as medium/large as the primary outcome since effusions of this size are of greater clinical relevance, though we also considered effusion-synovitis of any size in a sensitivity analysis. We examined a combined effusion-synovitis and/or Hoffa-synovitis outcome in sensitivity analyses. Nonparametric bootstrapped 95% confidence intervals were calculated from 2000 bootstrapped samples drawn with replacement, with the sample size based on the number of unique participants. The sample size of the bootstrapped samples was based on the number of unique participants represented, so as not to overstate the precision of our estimates (reflected by the width of the confidence intervals), given that our sample included repeated measures. Physical examination maneuvers and participant-reported symptoms were examined separately and in combination.

While MRI scans were typically performed on the same day as the physical examination, occasionally the MRIs were acquired on a different day due to scheduling challenges. Observations were only included in the analysis if the physical examination occurred no more than 7 days from the MRI. A sensitivity analysis included only those observations with a physical examination and MRI performed on the same day, since inflammation in the knee can potentially fluctuate over a few days.

Results

Semi-quantitative MRI readings of effusion-synovitis from POMA were available from 355 knees in the early OA sample contributed by 323 participants, and from 225 knees in the late-stage OA sample contributed by 195 participants. After excluding MRIs that occurred more than 7 days from the physical exam, 745 observations from 344 knees contributed by 312 participants were available from the early OA sample, and 392 observations were available from 216 knees contributed by 186 participants from the late-stage OA sample (Fig. 2). Early OA knees contributed an average of 2.2 observations, while late-stage OA knees contributed an average of 1.8 observations.

Participants in the early OA sample had a mean age of 60 years, were predominately female (67%), and overweight or obese (81%), with racial representation primarily of whites (81%) and African Americans (16%). Participants in the late-stage OA sample had a mean age of 65 years, with the majority female (57%), and overweight or obese (84%), representing whites (88%) and limited African Americans (7%). The early OA sample had no or minimal radiographic evidence of OA at baseline, with 39% KL 0 and 61% KL1. The late-stage OA sample had evidence of advanced OA, with over 70% of knees graded at KL 3 or 4 from the baseline x-ray, and KOOS pain scores reflective of greater pain levels (Table I). The early OA sample represents early disease, while the late-stage OA sample represents more severe end-stage disease.

The prevalence of medium/large effusion-synovitis in the early OA sample was 16% (121/745 observations). Dichotomizing responses to the question about swelling as “never” vs any, and dichotomizing pain when straightening the knee fully as “none” vs

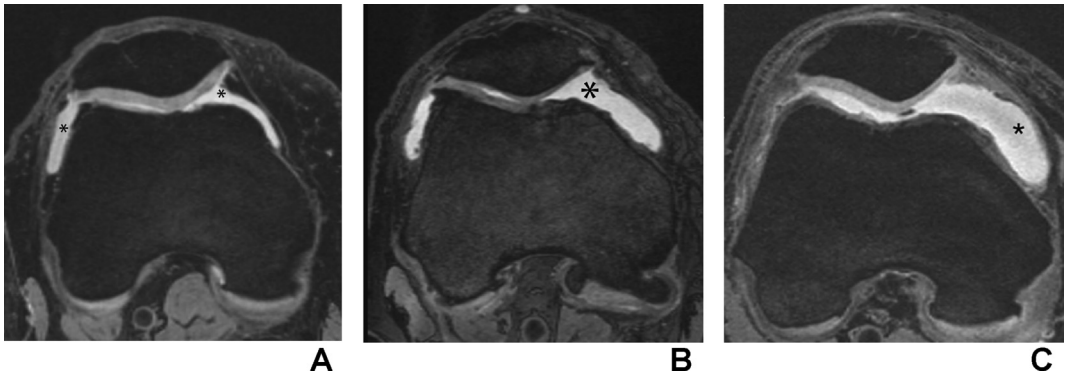

Fig. 1. Effusion-synovitis on MRI is defined by the amount of capsular distension on axial fluid-sensitive sequences; A. Grade 1 effusion-synovitis is shown on this axial image is depicted as intra-articular fluid-equivalent signal (asterisks). B. Grade 2 effusion-synovitis is shown representing a moderate amount of capsular distension (asterisk). C. A large amount of distension is defined as grade 3 effusion-synovitis (asterisk). Note that intra-articular joint fluid cannot be differentiated from synovial thickening that also appears hyperintense on T2-weighted images.

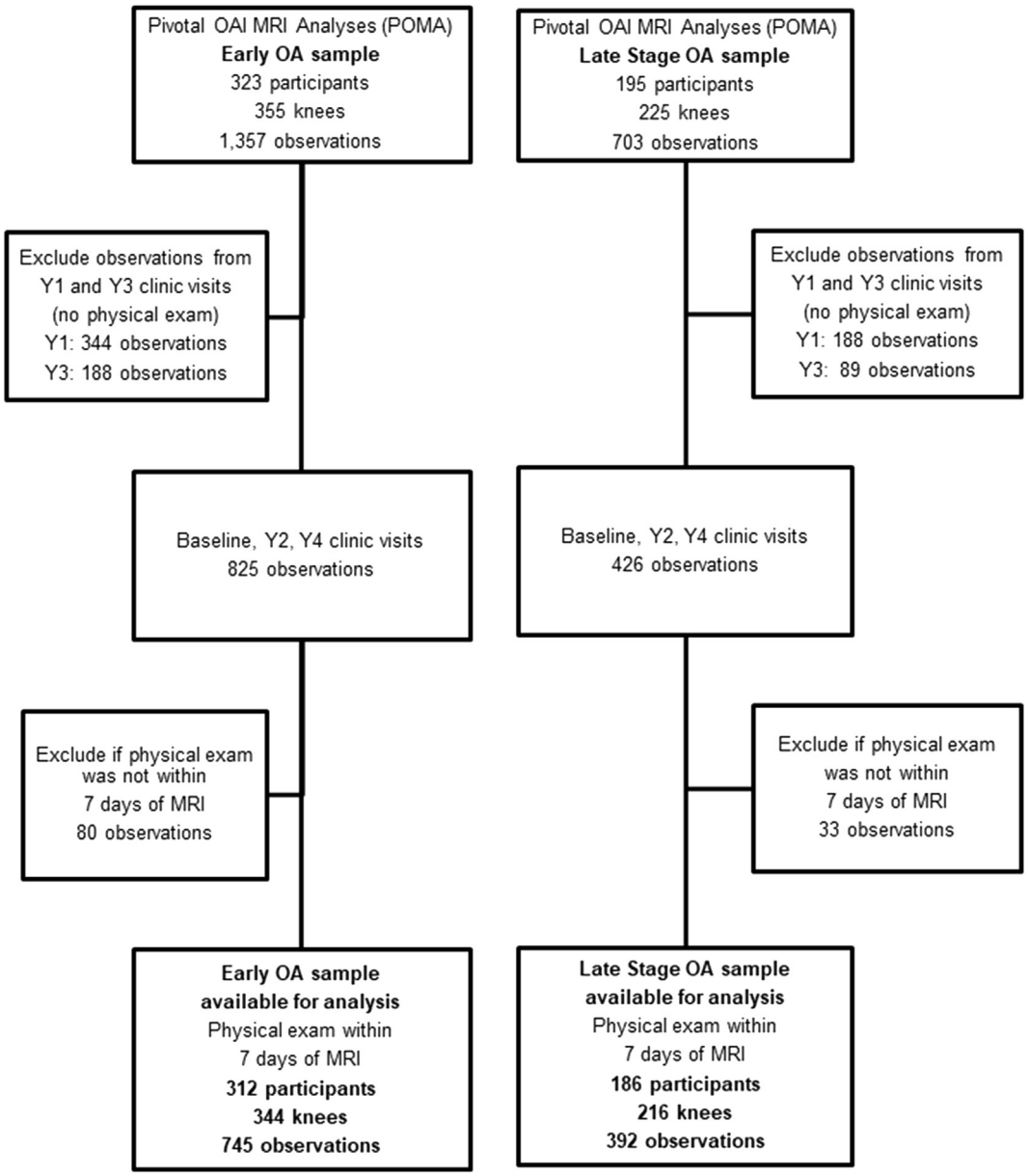

Fig. 2. Participant flow diagram.

any, achieved the minimum distance between the ROC curve and the point (0,1), representing 100% sensitivity and 100% specificity [Fig. 3(A) and (B)]. Considered collectively, a positive finding for either physical examination maneuver and/or any participant-reported symptoms of swelling achieved a sensitivity of 81.0 [95% CI: 70.0, 91.3], and 43.6% of the observations had at least one of these positive findings (Table II). Among those knees without medium/large effusion-synovitis, 97.9% [95% CI: 95.9, 99.3] were negative for both the BS and PT, with 95.8% [95% CI: 93.3, 98.1] negative on PT; only 5.1% of the observations had a positive PT, and only 2.6% had both positive BS and PT. Participants who reported both swelling and pain when straightening the knee fully (11.7% of the sample) had the highest probability of medium/large effusion-synovitis on MRI (PPV 50.0 [95% CI: 34.2, 66.7]), followed by participants reporting at least one symptom and with at least one positive examination finding (9.7% of the sample; PPV 48.6 [95% CI: 30.1, 67.3]). Among participants without symptoms and negative exam findings in the early OA sample (56.4% of the sample), 94.4% [NPV 95% CI: 90.9, 97.6] did not have medium/large effusion-synovitis seen on MRI. The highest estimated LR+ was for the simultaneous report of both symptoms (LR+ 5.19 [95% CI: 2.9, 9.7]), and simultaneous positive knee exam finding and at least one symptom (LR+ = 4.99 [95% CI: 2.6, 10.4]). Medium/large effusion-synovitis was best ruled out by the lack of any positive exam finding or symptom (LR− 0.30 [95% CI: 0.14, 0.48]).

The prevalence of medium/large effusion-synovitis in the late-stage OA sample was 54% (211/392 observations). Report of any swelling or pain when straightening the knee were considered positive findings based on the results of the discrete ROC curves [Fig. 3(C) and (D)], the same dichotomization of responses used in the early OA analysis. Similar to the early OA sample, the highest sensitivity in the late-stage OA sample was observed with a positive finding for any of the physical examination maneuvers and/or symptoms (88.9% [95% CI: 82.5, 94.7], though 81.3% of the sample had at least one positive finding (Table III)). Also similar to the early OA sample, specificity was highest in the late-stage OA sample for

Table I
Baseline characteristics in early and late-stage osteoarthritis samples

	Early OA sample	Late-stage OA sample
Participant-level	$n = 312$	$n = 186$
Age (years), mean (Standard deviation [SD])	60.3 (8.7)	64.7 (8.5)
Female	66.7%	57.0%
Race		
White	81.1%	88.1%
African American	15.7%	7.0%
Other	3.2%	4.9%
BMI, mean (SD)	28.9 (4.5)	29.5 (4.6)
BMI Category		
Normal	19.2%	16.1%
Overweight	42.0%	38.2%
Obese	38.8%	45.7%
Knee-level	$n = 344$	$n = 216$
Kellgren–Lawrence grade		
0	38.7%	3.8%
1	61.3%	4.3%
2		19.2%
3		35.1%
4		37.5%
KOOS Knee Pain Score, mean (SD)	86.4 (15.8)	68.8 (18.5)

Note: 8 late-stage OA knees were missing Kellgren–Lawrence grade at baseline.

PT. Only 9.2% had positive PT and only 6.4% had simultaneous positive BS and PT. The combination of at least one positive examination finding and at least one symptom yielded the highest PPV (68.9 [95% CI: 56.5, 81.0]), though this should be interpreted in the context of a 54% prevalence in this late-stage OA sample, and with modest LR+ (1.9 [95% CI: 1.2, 3.5]).

The prevalence of any effusion-synovitis was 56.2% in the early OA sample (with 16.2% medium/large), and 81.6% in the late-stage OA sample (with 53.8% medium/large). The sensitivities of the exam maneuvers and symptoms were lower, particularly in the early OA sample, due to the challenge of detecting small effusions, with resulting lower NPVs (Supplemental Tables 1 and 2). However, the PPVs were considerably higher, due to the higher prevalence.

In a sensitivity analysis excluding MRIs that did not occur on the same day as the physical exam, 591 observations were available for analysis in the early OA sample, contributed by 298 knees from 272 participants. In the late-stage OA sample, 311 observations from 184 knees contributed by 160 participants were available for analysis restricted to the same day physical examination and MRI. Results were not remarkably different and did not change our findings (data not shown).

We examined a combined effusion-synovitis and/or Hoffa-synovitis outcome in an additional sensitivity analysis, and found

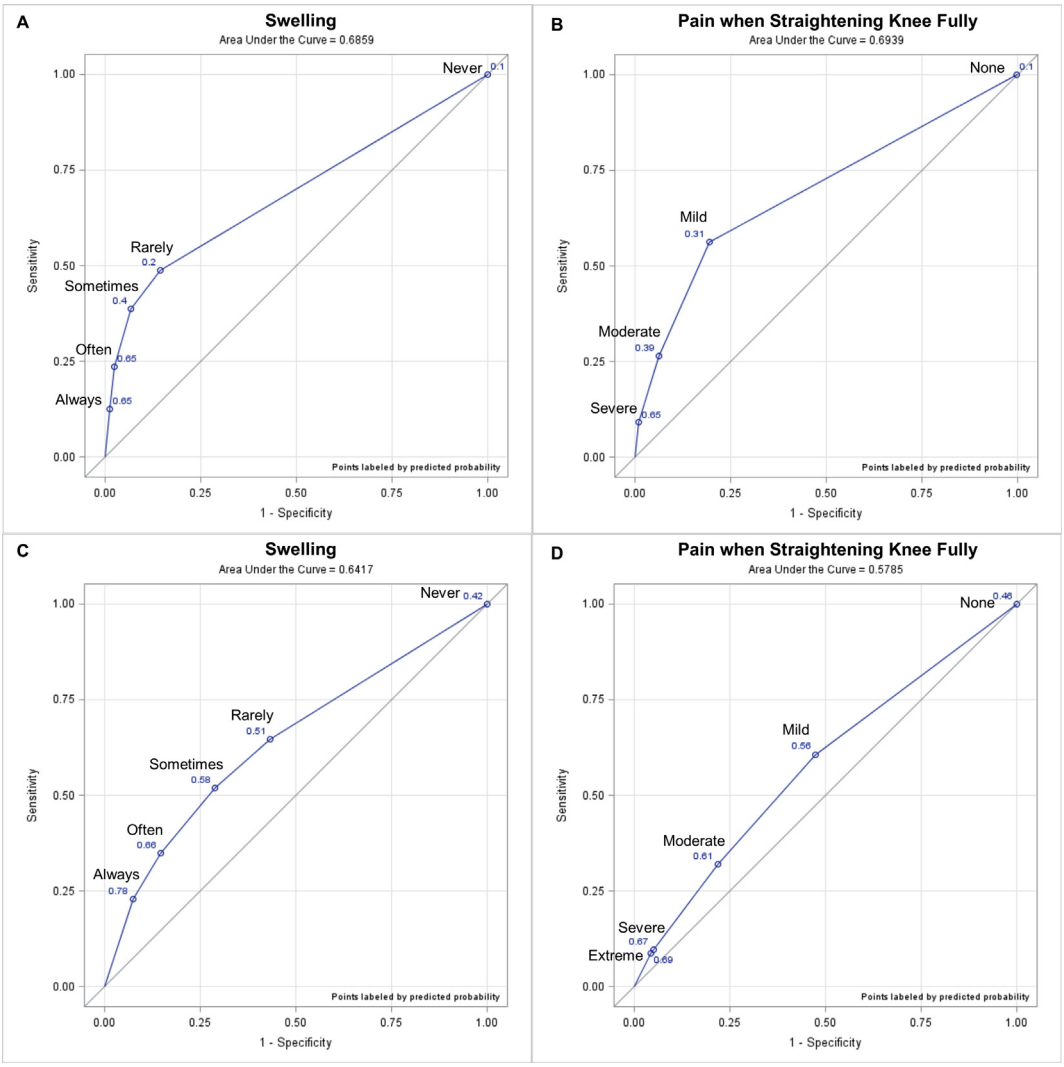

Fig. 3. ROC curves for medium/large effusion-synovitis; A. Swelling in early OA knees, B. Pain when straightening knee fully in early OA knees, C. Swelling in late-stage OA knees, D. Pain when straightening knee fully in late-stage OA knees.

Table II
Diagnostic performance of physical exam maneuvers and participant-reported symptoms for the presence of medium/large effusion-synovitis, among early OA knees

	Neg (%)/Pos (%)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR− (95% CI)
Exam maneuvers							
BS	83.4/16.6	38.1 (25.5, 52.4)	87.6 (83.3, 91.5)	37.2 (24.5, 50.0)	88.0 (84.0, 91.8)	3.08 (1.8, 4.9)	0.71 (0.55, 0.86)
PT	94.9/5.1	9.6 (2.2, 18.6)	95.8 (93.3, 98.1)	29.7 (8.3, 55.6)	84.9 (80.7, 89.0)	2.25 (0.5, 6.3)	0.94 (0.84, 1.02)
BS and/or PT	81.2/18.8	42.2 (28.9, 56.5)	85.6 (81.2, 89.6)	35.8 (23.8, 48.5)	88.7 (84.8, 92.4)	2.94 (1.9, 4.6)	0.67 (0.51, 0.83)
Both BS and PT	97.4/2.6	5.2 (0.0, 12.8)	97.9 (95.9, 99.3)	31.6 (0.0, 66.7)	84.6 (80.3, 88.7)	2.46 (0.0, 10.9)	0.97 (0.89, 1.03)
Symptoms							
Swelling	79.9/20.1	48.7 (35.3, 62.2)	85.5 (81.3, 89.6)	39.2 (27.8, 51.7)	89.7 (85.7, 93.3)	3.35 (2.3, 5.1)	0.60 (0.44, 0.76)
Pain when straightening	74.5/25.5	56.2 (43.3, 70.1)	80.4 (75.6, 85.2)	35.8 (25.4, 46.8)	90.4 (86.5, 94.0)	2.87 (2.0, 4.1)	0.54 (0.37, 0.71)
Either symptom present	65.9/34.1	69.2 (56.3, 81.5)	72.7 (67.3, 78.0)	32.9 (24.0, 42.5)	92.4 (88.5, 95.8)	2.54 (1.9, 3.3)	0.42 (0.25, 0.60)
Both symptoms present	88.3/11.7	36.1 (23.1, 50.0)	93.0 (89.8, 96.0)	50.0 (34.2, 66.7)	88.3 (84.4, 92.1)	5.19 (2.9, 9.7)	0.69 (0.54, 0.83)
Exam maneuvers and symptoms							
Any positive exam finding and/or symptom	56.4/43.6	81.0 (70.0, 91.3)	63.8 (57.8, 69.5)	30.7 (22.7, 38.6)	94.4 (90.9, 97.6)	2.20 (1.8, 2.7)	0.30 (0.14, 0.48)
BS and/or PT and either symptom	90.3/9.7	29.6 (17.3, 43.3)	94.1 (91.2, 96.9)	48.6 (30.1, 67.3)	87.6 (83.8, 91.3)	4.99 (2.6, 10.4)	0.75 (0.60, 0.88)

Abbreviations: Negative, Neg; Positive, Pos.
Note: Prevalence of medium/large effusion-synovitis in this sample was 16.2%.

Table III
Diagnostic performance of physical exam maneuvers and participant-reported symptoms for the presence of medium/large effusion-synovitis, among late-stage OA knees

	Neg (%)/Pos (%)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+ (95% CI)	LR− (95% CI)
Exam maneuvers							
BS	66.2/33.8	40.3 (30.4, 50.0)	73.7 (63.8, 82.9)	63.8 (51.7, 75.7)	51.8 (42.7, 60.5)	1.53 (1.0, 2.5)	0.81 (0.65, 0.99)
PT	90.8/9.2	10.8 (5.1, 17.3)	92.7 (86.8, 97.6)	62.9 (38.5, 85.7)	47.5 (40.1, 55.3)	1.48 (0.6, 4.7)	0.96 (0.88, 1.05)
BS and/or PT	63.4/36.6	44.3 (34.4, 54.6)	72.3 (62.6, 81.9)	64.7 (52.5, 75.7)	53.1 (43.9, 62.6)	1.6 (1.1, 2.6)	0.77 (0.60, 0.96)
Both BS and PT	93.6/6.4	7.0 (2.2, 12.3)	94.4 (89.1, 98.8)	58.3 (28.0, 89.6)	47.3 (39.7, 54.3)	1.24 (0.4, 6.8)	0.99 (0.91, 1.06)
Symptoms							
Swelling	45.3/54.7	64.6 (55.1, 73.6)	56.8 (46.2, 67.4)	63.6 (53.3, 72.8)	57.8 (47.4, 68.1)	1.5 (1.1, 2.0)	0.62 (0.44, 0.86)
Pain when straightening	45.5/54.5	60.7 (51.0, 70.3)	52.5 (41.6, 62.6)	59.5 (50.0, 68.5)	53.7 (43.0, 64.8)	1.28 (1.0, 1.7)	0.75 (0.54, 1.02)
Either symptom present	27.9/72.1	79.9 (71.7, 87.6)	37.1 (26.9, 47.7)	59.9 (51.5, 67.9)	61.1 (47.9, 75.0)	1.27 (1.1, 1.6)	0.54 (0.31, 0.85)
Both symptoms present	63.0/37.0	45.0 (35.6, 54.9)	72.2 (62.5, 81.4)	65.0 (53.6, 76.1)	53.4 (44.7, 62.7)	1.62 (1.1, 2.5)	0.76 (0.61, 0.94)
Exam maneuvers and symptoms							
Any positive exam finding and/or symptom	18.8/81.3	88.9 (82.5, 94.7)	27.7 (17.7, 37.8)	59.0 (50.7, 66.9)	68.1 (51.3, 82.9)	1.23 (1.1, 1.5)	0.40 (0.19, 0.73)
BS and/or PT and either symptom	71.9/28.1	36.3 (26.9, 46.2)	81.3 (73.0, 88.9)	68.9 (56.5, 81.0)	52.8 (44.1, 61.1)	1.94 (1.2, 3.5)	0.78 (0.64, 0.93)

Abbreviations: Negative, Neg; Positive, Pos.
Note: Prevalence of medium/large effusion-synovitis in this sample was 53.8%.

that sensitivity and LR+ of examination findings and symptoms were marginally lower compared to the effusion-synovitis outcome in the early OA sample (Supplemental Table 3), with no notable differences in the late-stage OA sample. Given that the physical exam maneuvers are intended to detect effusion and not Hoffa-synovitis, it is not surprising that diagnostic accuracy was marginally worse when the outcome included Hoffa-synovitis.

Discussion

Among early OA knees, diagnostic performance of physical exam maneuver findings, including the BS and PT, and patient-reported symptoms, including swelling and pain when straightening the knee fully, was modest for identification of medium/large effusion-synovitis when the exam maneuvers and symptoms were evaluated individually. Assessment of these symptoms individually had greater sensitivity than BS and PT, and only modestly lower specificity compared to the BS, with comparable PPVs, roughly double the prevalence in early OA knees. Combining information from the physical exam and reported symptoms achieved some improvement in the ability to rule in and rule out medium/large effusion-synovitis, albeit not to the extent desired for clinical diagnostic purposes. Among late-stage OA knees, physical exam maneuvers and symptom information had little utility in ruling in and out medium/large effusion-synovitis, in the context of a much higher prevalence.

In the early OA sample, among participants with medium/large effusion-synovitis, 81% had at least one symptom or positive exam finding; thus, combined physical exam and symptom assessment provides the most sensitive approach for identification of knees with effusion-synovitis during an early OA stage of disease. Among participants without medium/large effusion-synovitis, 97.9% were negative for both BS and PT, predominately reflecting the higher specificity of PT findings (95.8%) compared to BS (87.6%). However, only 2.6% of the sample was positive for BS and PT simultaneously, and 5.1% for PT, limiting the utility of this maneuver given how infrequently it yields a positive finding. Participant report of both knee symptoms, swelling and pain when straightening the knee fully, yielded the highest probability of effusion-synovitis (50.0%), followed by the presence of at least one examination finding and at least one symptom (48.6%), among the early OA sample with a prevalence of 16.2%. Thus, report of either both symptoms, or at least one positive exam finding and at least one symptom, could be used to identify participants at marked increased risk of effusion-synovitis during an early stage of disease, either for screening purposes in clinical evaluation, or for enrichment of a study sample for an inflammatory phenotype; though the probability is not sufficiently high for diagnostic purposes. Participants who reported no symptoms and had no positive exam findings had a 94.4% probability of no medium/large effusion-synovitis, nearly ruling out this MRI finding in early OA knees.

In the analysis of late-stage OA knees, the confidence interval for the PPV of the exam maneuvers and symptoms included the estimated prevalence of medium/large effusion-synovitis in the sample, 53.8%, and thus we do not have strong evidence that selecting a knee based on a positive exam finding or participant-reported symptom would increase the probability of an inflammatory phenotype beyond drawing a knee at random with late-stage disease. The most notable finding was a PPV of 68.9% for knees with a simultaneous positive exam finding and at least one symptom. Further, the LR+ values in the analysis of late-stage OA knees were much closer to one.

Physical examination maneuvers have been shown to have modest accuracy for detecting knee inflammation[4–7,30–32]. Systematic reviews of the reliability and performance characteristics of physical examination maneuvers to detect knee disorders have also reported modest results[16,33–35]. Findings from earlier studies are difficult to interpret, as radiography, ultrasound, and intraoperative knee arthroscopy were used as the standard to evaluate the performance of physical examination findings to detect effusion, rather than the gold standard imaging method of MRI. Among patients with traumatic knee injuries, the combination of patient-reported knee swelling and the PT improved the PPV to detect moderate/severe knee effusions on non-CE MRI (i.e., 0.62) compared to either alone (0.40 and 0.43, respectively)[12]. A recent study based on a different subset of OAI participants compared the same physical examination maneuvers with effusion-synovitis on non-contrast MRI and found physical examination to be insensitive but highly specific, similar to our results[8]. The sample characteristics were more similar to our late-stage OA sample. The performance characteristics of the BS and the PT test were evaluated individually and not in combination, and patient-reported swelling was not considered in that study.

Evaluations of diagnostic yield based on patient-reported symptoms of swelling have been limited, with one study of symptomatic knees reporting poor sensitivity of knee swelling, tenderness, pain, and tenderness/pain based on radiographic evidence[32]. Another study reported a sensitivity of 42.5% and specificity of 72.5% for patient-reported swelling based on ultrasound findings[31]. However, radiographs are limited for imaging inflammation, and ultrasound is reliant on the expertise of the operator, making the results difficult to compare to the standard of MRI-detected knee inflammation. A recent study reported low sensitivity but high specificity and low PPV of patient-reported swelling for the detection of effusion-synovitis on non-contrast MRI[9].

To our knowledge, our study is the first to evaluate the individual performance as well as the combination of patient-reported symptoms of swelling and physical examination maneuvers for evidence of knee inflammation on high-resolution MRIs in individuals with early or late-stage OA. Our findings suggest the combination of physical examination maneuvers and patient-reported symptoms improve diagnostic accuracy, with obvious clinical relevance given routine evaluation of symptoms in concert with physical examination maneuvers in the clinic setting, providing a more complete picture of patient history and physical status.

Knee inflammation has been implicated in the development and progression of knee OA[36]. Multiple structural phenotypes of knee OA have been suggested, and inflammation may be a key mediator[22,37,38]. Detection of knee inflammation early in the disease course based on symptoms and physical examination has important clinical implications. Inflammation in early OA may be an important therapeutic target[39,40]. A recent review article described different inflammatory pathway targets in OA and highlighted promising results for potential disease-modifying therapies[41]. Early detection of inflammation associated with OA in a clinical setting would allow earlier intervention to prevent subsequent joint damage. Multiple clinical trials are currently investigating interventions that target inflammation in knee OA, and our findings suggest that a combination of either patient-reported swelling or pain with knee straightening and a positive BS or a PT could be a potentially inexpensive clinical screening method for knee inflammation. Knee ultrasound could also be used as a secondary tool to confirm the presence of inflammation, as it is widely available, and less costly than MRI.

There are a few limitations to our study. Non-physician trained examiners conducted the physical examinations, rather than providers with routine clinical experience. Experienced physicians may be more skilled in performing these exam maneuvers and identifying effusion with greater sensitivity and specificity. In addition, we did not assess intra- or inter-rater reliability within our study, though reliability of exam findings between observers varies considerably based on previous studies[4,5,31,32,35,42–45]. The OAI imaging protocol utilized non-contrast enhanced MRI, which cannot distinguish between effusion and synovitis, and thus the "gold standard" outcome in our analysis is necessarily a composite outcome, including both effusion and synovitis. Contrast-enhanced MRI is the true gold standard for detecting inflammation in knee OA, though not typically implemented in large observational studies or clinical trials. Use of contrast enhanced MRI would facilitate visualization of synovial fluid vs true synovitis, and thus would permit analyses of separate outcomes for effusion and synovitis. Since the physical exam maneuvers are used to detect fluid, an analysis of effusion only might yield higher estimates of diagnostic performance. Analysis of synovitis only may produce lower estimates of performance because the exam procedures are designed to detect excess synovial fluid. In addition, the BS may be falsely negative when there is a tense synovial effusion that does not permit detection of a bulge. Whether the patient-reported symptoms that we considered are more indicative of effusion or synovitis is unknown. The OAI questionnaires did not include any questions about redness or warmth, other cardinal signs of knee inflammation. The patient-reported symptom of pain with knee straightening could be present due to soft tissue problems other than knee effusion. Finally, the two participant samples were not community-based, nor random, limiting generalizability, as all participants had either early OA, defined by radiography, or late stage OA in the years prior knee replacement. Our samples, however, span the wide spectrum of disease severity of knee OA.

Conclusion

The modest diagnostic performance of physical exam maneuvers and patient-reported symptoms of swelling limits enthusiasm for exclusive reliance on individual findings to detect knee inflammation in a clinical setting. However, symptoms in combination with examination findings may be optimized to identify patients at increased risk of effusion-synovitis who might benefit from imaging to detect inflammation, as well as part of eligibility criteria to provide an inexpensive approach to enriching clinical trial participation for knees with an inflammatory phenotype.

Contributions

Conception and design (CKK), Analysis and interpretation of the data (all authors), Drafting of the article (AB, ELA, CKK) Critical revision of the article for important intellectual content (AB, ELA, FWR, AG, DJH, CKK), Final approval of the article (all authors), Provision of study materials or patients (CKK, FWR, AG), Statistical expertise (ELA, JW), Obtaining funding (CKK, DJH, FWR, AG), Administrative, technical, or logistical support (CKK), Collection and assembly of data (CKK, FWR, AG, DJH)

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JW None declared.

JT None declared.

FWR is CMO and Director of Research of Boston Core Imaging Lab, LLC.

AG is President of Boston Core Imaging Lab, LLC and provides consulting services to Sanofi, GE, Pfizer, AstraZeneca, OrthoTrophix, TissueGene and MerckSerono.

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Supplementary data

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