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The incident tibiofemoral osteoarthritis with rapid progression phenotype: development and validation of a prognostic prediction rule

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SUMMARY

Objectives: No clinical prediction rules were found for estimating the likelihood of developing incident radiographic tibiofemoral osteoarthritis (OA) with rapid progression. Such a tool would enhance prognostic capability for clinicians and researchers.

Design: We used two longitudinal datasets to independently derive (Multicenter Osteoarthritis Study) and validate (Osteoarthritis Initiative) a prognostic clinical prediction rule for estimating the probability of incident rapidly progressing radiographic knee OA in the following 4–5 years. Eligible subjects had at least one knee with a Kellgren and Lawrence (K&L) graded tibiofemoral joint of 0 or 1. Several potential risk factors were examined including obesity, age, knee alignment, frequent knee symptoms, contralateral knee OA and knee injury history. Multiple logistic regression was used to identify significant predictors and area under the receiver operating characteristic curve (AUC) was used to assess discrimination.

Results: A total of 1690 subjects participated in the derivation and 2422 subjects participated in the validation of the clinical prediction rule. The multivariable model displayed good discrimination with AUC of 0.79 in the derivation dataset and 0.81 in the validation dataset.

Conclusions: Persons with contralateral knee OA, a baseline index knee OA grade of 1, higher body mass index (BMI) and higher baseline Western Ontario and McMaster Universities arthritis index total scores were more likely to develop K&L grade of 3 or 4 within 5 years. Frequent knee symptoms at baseline were not a significant predictor. The prediction rule and nomogram can assist clinicians in estimating the probability of rapidly progressing radiographic knee OA and the nomogram can assist researchers conducting epidemiologic studies and clinical trials.

Knee osteoarthritis (OA) progresses in a heterogeneous way. Most patients gradually worsen over years or decades[1] but some demonstrate rapid disease progression[2,3]. Because of population heterogeneity in extent and rate of disease incidence and progression, strong emphasis has recently been placed on the identification of homogeneous phenotypes to guide prognosis and targeted treatment[4–7]. A European League Against Rheumatism (EULAR) committee has placed its highest priority on prognostic studies designed to identify phenotypes that show rapid OA progression[4]. The rationale for this recommendation was that this work could lead to randomized trials of new and potentially more effective interventions and it could lead to the development of clinical prediction tools that could assist clinicians.

Studies of prognostic models of incident knee OA are surprisingly scarce. We found only two studies that first developed a prediction model and then validated the model on an independent dataset[6,7]. Both studies were designed for the prediction of either incident radiographic[6,7] or symptomatic[7] tibiofemoral OA. We

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found no studies that developed and validated a prognostic prediction model for incident radiographic tibiofemoral OA with rapid progression. We define rapidly progressing radiographic tibiofemoral OA as knees with a baseline Kellgren and Lawrence (K&L) grade of 0 or 1 that progress to a K&L grade of 3 or 4 within 5 years.

The purpose of this study was to develop and validate a clinically useful and research appropriate prognostic clinical prediction rule for incident tibiofemoral joint radiographic OA with rapid progression. The prediction rule was developed using publically available Multicenter Osteoarthritis Study (MOST) data[8] and was validated using publically available Osteoarthritis Initiative (OAI) data[9]. To our knowledge, this is the first prognostic clinical prediction rule of incident knee OA with rapid progression.

Methods

We used the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) guidelines[10].

Data source for development cohort

Data collected for the MOST, a 7-year National Institutes of Health funded community-based cohort study of 3026 persons with tibiofemoral OA or at high risk for developing tibiofemoral OA were used to derive the clinical prediction rule[8]. Participants who did not have pre-existing tibiofemoral radiographic OA had one or more of the following: body mass index (BMI) indicating overweight or obesity, knee pain, or a history of knee injury or surgery. Subjects between the ages of 50 and 79 years were recruited from the communities surrounding two sites (University of Iowa, Iowa City, USA and the University of Alabama at Birmingham, Birmingham, Alabama, USA). The human subjects review boards of all involved sites reviewed and approved the study and all subjects provided written informed consent. Enrollment began in 2003 and ended in 2005 (see details at http://most.ucsf.edu/studyoverview.asp). Data were obtained via a public use agreement from the MOST investigators. Our focus in this study was on data obtained during the first 5 years.

Data source for the validation cohort

The OAI is a 9-year National Institutes of Health and privately funded cohort study of 4674 persons either with tibiofemoral OA or, much like MOST, at high risk of developing tibiofemoral OA[9]. The OAI data were used to validate the clinical prediction rule developed using the development cohort. Subjects between the ages of 45 and 79 years were recruited from communities surrounding the University of Maryland in Baltimore, Maryland, USA, the Ohio State University in Columbus, Ohio, USA, the University of Pittsburgh in Pittsburgh, Pennsylvania, USA and Memorial Hospital of Rhode Island, in Pawtucket, Rhode Island. Human subjects review boards of all sites approved the study and all subjects provided written informed consent. Enrollment began in 2004 and ended in 2006 (see details at http://www.oai.ucsf.edu/). Data were obtained via a public use agreement from the OAI investigators. Our focus was on data obtained during the first 4 years.

Participants

Because both OAI and MOST focused on OA incidence and progression, both datasets included persons with and without knee symptoms at baseline. We were interested in studying persons with painful knees as well as persons who did not have knee pain at the time of admission. Symptomatic persons are potential care seekers while persons with no pain but who are at risk for developing knee OA are relevant for studies of OA prevention and for epidemiologic studies of OA.

To be eligible, participants in both the development and validation cohorts had to have K&L grade[11] of either 0 or 1 in one or both knees at baseline. In addition, participants had to have follow-up radiographs. In the case of MOST, radiographs were obtained at 30- and 60-month follow-up visits and our interest was in whether K&L grade advanced from 0 or 1 to either grade 3 or 4 over the study period. Knees with K&L grade of 2 or greater at baseline were classified as having radiographic OA and were not considered for rapid progression. We included persons with bilateral rapid progression from K&L grade of 0 or 1 bilaterally to K&L grade of 3 or 4 ($n = 26$ in MOST, $n = 9$ in OAI). For OAI, radiographs were obtained yearly for the first 4 years of study and we identified persons with knee(s) that either did or did not progress from K&L of 0 or 1 to grade of 3 or 4 over the 4-year period. For both the OAI and MOST, if a knee progressed to a K&L grade of 3 or 4 prior to the 5-year follow-up, in the case of MOST, or the 4-year follow-up in OAI, the knee was coded as a case knee. If a knee radiograph indicated less than a K&L grade of 3 or 4 at the 60-month or 4-year follow-up and all prior follow-ups, the knee was coded as a control knee. If radiographic data at the final follow-up were missing and the knee had not progressed to K&L grade of 3 or 4 at a prior visit, the data were coded as missing for that knee.

Radiographs were obtained in both studies using a validated flexed knee protocol[12,13] and radiographs were read by highly experienced and reliable radiographic readers at a central site. An extensive adjudication process with rheumatologists or a musculoskeletal radiologist was used for K&L grades for all knees over all time periods. Test–retest reliability was substantial to almost perfect[14] with weighted κ coefficients for both K&L grades ranging from 0.70 to 0.80 for 300 randomly selected knee films[15]. Readers were blinded to clinical data and the baseline radiograph when reading the final follow-up radiograph. Intervention was not provided as part of either MOST or OAI.

Outcome

The outcome of interest was the presence or absence of knee-specific radiographic worsening from a K&L grade of 0 or 1 at baseline to a K&L grade of 3 or 4 over the study period. For MOST, this was a 5-year period and for the OAI, the time period of interest was 4 years. The time periods for the two datasets were different because OAI did not collect radiographic data at the 5-year time point.

Predictors

We selected candidate predictor variables based on prior published evidence suggesting a risk factor/prognostic role in knee OA incidence or progression[16–19]. For both the development and validation datasets these included the following person-level variables: age, sex, presence of OA in other joints, BMI, depressive symptoms, and the average Western Ontario and McMaster Universities arthritis index (WOMAC) total score of both knees. The WOMAC total score is the sum of the WOMAC Pain, Disability and Stiffness subscales for the Likert version 3.1. The psychometric properties of WOMAC have been studied extensively and found to be both reliable and valid[20]. The total possible score for WOMAC total is 96 with higher scores representing greater pain, stiffness, and loss of function. For knee-level variables, we used the following: presence of frequent knee symptoms (yes or no), presence of contralateral radiographic knee OA K&L grade of 2 or greater (yes or no), baseline K&L grade of either 0 or 1, prior knee surgery (yes or no), prior knee injury (yes or no) and a radiographic