

The Combination of an Inflammatory Peripheral Blood Transcriptome and Imaging Biomarkers Enhance Prediction of Radiographic Progression in Knee Osteoarthritis.

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Research article

Keywords: Osteoarthritis, radiographic progression, joint space narrowing, transcriptome biomarkers, bone marrow lesion, and magnet resonance imaging

Posted Date: February 13th, 2020

DOI: <https://doi.org/10.21203/rs.2.23422/v1>

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Version of Record: A version of this preprint was published on September 10th, 2020. See the published version at <https://doi.org/10.1186/s13075-020-02298-6>.

Abstract

Objective

Predictive biomarkers of progression in knee osteoarthritis are sought to enable clinical trials of structure modifying drugs. A peripheral blood leukocyte (PBL) inflammatory gene signature, MRI-based bone marrow lesions (BML) and meniscus extrusion scores), meniscal lesions, and osteophytes on x-ray each have been shown separately to predict radiographic joint space narrowing (JSN) in subjects with symptomatic knee osteoarthritis (SKOA). In these studies, we determined whether the combination of the PBL transcriptome and these imaging findings at baseline enhanced the prognostic value of either alone.

Methods

An inflammatory PBL transcriptome (increased mRNA for IL-1 β , TNF α , and COX-2), routine radiographs, and 3T knee MRI were assessed in two independent populations with SKOA: an NYU cohort, and the Osteoarthritis Initiative (OAI). At baseline and 24 months, subjects underwent standardized fixed-flexion knee radiographs and knee MRI. Medial JSN (mJSN) was determined as the change in medial JSW. Progressors were defined by a mJSN cut-point (≥ 0.5 mm/24 months). Models were evaluated by odds ratios (OR) and area under the receiver operating characteristic curve (AUC).

Results

We validated our prior finding in these two independent (NYU and OAI) cohorts, individually and combined, that an inflammatory PBL transcriptome predicted radiographic progression of SKOA after adjustment for age, gender, and BMI. Similarly, the presence of baseline BML and meniscal lesions by MRI or semi-quantitative osteophyte score on x-ray each predicted radiographic medial JSN at 24 months. The combination of the PBL transcriptome and medial BML increased the AUC from 0.66 ($p=0.004$) to 0.75 ($p<0.0001$) and the odds ratio from 6.31 to 19.10 ($p<0.0001$) in the combined cohort of 473 subjects. The addition of osteophyte score to BML and PBL transcriptome further increased the predictive value of any single biomarker. A causal analysis demonstrated that the PBL transcriptome and BML independently influenced mJSN.

Conclusion

The use of the PBL transcriptome together with imaging biomarkers as combinatorial predictive biomarkers, markedly enhances the identification of radiographic progressors. The identification of the SKOA population at risk for progression will help in the future design of disease-modifying OA drug trials and personalized medicine strategies.

Introduction

Osteoarthritis (OA) is a leading cause of pain and morbidity globally, with increasing incidence and prevalence as the population ages (1). OA is characterized by progressive and often relatively slow deleterious alteration of joint tissues, including cartilage, bone, and synovium (2–7). Yet, no approved disease-modifying OA drugs (DMOADs) exist that slow progression of the disease. Radiographic progression of knee OA in unselected populations, measured as joint space narrowing (JSN), is low – approximately 0.1–0.15 mm/year (8–10). However, in such studies, as many as 30–40 percent of the study population shows no evidence of JSN over 1–2 years, which presents a significant obstacle to DMOAD development (11–15). To address this challenge, researchers have turned to identify baseline imaging and blood-based prognostic biomarkers that can differentiate progressors from non-progressors among patients with symptomatic knee OA (SKOA).

We have previously shown that increased peripheral blood leukocyte (PBL) gene expression of inflammatory proteins IL-1 β , TNF- α , and COX-2 (inflammatory PBL transcriptome) was associated with radiographic progression of knee OA at 24

months (15–19). Similarly, separate studies indicate that the presence of bone marrow lesions (BML) on MRI is an imaging biomarker that identifies patients at higher risk for progression (20–22). Although each of these biomarkers has demonstrated individual utility, no studies have focused on whether a combination of inflammatory and imaging biomarkers improves prediction of radiographic progression more than a single biomarker alone (23–27). Maximizing the predictive value of baseline biomarkers will enable the powering and reduce the cost of future DMOAD studies (28).

The analyses reported here represent an extension of our existing cohort to 243 patients from a previous study of 111 patients, as well as an analysis of 204 SKOA patients selected from the OA Initiative (OAI). We determined the prognostic utility of the baseline PBL transcriptome, and MRI images, alone and in combination, as predictive biomarkers of SKOA radiographic progression. Additionally, we employed predictive multivariable models of a dichotomized outcome and used the area under the receiver operating characteristic curves (AUCs) to assess the predictive performance of baseline biomarkers to determine those most predictive of 24-month radiographic JSN. Our main aim was to identify baseline combinatorial biomarker(s) to predict and identification of patients at risk for “fast progression” of radiographic SKOA.

Patients And Methods

Patient population

NYU cohort. Based on a priori knowledge, we expect a minimum of 30% of participants to progress (defined as JSN ≥ 0.5 mm/24 months), and a minimum of 30% to show no evidence of progression (JSN =0mm/24 months). Therefore, we recruited 132 additional patients to our prior cohort of 111 patients with SKOA (n=243) who completed a 24-month NIH-funded prospective study evaluating biomarkers in OA (11, 12) (Figure 1), satisfying a power analysis to detect an effect size of 0.3 for biomarkers at significance level of 0.05 and power of 0.85.

NYU Cohort Inclusion and Exclusion Criteria: As part of an NIH-funded study, we recruited and followed for 24 months SKOA patients who met American College of Rheumatology (ACR) knee OA radiographic criteria [Kellgren-Lawrence (KL) grade ≥ 1] and clinical symptomatic criteria with at least 3 of the following: age >50 years, stiffness <30 min, crepitus, bony tenderness, bony enlargement, no palpable warmth (25). Patients having any of the following were excluded: any other form of arthritis (including rheumatoid arthritis, spondyloarthritis, active crystal arthropathy); body mass index (BMI) ≥ 33 ; any disorder requiring the use of systemic corticosteroids within 1 week of screening, history of bilateral knee replacements; major co-morbidities including diabetes mellitus, non-cutaneous cancer within 5 years of screening, chronic hepatic or renal disease, chronic infectious disease, congestive heart failure; and hyaluronan and/or corticosteroid injections to the affected knee within 3 months of screening. Some exclusion criteria, such as the BMI cutoff, were chosen to mitigate potential effects of the covariate on inflammatory peripheral blood leukocyte (PBL) transcriptome markers, which were investigated as a separate aim of this study and reported upon elsewhere (17). The Institutional Review Board at NYU Medical Center approved the protocol. Informed consent was obtained from all subjects.

Clinical assessments. All subjects had completed the Visual Analog Scale (VAS) and WOMAC pain assessments at baseline and every 6 months for the duration of the study. Pain questions were specific to the more painful knee (signal knee). Subjects also had a physical exam by a study physician at baseline and after 24 months.

NYU Imaging: Radiograph and MRI acquisition and scoring

Knee radiographs. Subjects underwent standardized weight-bearing fixed-flexion posteroanterior knee radiographs using the SynaFlexer™ X-ray positioning frame (Synarc) at baseline and 24 months as described previously (16, 29). The radiographic beam angle was optimized for the medial joint space compartment. Radiographic readings were done separately by two musculoskeletal radiologists (LR, JB) blinded to patient demographics, clinical information, and MRI readings. X-rays were scored for KL grade 0-4 (30), and medial and lateral joint space width (JSW) measured at the mid-portion of the joint space via electronic calipers. Joint space narrowing (JSN) was calculated as the change in JSW, in

millimeters, from baseline to 24-month follow up. Disagreements between the two readers were resolved by consensus. Cohen's kappa coefficient for interrater agreement on KL grades was 0.85 and 0.77 for the right knee and left knee, respectively, and kappas for JSW were ≥ 0.93 for medial compartments of both the right and left knees. Based on the high inter-reader correlations, a single reader (LR) was employed for the 24-month follow up. Osteophyte scoring - both medial and lateral osteophytes in tibial and femoral regions scored semi-quantitatively (0-3) [0= absent, 1-mild, 2-moderate, and 3= severe]. Since the majority of both the NYU and OAI subjects (approximately 80%) had medial compartment disease, we restricted our analysis to medial radiographic JSN progressors.

NYU Knee MR imaging protocol. Of the 243 subjects enrolled, only 111 subjects had MR imaging performed [on a 3.0T clinical scanner (Magnetom Tim Trio; Siemens Medical Solutions, Erlangen, Germany) using an eight-channel transmit-receive phased-array knee coil (In vivo Corporation, FL)]. The knee imaging protocol consisted of a sagittal 3D-high resolution T1-weighted-fast low angle shot (FLASH) sequence with selective water excitation (TR/TE = 25/4ms; flip angle = 25; FOV = 15x15 cm; slice thickness = 1.5 mm; matrix = 512x384; receiver bandwidth = 200Hz/pixel) as well as sagittal T2-weighted fat-saturated spin echo (TR/TE = 4000/75 ms; FOV = 15x15 cm; slice thickness = 3 mm; matrix = 256x128; receiver bandwidth = 130Hz/pixel).

NYU Knee MR assessments: WOMS scoring. A musculoskeletal radiologist (GC), blinded to the clinical and radiographic information, but not blinded to acquisition time point, performed Whole-organ Magnetic Resonance Imaging Score (WORMS) scoring on sagittal T2-weighted fat-saturated images and sagittal T1-weighted 3-D spoiled gradient-echo images (31). Specifically, cartilage morphology (score of 0-6) and subarticular bone marrow lesions (BML, a score of 0-3) were scored within the anterior, central, and posterior regions of the medial and lateral tibial plateaus; central and posterior regions of the medial and lateral femoral condyles were also scored. Medial and lateral meniscal morphology (score of 0-4) were also evaluated. Inter-rater reliability was assessed by scoring 10 subjects in two separate sessions, one week apart. Paired t-tests, applied for assessing differences for cartilage, BML and meniscus readings (p-values 0.354, 0.797 and 0.766 for cartilage, BML and meniscus readings, respectively), showed that there were no significant differences, which verified reading reliability of our data. Cartilage medial scores were calculated as the sum of the medial femur central, medial femur posterior, medial tibia anterior, medial tibia central and medial tibia posterior regions. Cartilage lateral scores were calculated as the sum of lateral femur central, lateral femur posterior, lateral tibia anterior, lateral tibia central, and lateral tibia posterior regions. Overall, cartilage scores were calculated by summing lateral and medial cartilage scores. BML medial scores were calculated as the sum of the medial femur central, medial femur posterior, medial tibia anterior, medial tibia central and medial tibia posterior regions. BML lateral scores were calculated as the sum of lateral femur central, lateral femur posterior, lateral tibia anterior, lateral tibia central, and lateral tibia posterior regions. Overall, BML scores were calculated by summing lateral and medial BML scores.

The OAI Cohort. The OAI is a multi-center, longitudinal, prospective observational study of knee OA. The main goal of the OAI is to develop a public domain research resource to facilitate the scientific evaluation of biomarkers for knee OA as potential surrogate endpoints for disease onset and progression. Participants were selected from the [Osteoarthritis Initiative \(OAI; http://www.oai.ucsf.edu/](http://www.oai.ucsf.edu/)), a longitudinal cohort of 4,796 participants with clinical, radiological, biochemical, and other data collected at baseline and annual follow-up visits. OAI recruited participants with SKOA, and also those with no OA but considered at high risk of incident OA. We selected 204 individuals with body mass index (BMI) ≤ 33 , and Kellgren-Lawrence (KL) score 2 or 3 in the signal knee and for whom we had high quality radiographs (32, 33) (Figure 1). Clinical, radiographic, and MRI data were obtained from the OAI database (<https://data-archive.nimh.nih.gov/oai>). MRI images. MRI images were scored for BMLs using the semi-quantitative (SQ) (MRI Osteoarthritis Knee Score) MOAKS system available at the OAI site. For each sub-region, MOAKS scores three features using an ordinal score for size, number of BMLs and percentage of lesion that is a BML. The OAI dataset includes both MRI and radiographic images. Baseline clinical data, MRI BML scores, radiographs (baseline and 24 months) and buffy coat samples for transcriptome studies were obtained.

OAI cohort: High Quality OAI (HQ-OAI) Radiographs. The OAI imaging acquisition techniques and reading protocols are publicly available at <http://oai.epi-ucsf.org/datarelease>. Baseline OA severity was assessed on knee radiographs centrally read and graded according to the Kellgren–Lawrence (KL) system (30). Briefly, bilateral posteroanterior fixed-flexion weight-bearing radiographic views were obtained using a SynaFlexer™ frame (Synarc, Newark, CA, USA). The detailed Radiographic Procedure Manual is available online (<https://oai.epiucsf.org/datarelease/operationsManuals/RadiographicManual.pdf>). We selected a cohort of 443 cases, whose knee radiographs had high quality MTP alignment (defined as the inter-margin distance (IMD) of ≤ 1.70 mm at baseline and 24-month films (32). Furthermore, from this high quality sub-cohort, we have selected patients whose BMI is < 33 and signal knee (painful knee) with KL 2 or 3 were selected for this study (Figure 1).

MR image acquisition and quantitative measures. Non-contrast MRIs were obtained on 3T Trio systems (Siemens Healthcare, Erlangen, Germany), and the complete pulse sequence protocol and sequence parameters have been described previously (34). **BML MOAKS Score:** MRI BML scores available for all the subjects for whom transcriptome data available were downloaded from the OAI site. Briefly, BML was scored using the semi-quantitative MRI Osteoarthritis Knee Score (MOAKS) system, which is available at the OAI site (35). For each sub-region, MOAKS scores three features using an ordinal score for size, number of BMLs, and percentage of lesion that is a BML. The utilization of study protocol and biospecimens were reviewed and approved by the NYU School of Medicine IRB.

Radiographic progression: For the medial JSN outcome variable, our definition of radiographic progression was similar to the case definitions described previously based on previously published reports (8, 10, 27). SKOA patients who had narrowing in the medial tibiofemoral compartment by at least 0.5 mm over 24 months from baseline in the signal knee. We defined non-progressors or no progression as no increase, defined as JSN ≤ 0.0 mm over 24 months.

Sample collection and assessment

PBL isolation and inflammatory gene expression. NYU cohort: at the time of baseline knee radiographs, non-fasting blood samples were collected in pyrogen-free heparinized tubes for PBL isolation using the Ficoll-Hypaque density gradient centrifugation. Total RNA was isolated from PBLs and from citrate buffy coats (OAI cohort) using the Qiagen RNeasy Kit (Qiagen) as described previously (15, 17). For both NYU and OAI studies, relative expression of inflammatory mRNA expression in PBLs was determined using Predesigned TaqMan primer sets (IL1B – Hs00174097_m1; TNFA – Hs00174128_m1; PTGS2 (COX-2) – Hs00153133_m1) (Applied Biosystems). qPCR was performed as previously described (15), normalized against housekeeping genes GAPDH and 18S, and fold change was calculated using the delta Ct method (36). For the OAI study, the relative fold-change data were calculated against super-control (n=100) obtained from OAI biorepository who did not develop knee OA over 8 years of follow up and the qPCR obtained CT values of each target(s) including the housekeeping genes were shared with the OAI biorepository team for de-identification and the following association studies.

OAI MRI BML Scores. BMLs were scored using the MRI OA Knee Score (MOAKS) system available at the OAI site (35). The OAI dataset includes both MRI and radiographic images, including osteophytes.

Statistical methods. The relationships between baseline clinical, demographic, and imaging variables, including Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, visual analog scale (VAS) pain, JSW, osteophytes, MRI-determined cartilage and BML scores, age, sex and BMI were determined by Spearman's correlation. Associations between variables were assessed by partial correlations controlling for age, sex, and BMI. Receiver operating characteristic (ROC) curves were constructed, and area under the curve (AUC) computed (AUC ranges from 0 to 1, with 1 indicating perfect predictivity and 0.5 indicating random guess) to determine the predictive power of MRI and/or PBL transcriptome biomarkers for progression (37). Logistic regression models were fitted with 10-fold cross-validation and repeated 100 times. AUC values were compared against random models for significance using DeLong's test (38). False discovery rate (FDR) was used to adjust the p values for multivariate comparison (39). To evaluate whether medial BML as an additional

predictor improved the regression model, we used 2 methods: 1) Delong’s test comparing the AUCs from the model with biomarkers plus medial BML against the model with biomarkers alone, and 2) ANOVA comparing linear regression models of JSN with biomarkers plus medial BML versus biomarkers alone.

Causal graph analysis was performed, for which we used the FCI algorithm in the TETRAD software package ([http://www.phil.cmu.edu/projects/tetrad/version 4.3.10-7](http://www.phil.cmu.edu/projects/tetrad/version%204.3.10-7)). This method is capable of discovering a causal graph that most closely resembles the data distribution (9). Independence testing was based on Fisher’s Z test, with the significance level set to 0.10. No data manipulation of any kind (e.g., transformation, imputation, thresholding) was applied; therefore, these analyses were not biased toward particular causal hypotheses.

Results

An inflammatory *PBL transcriptome* predicts fast radiographic progressors in both the NYU and OAI cohort. We recruited a total of 243 SKOA patients, followed in the clinics of NYU and analyzed the inflammatory PBL transcriptome as a predictive biomarker of radiographic progression. The baseline demographic and clinical characteristics of these subjects are summarized in Table 1. Of the 243 patients in the NYU cohort, 30 percent exhibited ≥ 0.5 mm mJSN at 24 months in the signal knee and were designated “fast-progressors” (8, 10, 40). PBL mRNA expression of IL-1 β , TNF α , and COX-2 at baseline significantly predicted fast radiographic progressors with AUCs that ranged from 0.62 to 0.68 ($p < 0.003$ to < 0.0001) (Table 2).

Table 1
NYU Cohort SKOA subjects (N = 243) baseline demographics and OA features.

Variable	Value
Age (years)	60.1 (10.6)
Sex (%):	
Male	33.30%
Female	66.70%
BMI (kg/m ²)	26.7 (3.6)
VAS (0-100)	42.3 (29.9)
WOMAC (0-100)	36.6 (24.7)
Joint space width (mm)	3.65 (1.34)
MRI (n = 111):	
Mean medial cartilage WORMS score (0–30)	14.9 (8.3)
Mean medial BML WORMS score (0–15)	1.1 (1.9)
Data shown are the mean (SD), total number or percent affected, as indicated. SKOA = symptomatic knee OA; BMI = body mass index; VAS = Visual Analog Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; WORMS = Whole-organ Magnetic Resonance Imaging Score; BML = Bone Marrow Lesion	

Table 2

The area under the receiver operating characteristic curves (AUC) of PBL transcriptome biomarkers to radiographic fast progressors of JSN (> 0.5 mm) at 24 months in patients with SKOA in NYU extended (n = 243) and OAI (n = 204) cohorts.

Progressors (JSN > 0.5 mm) vs. non- progressors (JSN ≤ 0 mm)	AUC (CI)	P value
NYU Cohort (n = 243)		
IL-1 β	0.62 (0.53–0.70)	0.003
COX-2	0.68 (0.60–0.75)	< 0.0001
TNF α	0.66 (0.57–0.74)	< 0.0001
IL-1 β + TNF α + COX-2	0.60 (0.52–0.69)	0.007
IL-1 β + TNF α + COX-2 + Age + Sex + BMI	0.66 (0.58–0.74)	< 0.0001
OAI Cohort (n = 204)		
IL-1 β	0.75 (0.66–0.85)	< 0.0001
COX-2	0.65 (0.54–0.75)	0.003
TNF α	0.70 (0.60–0.81)	< 0.0001
IL-1 β + TNF α + COX-2	0.69 (0.59–0.79)	< 0.0001
IL-1 β + TNF α + COX-2 + Age + Sex + BMI	0.59 (0.48–0.70)	0.0051
NYU + OAI combined Cohort (n = 447)		
IL-1 β	0.66 (0.60–0.72)	< 0.0001
COX-2	0.66 (0.59–0.72)	< 0.0001
TNF α	0.67 (0.60–0.73)	< 0.0001
IL-1 β + TNF α + COX-2	0.63 (0.57–0.70)	< 0.0001
IL-1 β + TNF α + COX-2 + Age + Sex + BMI	0.61 (0.54–0.68)	0.0006
JSN = joint space narrowing; SKOA = symptomatic knee OA; AUC = Area under the (receiver operating characteristic) curve; All comparisons are versus non-progressors (JSN ≤ 0 mm). NYU cohort: non-progressors (n = 115) and fast progressors (n = 72); OAI cohort: non-progressors (n = 76) and fast progressors (n = 44).		

To replicate these NYU Cohort PBL transcriptomic studies in an independent population, we next examined radiographic progression in an OAI Cohort (n = 204) of subjects with symptomatic knee osteoarthritis. “Fast progression” was observed in 22 percent of the OAI Cohort. Increased mRNA expression of IL-1 β , TNF α , and COX-2 significantly predicted JSN fast progressors (\geq 0.5 mm at two years) with AUCs that ranged from 0.65 to 0.75 ($p < 0.003$ to < 0.0001) (Table 2). In the combined NYU and OAI cohort of 447 subjects, the significance of an inflammatory PBL transcriptome was retained (Table 2) in predicting fast radiographic progressors (AUC 0.66 to 0.67 ($p < 0.001$)).

MRI cross-sectional imaging, radiographic, and symptom relationships. The association of baseline MRI-scored variables with clinical and radiographic features at baseline and 2 years is shown in Table 3. Baseline medial tibial central BML scores associated significantly, but modestly, with baseline WOMAC scores for pain ($r = 0.19$, $p = 0.048$) and 24-month VAS pain reports ($r = 0.20$, $p = 0.043$) (Table 3). Additionally, medial tibial central BML associated moderately with baseline KL scores and associated inversely with baseline JSW (Table 3, $r = 0.21$, $p < 0.01$; $r = -0.22$, $p = 0.018$, respectively). Cartilage scores in all WOMMS medial subregions, separately and/or summed, were also associated with baseline KL scores (r values ranging from 0.27 to 0.34 depending on the specific subregion, all p values < 0.01 ; Table 3). Similarly, cartilage

scores in nearly all medial subregions were inversely associated with baseline JSW (r values ranging from - 0.27 to -0.33, all p values < 0.01). Meniscus overall readings were also associated with baseline WOMAC pain and associated inversely with mJSW at 24 months (r=-0.34, p < 0.01).

Table 3

Association of baseline MRI-scored medial WOMMS variables with clinical and radiographic features at baseline and 24 months – NYU Cohort (n = 111).

	Baseline WOMAC pain	Baseline VAS pain	24 Month WOMAC pain	24 Month VAS pain	Baseline Signal KL	24 Month Signal KL	Delta Signal KL	Baseline Medial JSW	24 Month Medial JSW	Medial JSN
Cartilage Overall	0.09 (0.34)	0.01 (0.94)	0.07 (0.45)	0.10 (0.29)	0.33 (< 0.01)	0.44 (0.01)	0.20 (0.03)	-0.28 (< 0.01)	-0.34 (0.01)	0.13 (0.15)
Cartilage Medial Overall	0.15 (0.12)	0.12 (0.22)	0.09 (0.34)	0.09 (0.38)	0.36 (< 0.01)	0.44 (0.01)	0.14 (0.15)	-0.32 (< 0.01)	-0.41 (0.01)	0.10 (0.29)
BML Overall	0.07 (0.45)	0.09 (0.36)	0.04 (0.66)	0.10 (0.28)	0.31 (< 0.01)	0.35 (0.01)	0.05 (0.58)	-0.13 (0.16)	-0.22 (0.02)	0.14 (0.14)
BML Medial Overall	0.10 (0.30)	0.13 (0.18)	0.04 (0.69)	0.07 (0.48)	0.31 (< 0.01)	0.32 (0.01)	-0.003 (0.98)	-0.17 (0.07)	-0.28 (0.01)	0.19 (0.05)
Meniscus Overall	0.20 (0.04)	0.15 (0.11)	0.08 (0.38)	0.13 (0.18)	0.30 (< 0.01)	0.41 (0.01)	0.16 (0.10)	-0.24 (0.01)	-0.34 (0.01)	0.23 (0.02)
Cartilage Medial Femur Central	0.13 (0.17)	0.15 (0.12)	0.02 (0.87)	0.01 (0.90)	0.27 (< 0.01)	0.36 (0.01)	0.16 (0.09)	-0.31 (< 0.01)	-0.40 (0.01)	0.08 (0.42)
Cartilage Medial Femur Posterior	0.12 (0.22)	0.08 (0.44)	0.15 (0.13)	0.12 (0.21)	0.34 (< 0.01)	0.42 (0.01)	0.13 (0.19)	-0.33 (< 0.01)	-0.35 (0.01)	0.04 (0.67)
Cartilage Medial Tibial Anterior	0.15 (0.13)	0.11 (0.28)	0.09 (0.42)	0.08 (0.44)	0.32 (< 0.01)	0.39 (0.01)	0.13 (0.16)	-0.27 (< 0.01)	-0.32 (0.01)	0.03 (0.78)
Cartilage Medial Tibial Central	0.13 (0.17)	0.17 (0.08)	0.11 (0.25)	0.12 (0.20)	0.29 (< 0.01)	0.37 (0.01)	0.15 (0.11)	-0.31 (< 0.01)	-0.41 (0.01)	0.12 (0.21)
Cartilage Medial Tibial Posterior	-0.04 (0.68)	-0.07 (0.50)	-0.09 (0.38)	-0.06 (0.53)	0.27 (< 0.01)	0.31 (0.01)	0.07 (0.48)	-0.08 (0.38)	-0.19 (0.05)	0.05 (0.61)
BML Medial Femur Central	0.03 (0.77)	0.09 (0.34)	-0.05 (0.63)	0.03 (0.74)	0.17 (0.08)	0.22 (0.02)	0.07 (0.45)	-0.10 (0.28)	-0.21 (0.03)	0.10 (0.30)

Data shown are Spearman correlation coefficients, adjusted for age, sex, and BMI. P-values for the correlations are in parentheses. Significant p-values are presented in bold font. WOMMS = Whole-organ Magnetic Resonance Imaging Score; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; VAS = Visual Analog Scale; KL = Kellgren-Lawrence grade; JSW = Joint space width; JSN = joint space narrowing; BML = Bone Marrow Lesion.

	Baseline WOMAC pain	Baseline VAS pain	24 Month WOMAC pain	24 Month VAS pain	Baseline Signal KL	24 Month Signal KL	Delta Signal KL	Baseline Medial JSW	24 Month Medial JSW	Medial JSN
BML Medial Femur Posterior	0.06 (0.53)	0.004 (0.96)	0.03 (0.79)	0.10 (0.28)	0.09 (0.35)	0.12 (0.22)	0.03 (0.75)	-0.05 (0.62)	-0.10 (0.29)	0.11 (0.24)
BML Medial Tibial Anterior	0.19 (0.05)	0.18 (0.07)	0.09 (0.38)	0.11 (0.28)	0.04 (0.65)	0.08 (0.43)	0.05 (0.64)	-0.05 (0.61)	-0.19 (0.05)	0.22 (0.02)
BML Medial Tibial Central	0.19 (0.05)	0.15 (0.12)	0.15 (0.13)	0.20 (0.04)	0.21 (0.03)	0.28 (0.01)	0.09 (0.35)	-0.22 (0.02)	-0.34 (0.01)	0.22 (0.02)
BML Medial Tibial Posterior	-0.04 (0.72)	0.02 (0.80)	-0.05 (0.61)	-0.06 (0.56)	0.11 (0.24)	0.13 (0.16)	0.04 (0.70)	-0.03 (0.73)	0.00 (0.97)	-0.01 (0.94)
<p>Data shown are Spearman correlation coefficients, adjusted for age, sex, and BMI. P-values for the correlations are in parentheses. Significant p-values are presented in bold font. WORMS = Whole-organ Magnetic Resonance Imaging Score; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; VAS = Visual Analog Scale; KL = Kellgren-Lawrence grade; JSW = Joint space width; JSN = joint space narrowing; BML = Bone Marrow Lesion.</p>										

Table 4

Mean cartilage and BML scores in 24-month JSN non-progressors compared to fast progressors in NYU (2A) and OAI (2B) SKOA.

Table 4A – NYU	Non-Progressors JSN 0 mm (n = 39) Mean (SD)	Fast Progressors JSN \geq 0.5 mm (n = 45) Mean (SD)	P- Value	FDR
Cartilage Medial Overall (0–30)	13.88 (8.61)	15.42 (8.71)	0.42	0.42
Cartilage Lateral Overall (0–30)	3.56 (6.62)	5.24 (7.89)	0.298	0.398
BML Medial Overall (0–15)	0.59 (1.14)	1.78 (2.22)	0.003	0.014
BML Lateral Overall (0–15)	0.33 (0.80)	0.16 (0.47)	0.214	0.398
Table 4B – OAI	Non-Progressors JSN 0 mm (n = 29) Mean (SD)	Fast Progressors JSN \geq 0.5 mm (n = 34) Mean (SD)	P- Value	FDR
Cartilage loss Medial (0–36)	4.21 (2.90)	7.09 (3.78)	0.006	0.014
Cartilage loss Lateral (0–36)	5.04 (4.09)	2.32 (2.80)	0.012	0.025
BML Medial Overall (0–36)	1.21 (1.82)	3.27 (2.31)	0.002	0.013
BML Lateral Overall (0–36)	2.23 (2.84)	0.98 (1.50)	0.072	0.102
Abbreviations: WORMS = Whole-organ Magnetic Resonance Imaging Score; BML = bone marrow lesion; JSN = joint space narrowing; FDR = false discovery rate. JSN values are expressed in mm as mean \pm standard deviation (SD). All comparisons are versus non-progressors (JSN \leq 0 mm). Significant p-values are represented in bold font.				

Baseline MRI medial BML (mBML) and meniscus scores predict the progression of radiographic findings. BML detected by MRI has been associated with radiographic progression of knee OA (20–22, 41). We analyzed MRI findings in our two OA cohorts to determine whether: 1) MRI findings predicted the subset of fast progressors (JSN > 0.5 mm). We note that in the NYU cohort, MRI was available for the initial 111 enrollees previously described (12). Consistent with prior literature, fast progressors (\geq 0.5 mm) in the NYU cohort had significantly higher baseline medial BML scores (1.78 ± 2.22) than non-progressors (0.59 ± 1.14 ; $p < 0.003$; Table 4A). Similarly, in the OAI cohort, medial BML scores were also higher in the fast-progressor cohort (1.21 vs. 3.27 ; $p < 0.002$).

In the OAI cohort, “Cartilage Loss Medial” was also associated with progression, though this was not observed in the NYU cohort (Table 4B). In the combined cohort, association of medial BML alone with mJSN is also shown in Table 5 (AUC = 0.69; 95%CI (0.60–0.79; $p < 0.0001$). The odds ratio (OR) for fast progression associated with medial BML was 2.51 (95% CI: 1.49–4.20; $p < 0.0001$) Table 6). In the NYU cohort, the MRI meniscus score correlated ($r = 0.23$; $p = 0.02$) with mJSN (Table 3), though AUC (0.056; $p = 0.178$) was modest and not significant in the dichotomized radiographic progression analysis (progressors vs. non-progressors). When meniscal findings were combined with BML, the AUC for either alone increased significantly to 0.76 ($p = 0.001$; Table 7).

Table 5

The area under the receiver operating characteristic curves (AUC) comparing baseline PBL transcriptome biomarkers, with and without medial BML, to predict 24-month fast radiographic knee OA progression in the combined NYU and OAI cohorts.

NYU + OAI Combined - Biomarkers			Biomarkers + Baseline Medial BML			
Fast Progressors (JSN > 0.5 mm) vs. Non-Progressors (JSN ≤ 0.0 mm)	AUC (95% CI)	Adjusted Pvalue for model	Fast Progressors (JSN > 0.5 mm) vs. Non-Progressors (JSN ≤ 0.0 mm)	AUC (95% CI)	Pvalue for model	P value for Model performance Increase
COX-2	0.69 0.60– 0.78	0.000	COX-2	0.76 0.68– 0.85	0.000	0.047
IL-1 β	0.70 0.62– 0.79	0.000	IL-1 β	0.75 0.66– 0.83	0.000	0.173
TNF α	0.36 0.27– 0.46	0.003	TNF α	0.66 0.56– 0.75	0.001	0.000
IL-1 β /COX-2/TNF α	0.66 0.56– 0.75	0.001	IL-1 β /COX-2/TNF α	0.75 0.67– 0.84	0.000	0.021
Baseline BML	0.69 0.60– 0.79	0.000	Baseline BML			
Medial osteophytes	0.57 0.47– 0.66	0.107	Medial osteophytes	0.69 0.60– 0.78	0.000	0.004
Lateral osteophytes	0.68 0.59– 0.78	0.000	Lateral osteophytes	0.75 0.66– 0.83	0.000	0.020
Osteophytes All	0.65 0.56– 0.75	0.002	Osteophytes All	0.73 0.65– 0.82	0.000	0.011
IL-1 β /COX-2/TNF α + Medial osteophytes	0.65 0.55– 0.74	0.002	IL-1 β /COX-2/TNF α + Medial osteophytes	0.75 0.67– 0.83	0.000	0.014
IL-1 β /COX-2/TNF α + Lateral osteophytes	0.75 0.66– 0.83	0.000	IL-1 β /COX-2/TNF α + Lateral osteophytes	0.80 0.72– 0.87	0.000	0.043
IL-1 β /COX-2/TNF α + All osteophytes	0.73 0.64– 0.81	0.000	IL-1 β /COX-2/TNF α + All osteophytes	0.78 0.70– 0.86	0.000	0.027
All markers	0.78 0.70– 0.86	0.000	All markers			

PBL = peripheral blood leukocyte; BML = Bone Marrow Lesion; JSN = joint space narrowing; COX-2 = cyclooxygenase-2; IL-1 β = interleukin-1 beta; TNF α = tumor necrosis factor alpha; 95% CI = 95% confidence intervals. All comparisons are versus non-progressors (JSN ≤ 0 mm). Significant p-values are represented in bold font. Total number of Progressors (n = 66) and Non-Progressors (n = 63) in the combined cohort.

Table 6

The odds ratios (OR) comparing baseline PBL transcriptome biomarkers and osteophytes with and without medial BML to predict 24-month fast radiographic knee OA progression in the combined NYU and OAI cohorts.

NYU+ OAI Combined - Biomarkers			Biomarkers + Baseline Medial BML			
Fast Progressors (JSN > 0.5 mm) vs. Non-Progressors (JSN ≤ 0.0 mm)	Odds Ratio (95% CI)	Adjusted P value for model	Fast Progressors (JSN > 0.5 mm) vs. Non-Progressors (JSN ≤ 0.0 mm)	Odds Ratio (95% CI)	Adjusted P value for model	P value for Model performance increase
COX-2	3.52 0.92–13.41	0.014	COX-2	8.75 1.39–54.93	0.000	0.000
IL-1 β	2.20 0.60–8.08	0.064	IL-1 β	4.83 0.84–27.53	0.000	0.000
TNF α	1.08 0.74–1.56	0.709	TNF α	3.18 1.21–8.30	0.000	0.000
IL-1 β /COX-2/TNF α	6.31 0.36–108.13	0.024	IL-1 β /COX-2/TNF α	19.10 0.56–646.14	0.000	0.000
Baseline BML	2.51 1.49–4.20	0.000	Baseline BML			
Medial osteophytes	1.68 0.75–3.76	0.190	Medial osteophytes	4.43 1.09–17.89	0.000	0.000
Lateral osteophytes	3.57 1.46–8.71	0.001	Lateral osteophytes	9.93 2.18–45.18	0.000	0.000
All osteophytes	4.51 0.66–30.65	0.005	All osteophytes	12.04 0.86–167.94	0.000	0.000
IL-1 β /COX-2/TNF α + Medial osteophytes	10.72 0.24–460.90	0.028	IL-1 β /COX-2/TNF α + Medial osteophytes	32.12 0.36–2816.68	0.000	0.000
IL-1 β /COX-2/TNF α + Lateral osteophytes	63.59 1.14–3542.23	0.000	IL-1 β /COX-2/TNF α + Lateral osteophytes	260.52 2.21–30579.34	0.000	0.000
IL-1 β /COX-2/TNF α + All osteophytes	71.11 0.41–12274.84	0.000	IL-1 β /COX-2/TNF α + All osteophytes	348.83 0.82–148158.88	0.000	0.000
All markers	348.83 0.82–148158.8	0.000	All markers	348.83 0.82–148158.8	0.000	NaN

PBL = peripheral blood leukocyte; BML = Bone Marrow Lesion; JSN = joint space narrowing; COX-2 = cyclooxygenase-2; IL-1 β = interleukin-1 beta; TNF α = tumor necrosis factor alpha; 95% CI = 95% confidence intervals. All comparisons are versus non-progressors (JSN ≤ 0 mm). Total number of Progressors (n = 66) and Non-Progressors (n = 63) in the combined cohort

Table 7

The area under the receiver operating characteristic curves (AUC) comparing baseline PBL transcriptome biomarkers, with and without medial BML, to predict 24-month fast radiographic knee OA progression in the NYU cohort (N = 111).

Biomarkers				Biomarkers + Baseline Medial BML				
Fast Progressors (JSN > 0.5 mm) vs. Non-Progressors (JSN ≤ 0.0 mm)	AUC	95% CI	Adjusted Pvalue for model	Fast Progressors (JSN > 0.5 mm) vs. Non-Progressors (JSN ≤ 0.0 mm)	AUC	95% CI	Adjusted Pvalue for model	Adjusted P value for Model performance Increase
COX-2	0.71	0.60–0.83	0.001	COX-2	0.79	0.69–0.89	0.000	0.107
IL-1 β	0.68	0.56–0.80	0.004	IL-1 β	0.75	0.65–0.86	0.000	0.172
TNF α	0.38	0.26–0.50	0.048	TNF α	0.61	0.49–0.74	0.036	0.050
IL-1 β /COX-2/TNF α	0.67	0.56–0.79	0.004	IL-1 β /COX-2/TNF α	0.78	0.68–0.88	0.000	0.082
Baseline BML	0.67	0.55–0.79	0.004	Baseline BML				
Osteophytes-medial	0.57	0.44–0.69	0.146	Osteophytes-medial	0.64	0.52–0.76	0.014	0.131
Osteophytes - lateral	0.61	0.48–0.73	0.069	Osteophytes - lateral	0.68	0.57–0.80	0.002	0.095
Osteophytes- All	0.56	0.44–0.69	0.160	Osteophytes - All	0.63	0.51–0.75	0.016	0.127
Meniscus-sum	0.56	0.43–0.68	0.178	Meniscus-sum	0.69	0.58–0.81	0.001	0.092
IL-1 β /COX-2/TNF α + Medial Osteophytes	0.68	0.57–0.80	0.003	IL-1 β /COX-2/TNF α + Medial Osteophytes	0.76	0.65–0.86	0.000	0.082
IL-1 β /COX-2/TNF α + Lateral Osteophytes	0.72	0.61–0.83	0.000	IL-1 β /COX-2/TNF α + Lateral Osteophytes	0.78	0.68–0.88	0.000	0.097
IL-1 β /COX-2/TNF α + All Osteophytes	0.70	0.58–0.81	0.002	IL-1 β /COX-2/TNF α + All Osteophytes	0.75	0.64–0.86	0.000	0.127
IL-1 β /COX-2/TNF α + Meniscus	0.73	0.62–0.84	0.000	IL-1 β /COX-2/TNF α + Meniscus	0.76	0.66–0.86	0.000	0.342

PBL = peripheral blood leukocyte; BML = Bone Marrow Lesion; JSN = joint space narrowing; COX-2 = cyclooxygenase-2; IL-1 β = interleukin-1 beta; TNF α = tumor necrosis factor alpha; 95% CI = 95% confidence intervals. All comparisons are versus non-progressors (JSN ≤ 0 mm). Total number of Progressors (n = 44) and Non-Progressors (n = 39).

Biomarkers				Biomarkers + Baseline Medial BML				
All markers	0.75	0.64– 0.86	0.000	All markers	0.75	0.64– 0.86	0.000	1.000
PBL = peripheral blood leukocyte; BML = Bone Marrow Lesion; JSN = joint space narrowing; COX-2 = cyclooxygenase-2; IL-1 β = interleukin-1 beta; TNF α = tumor necrosis factor alpha; 95% CI = 95% confidence intervals. All comparisons are versus non-progressors (JSN \leq 0 mm). Total number of Progressors (n = 44) and Non-Progressors (n = 39).								

Combinatorial biomarkers (medial BML scores and PBL transcriptome) enhance prediction of radiographic progression in the combined NYU and OAI cohorts. Having shown that an inflammatory *PBL transcriptome* and BML by MRI individually predicted radiographic progression in our cohorts, we next determined whether any combination of biomarkers had greater predictive value than a single biomarker alone in the combined cohort.

We first examined the predictive value of the combination of baseline medial BML scores and PBL inflammatory transcriptome markers by AUC analyses. The association of BML alone with fast progressors (JSN \geq 0.5 mm) in the combined cohort was AUC=0.69; (95%CI (0.60-0.79), $p < 0.0001$; Table 5). In each instance, the combination of medial BML and individual *PBL transcriptome* increased the predictive value of either biomarker alone. Specifically, the combination of medial BML and PBL COX-2 expression (AUC 0.76, $p < 0.0001$) yielded the maximal predictive power for fast progressors (Table 5). Additionally, the increased AUC model performance was significant for transcriptome (COX-2, IL1 β , TNF α) in combination with BML (Table 5) in predicting radiographic progression.

In addition to calculating the AUCs, we also determined the OR for progression for each biomarker, alone and in combination. As shown in Table 6, OR for baseline PBL COX-2 and IL-1 β predicting fast progressors (JSN \geq 0.5 mm) were 3.52 and 2.20 respectively, and a combination of all three PBL transcriptome biomarkers (IL-1 β + TNF α + COX-2) had an OR of 6.31. The addition of baseline medial BML to PBL IL-1 β , COX-2, and TNF α transcriptome markers increased the OR significantly to 19.10 ($p < 0.0001$).

Baseline radiographic osteophytes scores and progression of joint space narrowing. Since osteophytes have also been reported to associate with radiographic progression in knee OA (42-45), we added osteophyte assessment to our predictive models in the combined cohort. As shown in Table 6, higher medial and lateral osteophyte scores increased the OR for progression to 4.51 ($p < 0.005$). The combination of the PBL transcriptome and osteophytes increased the OR to 71.11 ($p < 0.0001$), while the combination of baseline BML, osteophytes, and transcriptome biomarkers further increased OR to 348.83 ($p < 0.0001$). Similarly, AUC analysis indicated that the predictive value of osteophytes alone significantly increased when combined with PBL transcriptome or BML by MRI (Table 5).

Causal graph analysis. To further explore interactions of baseline radiographic (osteophytes) MRI features (medial BML, cartilage, and meniscus), and PBL transcriptome biomarkers, we performed causal graph analysis to determine the inter-dependent pathways of these factors on continuous JSN over 24 months (Figure 2). Baseline PBL COX-2 gene expression and baseline medial BML each independently played a causal role or positively influenced JSN. However, the open circles adjacent to several predictors, including gender, age, BMI, and osteophytes, indicate that there may be hidden confounders, which may influence their relationships with JSN. These new data demonstrate that the PBL transcriptome COX-2 and medial BML, independently from other MRI or radiographic features, influence radiographic JSN progression.

Discussion

In the studies here reported, we analyzed two independent cohorts totaling 447 subjects with symptomatic knee OA to determine the prognostic value of baseline PBL transcriptome, semi-quantitative osteophyte score and MRI features, alone and in combination, as biomarkers of radiographic progression in SKOA. Several observations are noteworthy. First, in an expanded NYU Cohort and an independent OAI population, we validated our earlier finding that an inflammatory PBL

transcriptome is a predictive biomarker of OA radiographic progression, consistent with a state of chronic low-grade inflammation in those at risk for progression [15]. Second, consistent with prior literature, medial BML by MRI and osteophyte score by x-ray were associated with radiographic progression at 2 years. Third, and most importantly, we showed that the combinatorial biomarker of the PBL transcriptome, medial BML, and osteophyte scores markedly increased the predictive value over that of each biomarker alone.

In our analysis of the NYU cohort, we show that baseline medial tibial BMLs were moderately associated with WOMAC and VAS pain, consistent with most prior studies (46, 47). However, none of the MRI findings were predictive of worsening WOMAC or VAS pain at 2 years. In our study (adjusting for age, sex, and BMI) and in agreement with others (21, 48), we observed a strong inverse correlation of baseline medial BMLs with radiographic JSW and a positive correlation with increased JSN over 24 months (Table 3).

Causal analysis of our data indicates that PBL transcriptome biomarkers and BML are each independently associated with radiographic progression. Therefore, since these features appear to represent discrete pathogenic processes, it is not surprising that the combination of both genomic and MRI biomarkers significantly increases the prediction of radiographic progression. In addition, we show that the addition of osteophyte scores also enhanced the predictive value of the individual PBL and MRI biomarkers. To our knowledge, this is the first study that has shown the improved prognostic capability for knee OA progression based on a combination of MRI imaging (medial BML), genomic, and radiographic findings.

There have been other recent publications that show the predictive value of genomic or imaging biomarkers on progression. A recent FNIH (Foundation of the NIH) study as part of the OA biomarker consortium identified several promising candidates systemic biomarkers such as urine collagen (uCTXII and uCTX1a) as predictors of pain and structural worsening of OA (49). The final baseline model included uCTXII and sNTXI and had an AUC of 0.586. Similar to the unbiased causal analysis of various biomarkers (Fig. 2) in this study, Loeser and associates have also identified through in an unbiased machine learning approach also identified BML, osteophytes, and medial meniscal extrusion as potential biomarkers in identifying radiographic (> 0.7 mm at 48 months) and pain progressors in the OAI cohort (42). Dunn et al. have studied the peripheral blood methylation status in the radiographic progressors relative to non-progressors in a small cohort of OAI subjects. The epigenetics patterns in peripheral blood mononuclear cells had an AUC of 0.81 in predicting radiographic progressors (50).

What distinguishes our study here is the predictive value of combining genomic biomarkers of inflammation with imaging findings. The combination of biomarkers used together results in predictive values (AUC, odds ratios) for progression that exceeds those reported previously for biochemical or imaging alone. In contrast to traditional biochemical markers of cartilage turnover, these data highlight the importance of combining discrete pathogenic events in driving structural progression in OA.

What is the importance of these findings? In addition to shedding light on discrete pathogenic processes, the identification of biomarkers predictive of progression is of fundamental importance for the development of new treatment targets through increased efficiencies of trials of disease-modifying agents (49). There are many obstacles to structure modification studies in OA, including heterogeneity in etiology and the variability in the progression of the disease in clinical trial populations. In ours and prior studies, as many as 25–30% of knee OA patients will not progress over a 2-year study period, and as few as 25–30% will progress at a rate that exceeds 0.5 mm (11–15, 51). Therefore, in order to adequately power a clinical trial that demonstrates the efficacy of a structure modifying agent, a need exists to identify biomarkers that can identify a population at risk for disease progression. Therefore, prognostic biomarkers have been sought by industry, frustrated by the challenges of drug development in OA. To date, no single prognostic biomarker has been sufficient, and the predictive value of those described have been modest (e.g., OR of 1.2–1.4) (49). In our studies, we

show that the predictive value of an inflammatory PBL transcriptome alone is comparable to that of BML by MRI, with OR in the range of 2–4.

One of the limitations of these findings is that none of the biomarkers studied, alone or in combination, predicted symptomatic worsening at 2 years – a time frame chosen to represent a feasible time period for clinical trials. In part, this may be due to the limited period of observation, as compared, for example, to the 48 month period of follow-up in the FNIH study (42). Furthermore, BML and cartilage readings are semi-quantitative, and it is possible that with more advanced scoring systems, precise evaluation of BML and cartilage volume or size would further improve the progression prediction. Moreover, a poorly understood feature brought to light in the OAI studies, is that WOMAC scores do not deteriorate significantly among the subjects followed (42). The presumption remains that slowing structural progression at 2 years will prove to be a surrogate for improved function and decreased need for joint replacement at future time points after 2 years. This is a conundrum yet to be demonstrated, most recently in the FGF-18 trial, which resulted in an improvement in total femorotibial joint cartilage thickness after 2 years but no symptomatic relief (52). Ideally, however, future treatments will provide both symptomatic relief and attenuate disease progression.

Conclusions

In summary, we demonstrate that the combination of genomic (PBL transcriptome), MRI (BML) and radiographic (osteophyte score) biomarkers significantly enhance the predictive value of any individual biomarker in identifying knee OA patients at risk for radiographic progression. The use of predictive biomarkers to identify an OA population at risk for progression is needed for the future design of disease-modifying OA drug trials and personalized medicine strategies.

Abbreviations

OA
osteoarthritis
SKOA
symptomatic knee osteoarthritis
KL grade
Kellgren- Lawrence grade
JSW
Joint Space Width
JSN
Joint Space Narrowing
BML
Bone Marrow Lesion
PBL
Peripheral Blood Leukocyte Cells
IL-1 β
interleukin 1 beta
TNF α
tumor necrosis factor alpha
COX-2
cyclooxygenase 2
WOMAC
Western Ontario and McMaster Universities Osteoarthritis index
VAS
Visual Scale Analog

WORMS

Whole-Organ Magnetic Resonance Imaging Score

BMI

Body Mass Index

AUC

Area Under the receiver operating characteristic Curves

OR

Odds Ratio

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE:

The current study was performed in accordance with the ethical standards of the Helsinki Declaration, and studies (#i9018 and i12-03682) were approved by the Institutional Review Board (IRB) of NYU School of Medicine. All patients provided written, informed consent to participate in the study.

CONSENT FOR PUBLICATION

Not applicable

AVAILABILITY OF DATA AND MATERIALS

Please contact author for data requests. OAI data are available from OAI.epi-uscf.org

COMPETING INTERESTS

Drs. Abramson and Attur have patent application (Patent number: 9804175) for the use of inflammatory transcriptome biomarkers to identifying patients at risk for knee OA progression.

FUNDING

The NYU and OAI cohort bio-specimens were collected as part of an NIH-funded study (National Institute of Arthritis and Musculoskeletal and Skin Diseases grant AR052873 to Dr. Abramson).

This work was also supported by the generous contributions of the William and Lynda Steere Foundation.

This manuscript was prepared using an OAI public use data set and does not necessarily reflect the opinions or views of the OAI investigators, the NIH, or the private funding partners.

ACKNOWLEDGEMENTS

The NYU and OAI cohort bio-specimens were collected as part of an NIH-funded study (National Institute of Arthritis and Musculoskeletal and Skin Diseases grant AR052873 to Dr. Abramson). This work was also supported by the generous contributions of the William and Lynda Steere Foundation. The authors would like to thank the staff and participants of the NYULOH Osteoarthritis Biomarkers Study.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Drs. Attur, Krasnokutsky, Zhou, and Abramson had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

Study conception and design. Attur, Krasnokutsky, Samuels, Rosenthal, and Abramson.

Acquisition of data. Attur, Krasnokutsky, Zhou, Samuels, Chang, Bencardino, Rosenthal, Rybak, Huebner, and Kraus.

Analysis and interpretation of data. Attur, Krasnokutsky, Zhou, Samuels, Chang, Bencardino, Rosenthal, Rybak, Huebner, Kraus, and Abramson.

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Figures

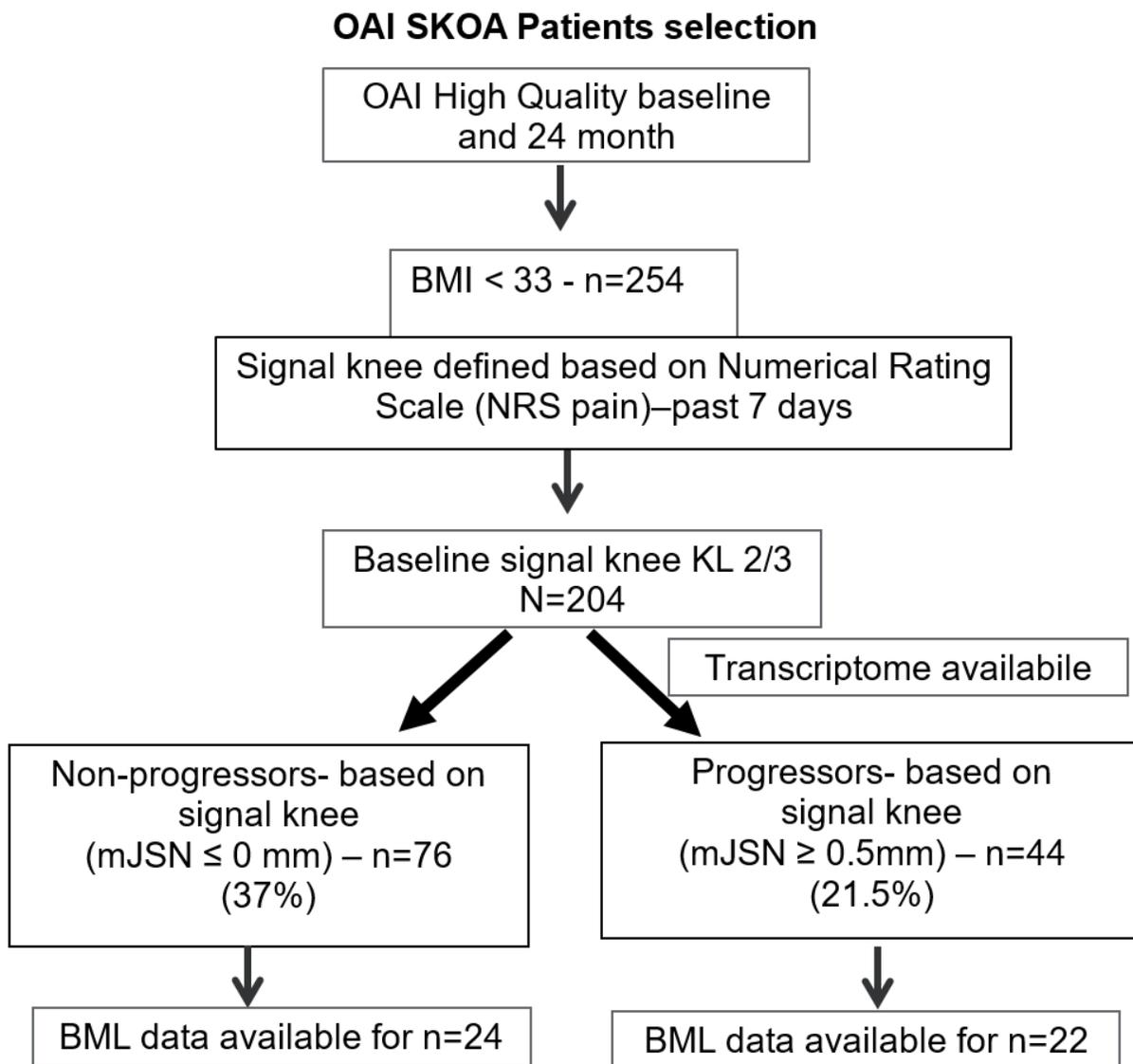


Figure 1

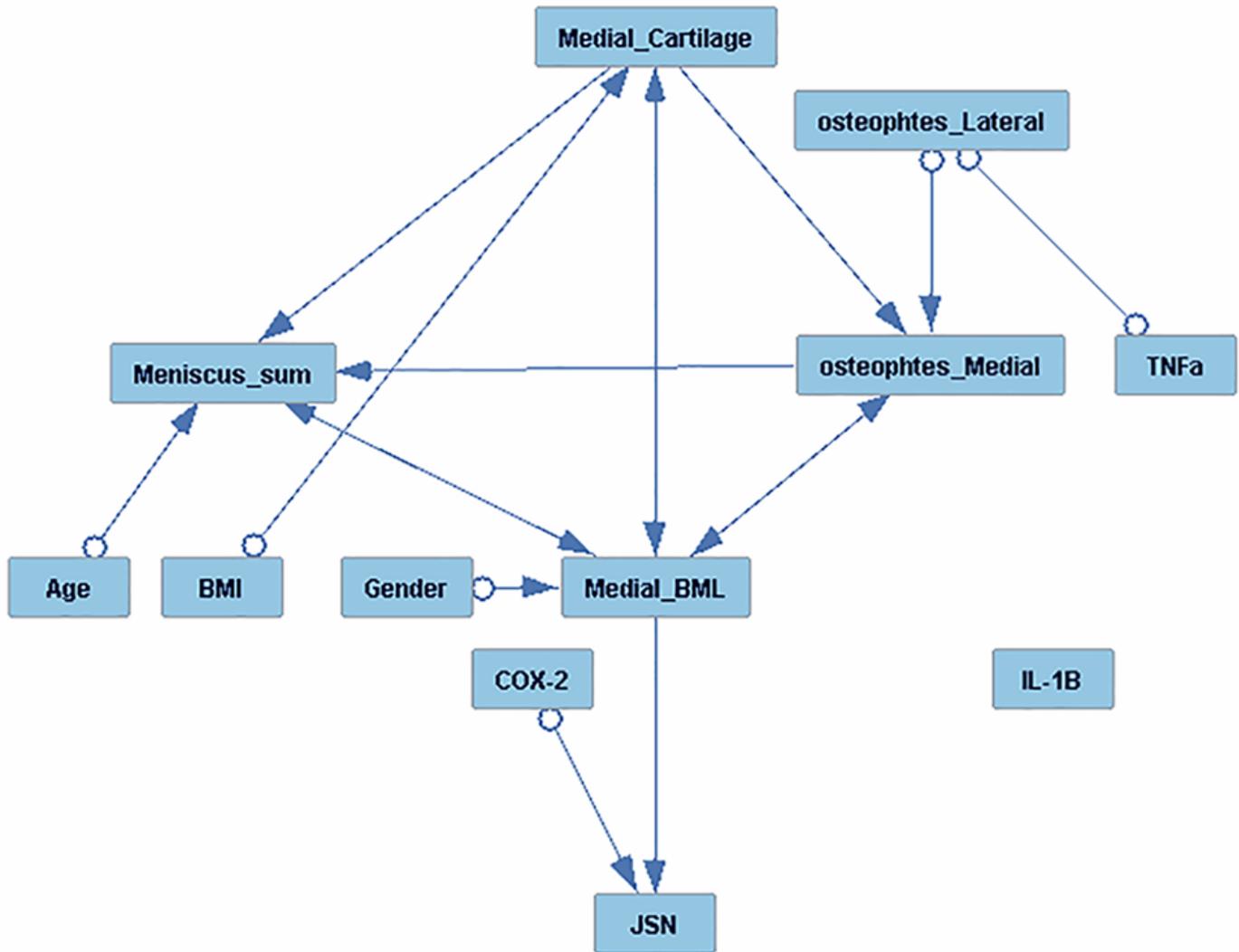


Figure 2

Causal graph analysis of NYU cohort baseline, PBL transcriptome, x-ray (radiographic) and MRI biomarkers along with age, sex, and BMI on medial JSN. FCI algorithm was used for causal graph analysis of all variables, to determine the interdependence of, PBL transcriptome, radiographic (medial and lateral osteophytes) MRI imaging markers (medial BML, meniscus and cartilage scores), and covariates (BMI, age, sex) on continuous radiographic JSN over 24 months. Edges with a single arrow denote causality, edges with double arrows denote hidden confounders, and marks (circles) on the edges denote uncertainty of causal orientation. JSN=joint space narrowing; PBL transcriptome markers: IL-1 β – interleukin -1 β ; TNF α – tumor necrosis factor α and COX-2- inducible cyclooxygenase-1.