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Association of patella alta with worsening of patellofemoral osteoarthritis-related structural damage: data from the Osteoarthritis Initiative

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SUMMARY

Objectives: To determine the association between Insall-Salvati ratio (ISR), a measure of patella alta, and worsening of Magnetic Resonance Imaging (MRI)-based osteoarthritis (OA)-related patellofemoral joint structural damages over 24-month in participants of the Osteoarthritis Initiative (OAI).
Design: Using weighted random sampling method, we selected a sample of 500 knees (from 1,677 knees with available baseline and 24-months MRI OA Knee Score (MOAKS) measurements), which is OAI-representative regarding knee OA-related factors (i.e., baseline age, sex, body mass index (BMI), and radiographic Kellgren–Lawrence grading). The ISR was measured in all enrolled knees using baseline sagittal 3T-MRI plane by three radiologists. Baseline and 24-month MOAKS variables for patellofemoral bone marrow lesions (BMLs), cartilage damages, and osteophytes were extracted, and the associations between ISR and 24-month worsening of these 3T-MRI features were evaluated using multivariable regression models. After computing receiver operating characteristic curves, the optimal cutoff point of ISR for indicating worsening of patellofemoral OA was determined. *P*-values were adjusted for multiple comparisons and false discovery rate (FDR) adjusted *P*-values were reported.
Results: In this longitudinal analysis, 24-month worsening of BML (odds ratio [OR] (95% confidence interval [95% CI]):11.18 (3.35–39.6), adjusted-p-value:<0.001) and cartilage scores (OR:7.39 (1.62–34.71), adjusted-p-value:0.042) in lateral patella was associated with higher baseline ISR. However, higher ISR was not statistically associated with medial patellar or medial and lateral trochlear BML or cartilage scores worsening. We determined the optimal cutoff point of ISR≥1.14 (95% CI: 1.083–1.284) for predicting lateral patellofemoral OA-related structural damages worsening over 24-months (sensitivity:73.73%; specificity: 66.67%).
Conclusions: Given the uncertainly surrounding the results, our overall findings suggest that ISR could be considered as a predictor of lateral patellofemoral OA-related structural damages worsening with the optimal cutoff point of ≥1.14 using knee sagittal MRI measurements.

Introduction

The patellofemoral (PF) joint is among the most common sites of radiographic osteoarthritis (OA) with a prevalence of 25% in general population aged more than 20-years[1]. Magnetic resonance imaging

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(MRI) and its application in assessment of the knee joint showed that early Patellofemoral (PF)-OA-related structural damages are seen among a larger proportion of population than what was previously reported[2]. MRI provides a unique opportunity to study early changes of OA-related structural damages involving periarticular bone, cartilage, and osteophyte in participants at risk or diagnosed with PF-OA. Also, the availability of serial MRI can help with understanding the natural history and associated risk factors of PF-OA[3–5].

Patella alta, defined as a high riding patella relative to the trochlear groove, has been linked to PF joint-related symptoms, such as PF post-traumatic instability[6,7]. Patella alta leads to diminished stability of the PF joint during knee motion, especially during knee extension. Moreover, several recent studies suggested the patella alta as a possible risk factor for PF-OA[4,5]. In these studies, it has been speculated that a high riding patella decreases the contact area between the patella and trochlea during knee extension. These abnormal mechanics can lead to patellar instability, PF joint malalignment, and increased shear forces and articular surface contact pressure, which may be considered as risk factors for PF-OA development/progression[8–10]. The Insall-Salvati ratio (ISR) is a validated and widely used index for evaluating patella alta[11]. The ISR is the length of the patellar tendon divided by the length of the patella, which can be measured using both lateral radiographs and sagittal-plane MRI of knee. To date, the majority of studies have used lateral knee radiographs to determine ISR[12], though with increasing use of MRI in assessment of knee OA, role of this modality to determine ISR is yet to be studied and a consensus in optimal cutoff point for this measure to diagnose patella alta in knee MRI is yet to be reached.[11,13] *Stefanik et al.* recently studied the association of patella alta (based on radiographs) with PF-OA using data from the Multicenter Osteoarthritis (MOST) cohort. In their study, they evaluated OA-related structural damages in knee MRI using the Whole-Organ Magnetic Resonance Imaging Score (WORMS)[5].

The publicly available large database of subjects with or at-risk of knee OA and high-quality MRIs collected in the Osteoarthritis Initiative (OAI) cohort, provide the opportunity to assess and confirm the contributing role of patella alta (measured by ISR) in developing longitudinal MRI-derived PF-OA-related structural damages worsening. This study is conducted to assess this question, to investigate the role of MRI-based ISR in predicting PF-OA worsening, as well as to determine an optimal cutoff point for ISR measurements for predicting PF-OA.

Methods

Study population

The OAI cohort is an ongoing multicenter project of 4,796 subjects (9,592 knees), either at-risk or diagnosed with knee OA (in addition to a small reference sub-cohort), who are followed to study associated factors with incidence/progression of knee OA (For details: https://data-archive.nimh.nih.gov/oai/). The OAI has been approved by institutional medical ethics review boards of the OAI centers (OAI Coordinating Center; Approval Number: 10–00532), and was recognized to be Health Insurance Portability and Accountability Act (HIPAA)-compliant.

Out of 9,592 knees from the OAI, there were available PF joint MRI reads using MRI Osteoarthritis Knee Scoring (MOAKS) method both at baseline and 24-month follow-up for 1,677 knees. These MOAKS measurements were performed in different OAI-based projects, and we collected and pooled all previously conducted measurements. Following deletion of duplicates (753 cases between different projects), for baseline PF MRI measurements, 473, 125, 328, and 751 knees were measured in the Foundation for the National Institutes of Health OA Biomarker Consortium (FNIH) (project no. 22), project no. 30, projects no. 63A-63F, and Pivotal OAI MRI Analyses (POMA) study (project no. 65), respectively. For 24-month PF MRI measurements, 472, 370, and 835 knees were measured in the FNIH (project no. 22), projects no. 63A-63F, and POMA (project no. 65) study, respectively.

Using these available PF MOAKS measurements, we conducted a weighted random sampling to select 500 knees (one knee of 472 participants, and both knees of 14 participants) as a sub-cohort with available MOAKS measurement similar to the rest of OAI with regard to OA-related risk factors (Supplementary Table 2). Demographic characteristics, clinical records, and imaging reading of these participants were extracted from the OAI database. Moreover, baseline knee MRI sequences were also gathered and read to determine the ISRs of each knee. Details of the study design are presented in Fig. 1.

Magnetic resonance imaging pulse sequence protocols

MRI was conducted using the same 3T-MRI scanners at four centers of the OAI sites (Trio, Siemens Healthcare, Erlangen, Germany). Details of OAI MRI pulse sequence protocols and parameters are reported elsewhere[14,15]. Briefly, the protocol included a coronal two-dimensional-(2D) intermediate-weighted-(IW)-turbo spino-echo-(TSE), sagittal three-dimensional-(3D) dual echo at steady state-(DESS), coronal and axial multiplanar reformations of the 3D-DESS, and sagittal IW-fat-saturated TSE sequences. Information regarding the details of the MRI sequence parameters is presented in Supplementary Table 1.

Insall-Salvati ratio measurement

ISR was defined as length of patellar tendon (*TL*), measured from the inferior patella pole to insertion of patellar tendon to the tibial tuberosity, divided by length of patella (*PL*), measured on the sagittal plane of knee MRI with the greatest diameter for this bone ($\frac{TL}{PL}$) (Fig. 2)[11]. To determine ISR of knees, baseline sagittal MRI (IW fat-saturated TSE sequences, taken while knees were fully extended) were evaluated by two musculoskeletal fellowship trained (CS and MH) and one board-certified (AP) radiologists, with more than 3-years of experience in assessing knee MRI, who were blinded to the outcomes of subjects. The intra-rater and inter-rater reliability of moderate to almost perfect for MRI-derived ISR have been reported using weighted kappa method[16].

Semi-quantitative assessment of patellofemoral joint

Structural damages related to PF-OA were scored using the validated MOAKS method, which is a semi-quantitative scoring system of OA-related features, including size/number of bone marrow lesions (BMLs), surface/full-thickness articular cartilage damages, and osteophyte sizes[15,17].

MOAKS scores for BMLs, cartilage damage (surface and full-thickness scores), and osteophyte were assessed in the patellar and trochlear regions (medial and lateral; four subregions total). BML size was scored using a 4-point grading system, where 0, 1, 2, and 3 corresponds to no involvement, <33%, 33–66%, and >66% of each subregions volume affected by BMLs, respectively. The number of BMLs were measured in each subregion. Cartilage surface area and extent of full-thickness articular damage were also determined with the same scale, where 0 was the absence of any damage, and 1, 2, and 3 showed damages involving <10%, 10–75%, and >75% of cartilage surface or full-thickness areas, respectively. Scoring of osteophyte size was categorized as absence of any lesions (0), small (1), medium (2), or large osteophytes (3). The intra-rater

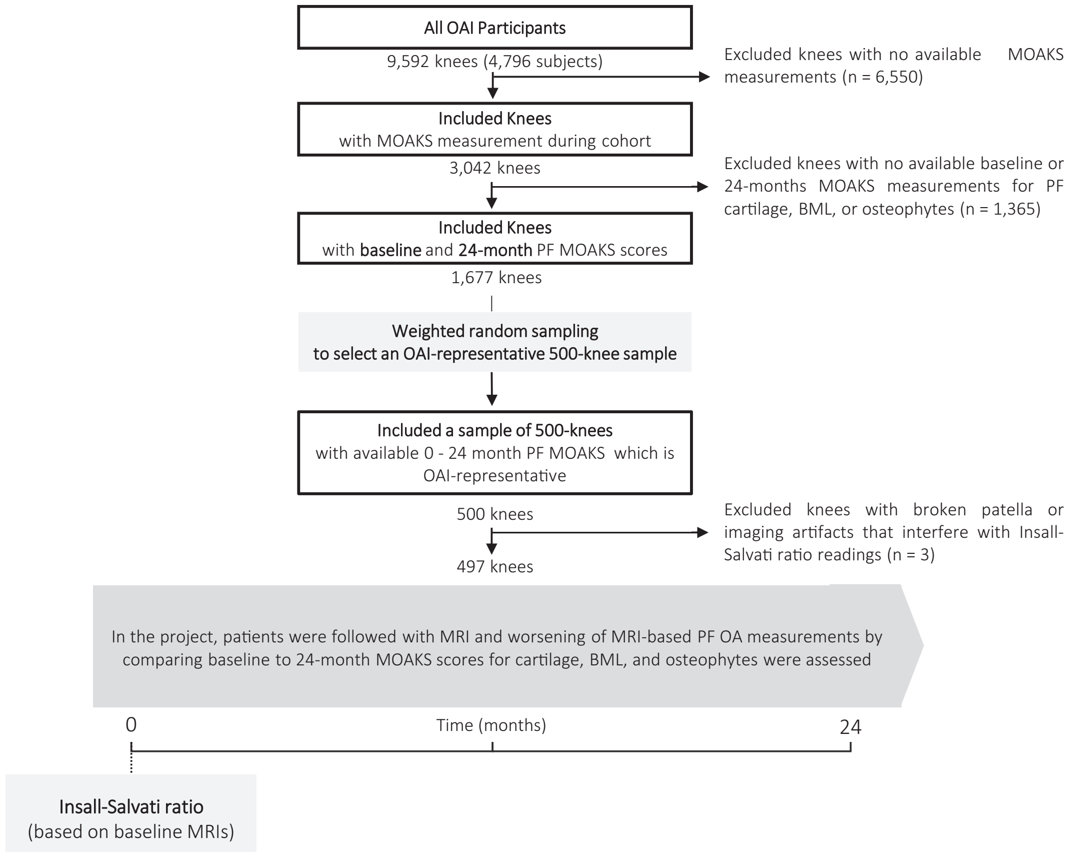

Fig. 1. Details of the study design including the selection criteria and timeline: Five hundred knees from the Osteoarthritis Initiative (OAI) project with available baseline and 24-months PF-MRI-measurements were selected using weighted random sampling method. Subjects were followed for 24-months, and the associations between the changes of PF-OA-related structural damages and baseline Insall-Salvati ratio were studied. MRI, Magnetic Resonance Imaging; OA, Osteoarthritis; OAI, Osteoarthritis Initiative; MOAKS, MRI OA Knee Score; PF, Patellofemoral; BML, Bone Marrow Lesion.

and inter-rater reliability of substantial to almost perfect (0.64–1.0 and 0.62–0.93, respectively) for all MOAKS measures of patellofemoral joint have been demonstrated by previous studies using weighted kappa method[15].

To evaluate worsening of BMLs, cartilage damage, and osteophytes on follow-up MRIs, we used the worsening criteria by *Runhaar et al.*[18] Briefly, scores of BMLs were assumed as worsened if any increases in BMLs size or numbers were seen, cartilage was reported as worsened if interval increase was reported in surface or full-thickness damage, and osteophytes were considered as worsened if increase was seen in osteophyte size compared to their baseline scores. Minor within-grade changes were also considered as worsening (at follow-up visit, a value of 0.5 was used to record a definite worsening, although the MOAKS score was similar to the baseline visit [score difference = 0], which was assemed as within-grade worsening). A region was categorized into the worsening group if any of its subregions were reported to experience worsening over 24 months.

Statistical analysis

We identified a sample of 1,677 knees with available baseline and 24-month PF-MOAKS scores, by pooling data of several projects that were defined within the OAI. We performed a weighted random sampling to select a 500-knee sample out of 1,677 knees, while weights in this process were calculated according to the distribution of baseline age (year), sex (male vs female), body mass index (BMI) (kg/m^2), and radiographic tibiofemoral Kellgren–Lawrence (KL) grade scores (range: 0–4) in the main OAI study. In this regard, we used a regression model to predict the probability of OAI participants to be included in the 1,677-sample, using the mentioned four variables as the predictors. The liklihoods were used to calculate weights as $\frac{1}{(1-probability\ to\ be\ included\ in\ the\ 1677-sample)}$, using the inverse probability weighting approach[19–21]. Subjects with the combination of mentioned four variables more similar to the average of OAI participants (mean ± standard deviation (SD) of age: 61.15 ± 9.19, mean ± SD of BMI: 28.62 ± 4.84, female gender (58.46%), and 0 KL grade (38.56%)) were more probable to be selected for the 500-knee sample, whereas the participants with less similar characteristics, would have lower weights[19]. Supplementary Table 2 shows a comparison of age, sex, BMI, and KL grade distributions between the selected 500-knee sample and the rest of the OAI participants. Pretest sample size calculation showed that small-sized (with a Cohen's $d = 0.2$) and medium-sized (with a Cohen's $d = 0.5$) effects (using logistic regression model) with power = 0.90 and alpha error = 0.05 could be assessed by evaluating 526 and 85 knees, respectively[22].

For longitudinal analysis, the associations between the worsening of PF-OA features (dependent variables) and baseline ISR (independent variable) were assessed using multivariable logistic regression models, adjusted for age, gender, and BMI (model 1) and further adjustments for history of anterior cruciate ligament (ACL) tearing (based on MOAKS), history of knee injury (acute injury that

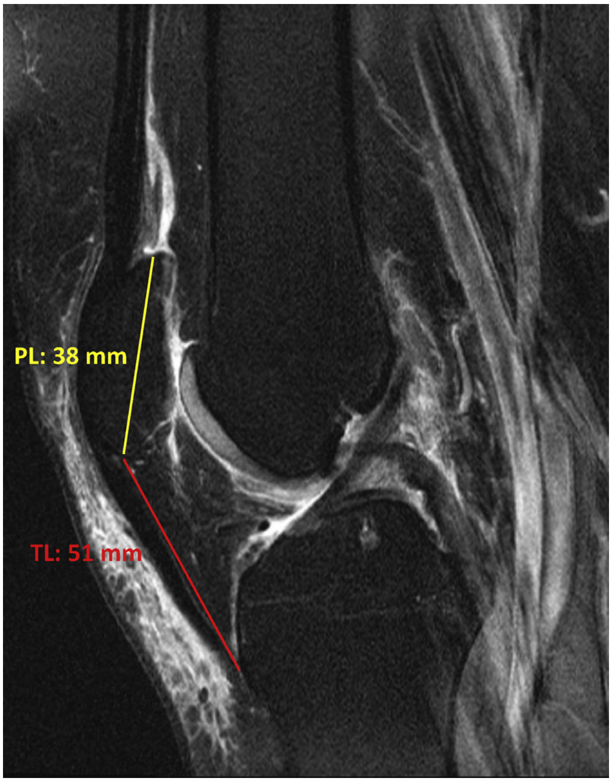

Fig. 2. Insall-Salvati ratio measurement: IW fat-saturated TSE sequence from the knee MRI of a 58 years-old female. The Insall-Salvati ratio was calculated by dividing the length of the patellar tendon (51 mm) by the length of the patella (38 mm) in mid-sagittal MRI (51/38 = 1.34) with the maximum length of patella. MRI, Magnetic Resonance Imaging; IW, Intermediate-weight; TSE, Turbo Spin-Echo.

cannot tolerate weight bearing for at least 2 days), knee alignment (based on physical exams, normal, varus, or valgus), and kneeling activity (frequency of more than 30 min of kneeling during a week) (model 2). In the longitudinal analyses, we only entered knees with scores of BML, cartilage, osteophytes lower than 3 (maximum score) at baseline, in order to minimize the ceiling effect. Calculated odds ratio (OR) for ISR in each model with its 95% confidence interval (95% CI) are reported here. We also drafted receiver operating characteristics (ROC) curves and calculated area under the curve (AUC) to determine optimal cutoff points of ISR, to define the highest sensitivity and specificity associated with longitudinal PF-OA-related structural worsening (defined as any worsening in BMLs, cartilage, or osteophyte scores), using the Youden's index. Values of the determined cutoff points, as well as their sensitivity and specificity were reported. The bootstrapping approach was followed to determine the 95% confidence interval (95% CI) of AUC, optimal cutoff points, and their sensitivity and specificity. Moreover, we evaluated the associations between ISR and our calculated optimal cutoff point with PF-OA-related damages worsening over the period of study.

Throughout this paper, continuous variables are shown in mean ± SD, while categorical data are presented in number (percentage). To conduct analyses, SPSS statistical software, version 24 (Chicago, IL, USA) and the R platform (v.3.2.5) were used. The "pROC" R packages were used to draw the ROC curves, and the "wrswoR" package was used for conducting the weighted random sample procedure[23]. *P*-values were adjusted for multiple comparisons using the Benjamini–Hochberg procedure, and the false discovery rate (FDR) adjusted *P*-value was calculated. Two-way FDR-adjusted *P*-values lower than 0.05 were assumed to be statistically significant.

Results

Average age and BMI of enrolled participants were 61.25 ± 8.98 and 28.85 ± 4.73, respectively; 55.4% of participants were female, and mean MRI-derived baseline ISR was 1.26 ± 0.21. Table I presents baseline demographic, physical, and imaging-derived characteristics of the included subjects.

Three knees out of the 500 knees were excluded due to evident broken patella in the MRI sequences or low quality and artifacts in the imaging that interfere with ISR reading. In the longitudinal analysis, higher baseline ISR was significantly associated with the worsening of BML scores in lateral patella (OR = 11.18 (3.35–39.6), FDR-adjusted-p-value:<0.001) and worsening of lateral patella cartilage score (OR = 7.39 (1.62–34.71), FDR-adjusted-p-value:0.042) (Table II). Our models didn't converge in assessing the association of longitudinal osteophyte scores worsening over period of the study due to small number of subjects with osteophytes worsening over 24-months (only four subjects had progressed). Furthermore, the association of ISR and PF-OA-related structural damage worsening (defined as any evident worsening in BMLs, surface or full-thickness cartilage, or osteophyte size scores) was only significant for lateral (but not medial) PF compartment (OR = 26.25 (4.62–174.13), FDR-adjusted-p-value:<0.001) (Table III).

Similarly, in the multivariable regression models, ISR was associated with baseline lateral (but not medial) PF-OA-related damage (defined as presence of any OA-related structural damage; MOAKS BMLs, cartilage, or osteophytes scores>1; OR = 15.65 (1.79–165.54), FDR-adjusted-p-value:<0.001) (Supplementary Table 4).

Further, we used the ISRs of subjects to determine the optimal cutoff point of ISR associated with 24-month MRI-based PF-OA worsening using ROC analysis (Fig. 3). In studying worsening of lateral PF-OA and ISR, we showed an AUC of 70.06% (95% CI: 61.70–77.84%, by 10,000 stratified bootstrap replicates) in the plotted ROC curve. The optimal cutoff point was an ISR≥1.14 (95% CI:1.08–1.28 by 2,000 stratified bootstrap replicates), which had a sensitivity of 73.73% (95% CI: 47.45–84.73%) and specificity of 66.67% (95% CI: 47.92–89.58%) [Fig. 3(B)]. Table III shows the association between patella alta which was defined based on the calculated cutoff point (ISR≥1.14 vs <1.14) and worsening of PF-OA-related structural damage. The same analyses for evaluating the associations between the baseline ISR and 24-month worsening of medial PF-OA [Fig. 3(A)] were also performed.

Discussion

In this study, we could confirm an association of higher ISRs with longitudinal PF-OA-related structural damages worsening over 24 months, including worsening of cartilage damage and BML in the lateral patella. Our results further show that an ISR of ≥1.14 (based on MRI) is the optimal cutoff for predicting lateral PF-OA worsening over 24-month.

Compared to the tibiofemoral joint, the risk factors associated with PF-OA have been less investigated, and only recently few studies reported that abnormal PF morphology features, such as trochlear dysplasia, patella alta, and patellar translation, are associated with development/progression of PF-OA[4,5,9,10,24,25]. Among these risk factors, a high riding patella is associated with patellar dislocation and instability. Moreover, it has been suggested that patella alta and its associated lateralization, decreased the contact area between the patellar articular surface and trochlea and increased the risk of PF-OA development[4,9,10]. Recently, *Lu et al.* showed increased odds of patellar cartilage lesions among subjects with high ISR, and confirmed the role of ISR in diagnosing patellar

Table I
Baseline demographic, physical, and radiographic characteristics of study population ($n = 500$)

Variable		Total
Age (year)		61.25 ± 8.98
Gender (female)		277 (55.40%)
Body mass index (Kg/m2)		28.85 ± 4.73
Insall-Salvati ratio (range 0.62–1.90) (based on MRI measurements)		1.26 ± 0.21
History of knee injury		138 (27.60%)
History of ACL injury (based on MRI measurements)		28 (5.60%)
Kneeling 30 min or more during typical week	None	360 (72.00%)
	One day per week or less	60 (12.00%)
	2–3 days per week	52 (10.40%)
	4–5 days per week	9 (1.80%)
	Nearly every day or every day	18 (3.60%)
Knee alignment (based on physical exams)	Neither	141 (28.20%)
	Varus	128 (25.60%)
	Valgus	229 (45.80%)
PASE score (range 2–417)		169.27 ± 80.73
Muscle strength (over 7 days)	Never	292 (58.4%)
	Seldom (1–2 days)	73 (14.6%)
	Sometimes (3–4 days)	84 (16.8%)
	Often (5–7 days)	51 (10.2%)
Radiographic tibiofemoral Kellgren and Lawrence grade	0	188 (37.60%)
	1	97 (19.40%)
	2	139 (27.80%)
	3	61 (12.20%)
	4	15 (3.00%)

Continuous variables are shown in mean ± SD, and categorical variables are presented as number (percentage).
Anterior Cruciate Ligament, ACL; Body Mass Index, BMI; Physical Activity Scale for the Elderly, PASE; MRI, Magnetic Resonance Imaging; Standard Deviation, SD.

cartilage lesions. However, the cross-sectional design of their study, the method used to diagnose cartilage lesions, and the confinement of the work to patellar cartilage lesions necessitate further evaluations to fully describe roles of ISR in development and worsening of PF-OA[26].

In another report, *Stefanik et al.* studied the association between high ISR and PF-OA-related BMLs, cartilage loss, and subchondral bone attrition, using data from the MOST cohort. In their baseline analysis, they showed that higher scores of BMLs and cartilage damage are seen among groups of subjects with higher ISR. They also followed their study population over 30-months and demonstrated that higher ISR is associated with greater odds of worsening of lateral BMLs and lateral/medial cartilage damage[4,5]. In our work, we have also shown the higher odds of lateral PF-OA-related MRI features worsening in subjects with higher ISR. In addition to previous reports using the MOST database, the OAI cohort which is the largest longitudinal study on knee OA including annual MRI, provides another opportunity to evaluate this question and to assess the value of ISR in predicting PF-OA development. Moreover, the availability of detailed demographic information and other risk factors of participants in the OAI as potential confounders, including kneeling activity, history of knee injury, and knee alignment yields the necessary data to adjust the regression models for possible bias due to baseline characteristics, and provides a more robust results than the *Stefanik et al.* paper, that had adjusted their models only for baseline age, gender, and BMI. Despite the use of different MRI-based scoring methods (WORMS vs MOAKS), and different cohorts (MOST vs OAI), results of cross-sectional and longitudinal evaluations confirmed the conclusion of the previous MOST cohort report. Also, we have performed analyses to determine the optimal cutoff value for the ISR in predicting the worsening of PF-OA structural damage.

To establish a diagnosis of patella alta several measurements have been introduced with different validity, including the Caton-Deschamps index and ISR, which are the two most popular measurements used by orthopedic surgeons and radiologists. The ISR was used for the characterization of patella alta in the context of patellar instability with a sensitivity of 60% and specificity of 88%[27]. Cutoff points of ISR were traditionally determined on plain lateral-radiographs. Although the ISR is now commonly applied to assess the presence of patella alta on knee MRI, consensus on the cutoff point of these measures for MRI is yet to be reached. Some studies used the same values as the ones for radiography[10,28], some introduced an ISR of>1.3 as the optimal cutoff in diagnosing patella alta[13], and *Shabshin et al.* suggested that even a higher cutoff of ISR>1.5 is optimal[11]. The assumption for calculation of cutoff points in these previous studies was mostly the hypothesis that *PL* and *TL*

Table II
Association of Insall-Salvati ratio and patellofemoral BML, cartilage, and osteophytes worsening over 24-months

Variables	Insall-Salvati ratio Mean ± SD for each subgroup	Logistic regression OR (95% CI)		
		Crude	Adjusted-1	Adjusted-2
BMLs worsening (Not worsened (number)|worsened (number))				
Medial Patellofemoral				
Medial patella	1.23 ± 0.21 ($n = 294$)|d1.25 ± 0.17 ($n = 61$)	1.50 (0.38–5.89)	1.36 (0.34–5.43)	2.18 (0.47–10.08)
Medial trochlea	1.24 ± 0.20 ($n = 301$)|1.24 ± 0.23 ($n = 50$)	1.23 (0.28–5.28)	1.30 (0.29–5.71)	1.09 (0.21–5.55)
Lateral Patellofemoral				
Lateral patella	1.23 ± 0.20 ($n = 294$)|1.32 ± 0.21 ($n = 63$)	**9.72 (2.54–38.48)** *	**9.94 (2.54–40.53)** *	**11.18 (3.35–39.6)** *
Lateral trochlea	1.24 ± 0.20 ($n = 292$)|1.24 ± 0.22 ($n = 59$)	1.07 (0.26–4.31)	1.19 (0.28–5.02)	0.49 (0.12–1.89)
Cartilage morphology worsening (Not worsened (number)|worsened (number))				
Medial Patellofemoral				
Medial patella	1.26 ± 0.20 ($n = 265$)|1.26 ± 0.22 ($n = 231$)	0.91 (0.39–2.11)	0.87 (0.37–2.06)	0.80 (0.27–2.38)
Medial trochlea	1.27 ± 0.21 ($n = 299$)|1.24 ± 0.21 ($n = 198$)	0.51 (0.21–1.20)	0.56 (0.23–1.35)	0.80 (0.27–2.37)
Lateral Patellofemoral				
Lateral patella	1.24 ± 0.21 ($n = 319$)|1.30 ± 0.21 ($n = 177$)	**3.47 (1.42–8.61)** *	**4.38 (1.72–11.4)** *	**7.39 (1.62–34.71)** *
Lateral trochlea	1.27 ± 0.21 ($n = 411$)|1.24 ± 0.19 ($n = 87$)	0.55 (0.18–1.68)	0.62 (0.19–1.92)	0.72 (0.15–3.38)

Continuous variables are shown in mean ± SD. Association of baseline MRI-based Insall-Salvati ratio (independent variable) and 24-month worsening of BML, cartilage, and osteophyte scores (dependent variables) were evaluated using multivariable regression models; adjusted-1 for age, gender, and BMI; adjusted-2, further adjustments for history of ACL tearing, history of knee injury, knee alignment, and kneeling activity. Regions were categorized in the worsening group if any of their subregions had worsened over the course of the study. Results of regression models are shown with ORs (95% CI). False discovery rate (FDR) adjusted *P*-value was calculated using the Benjamini–Hochberg procedure.
* Bold numbers: adjusted *P*-value <0.05 (<0.001 and 0.040, statistically significant); all other FDR-adjusted *P*-values were >0.05.
Anterior Cruciate Ligament, ACL; Body Mass Index, BMI; Bone Marrow Lesions, BML; Confidence Interval, CI; MRI, Magnetic Resonance Imaging; Odds Ratio, OR; Standard Deviation, SD.

Table III
Association of Insall-Salvati ratio and its optimal cutoff points with MRI-based patellofemoral osteoarthritis-related structural damages worsening over 24-months

Variables	Insall-Salvati ratio Mean ± SD or number (%)	Logistic regression OR (95% CI), *P-value*		
		Crude	Adjusted-1	Adjusted-2
Insall-Salvati ratio (Absence of any structural damage (number)|any structural damage (number))				
Medial patellofemoral	1.17 ± 0.16 (*n* = 31)|1.25 ± 0.21 (*n* = 337)	**9.10 (1.38–67.94)**	**9.79 (1.50–72.27)**	7.46 (1.00–64.85)
Lateral patellofemoral	1.14 ± 0.19 (*n* = 48)|1.27 ± 0.21 (*n* = 255)	**29.16 (5.59–173.33)** *	**30.07 (5.77–178.93)** *	**26.25 (4.62–174.13)** *
Optimal cutoff (Absence of any structural damage|any structural damage)				
Medial patellofemoral	16 (51.61%) | 226 (67.06%)	1.93 (0.91–4.06)	1.98 (0.93–4.21)	1.69 (0.75–3.77)
Lateral patellofemoral	18 (37.50%) | 183 (71.76%)	**4.24 (2.24–8.20)** *	**4.34 (2.28–8.46)** *	**4.20 (2.07–8.87)** *

Continuous variables are shown in mean ± SD, and categorical variables are shown in numbers (%). Association of MRI-based Insall-Salvati ratio and presence of patella alta based on the calculated optimal cutoff point in this study (≥1.14) (independent variables) with MRI-based patellofemoral osteoarthritis-related structural damages worsening after 24-months (dependent variables) were reported, using multivariable regression models adjusted-1 for age, gender, and BMI; adjusted-2, further adjustments for history of ACL tearing, history of knee injury, knee alignment, and kneeling activity. Results of regression models are shown with ORs (95% CI). False discovery rate (FDR) adjusted *P*-value was calculated using the Benjamini–Hochberg procedure.

* Bold numbers: adjusted *P*-value <0.05 (<0.001, statistically significant); all other FDR-adjusted *P*-values were >0.05.

Anterior Cruciate Ligament, ACL; Body Mass Index, BMI; Confidence Interval, CI; MRI, Magnetic Resonance Imaging; Odds Ratio, OR; Standard Deviation, SD.

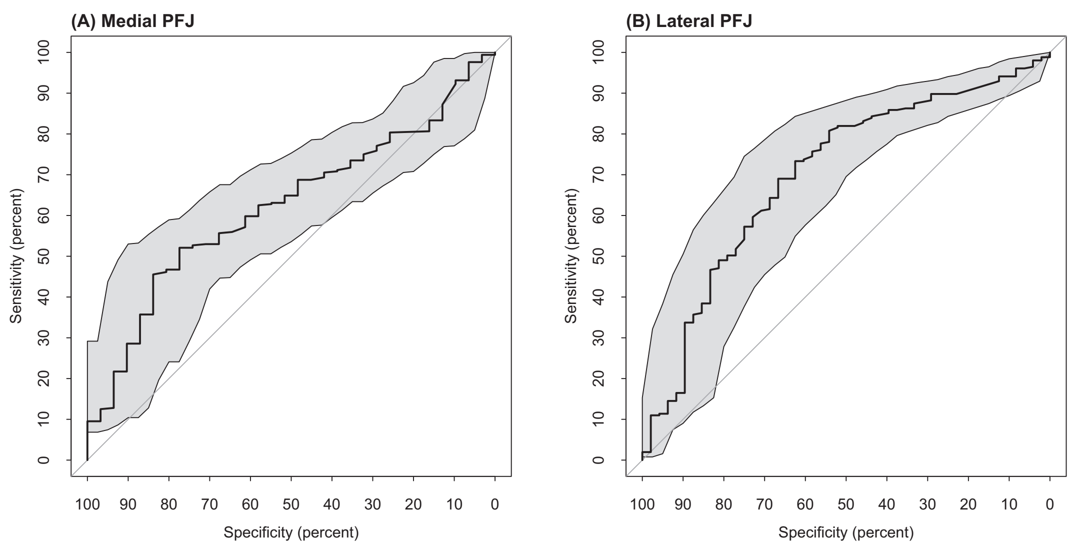

Fig. 3. Insall-Salvati ratio and longitudinal patellofemoral osteoarthritis over 24-months: Area under the curves and receiver operating characteristic curves of association of Insall-Salvati ratio and longitudinal medial (A) and lateral (B) MRI-based patellofemoral osteoarthritis-related damages worsening over 24-months. Area under the curves for the association between the Insall-Salvati ratio and patellofemoral osteoarthritis-related damages in medial (A, 62.34% (95% confidence interval 53.25–71.03%, by 10,000 stratified bootstrap replicates)) and lateral (B, 70.06% (95% confidence interval 61.70–77.84%, by 10,000 stratified bootstrap replicates) patellofemoral compartments are shown in these ROC curve. The optimal cutoff point for the medial curve (A) was determined as 1.24 (95% confidence interval 1.16–1.32 by 2000 stratified bootstrap replicates), sensitivity: 50.0% (95% confidence interval 36.0–67.56%), specificity: 82.23% (95% confidence interval 61.29–96.77%)) and for the lateral curve (B) was determined as 1.14 (95% confidence interval 1.08–1.28 by 2000 stratified bootstrap replicates), sensitivity: 73.73% (95% confidence interval 47.45–84.73%), specificity: 66.67% (95% confidence interval 47.92–89.58%)). MRI, Magnetic Resonance Imaging; ROC, Receiver Operating Characteristic.

must be equal and values higher than two standard deviation range of $\frac{TL}{PL} = 1$ (ISR>1.2 in some works, and ISR>1.3 in others) were statistically deviant and should be categorized in the group with patella alta. Similarly, *Shabshin et al.* classified 2.5% of patients with high extreme values of ISRs in the patella alta group. Vulnerability of this technique to selection bias (e.g., studying a population with higher ISR than normal) and analytic flaws (e.g., ISR is not necessarily normally distributed, whereas some studies showed a negatively or positively skewed pattern) question accuracy of these assumptions[11,28]. In this study, for the first time, we used Youden's index to maximize power of ISR in the diagnosing patella alta, which had higher odds of PF-OA-related structural damage worsening. Our results confirmed that a cutoff of ≥1.14 is an optimal measure in assessing this patellar abnormality, since it predicts the worsening of PF-OA features over time.

Our study has several limitations. We included an OAI-representative sample of 497 knees, and all OAI subjects were not evaluated due to the limited number of available PF-MOAKS measurements. Defining sub-cohort within the OAI might result in selection or confounding biases; we tried to address this issue by utilizing multiple covariate adjustments for potential effects exerted by set of unmatched variables. Second, in this work, we studied worsening of PF-OA-related structural changes and their associations with ISR and patella alta, both of which are chronic exposures and probably require longer follow-up periods than 24-month. Future investigations using longer follow-up MRI, which are available in the OAI, are needed. Third, dedicated radiographic views of the PF joint (e.g., sunrise view) and thus assessment of radiographic PF-OA at baseline or its progression using plain radiograph were not available in the OAI study. Additionally, the progression or development of symptoms related to the PF joint was not assessed, as there is large overlap between tibiofemoral and PF-OA-related symptoms. Fourth, despite observing significant associations between the ISR and PF-OA, many of the 95%CIs cover a wide range and high uncertainty level probably due to the low prevalence of worsening/non-worsening outcomes.

In summary, we demonstrated that higher ISR was associated with greater odds of BMLs and cartilage damage worsening in lateral patella over 24-months. Collectively, our results showed that higher ISR (and patella alta) is among the risk factors associated with lateral PF-OA. Based on the findings of PF-OA on MRI and their worsening over time, we determined an optimal cutoff point (ISR $\geq$1.14), which was considered to have acceptable sensitivity and specificity. We showed that ISR of $\geq$1.14 was related to 320% (95% CI: 107–787%) increase in the odds of lateral PF-OA-related damages worsening. However, the uncertainty of our findings is considerable and further researches are required to reduce this uncertainty.

Author contributions

Arya Haj-Mirzaian had full access to all the published data and takes responsibility for the integrity of the data and the accuracy of the data analysis presented in this manuscript.

Study concept and design: AHM, AG, FP, FWR, and SD.

Acquisition of data: AG, FWR, CS, MH, AP, and SD.

Analysis and interpretation of data: AHM, AG, FP, FWR, AP, CS, MH, BZ, JJS, and SD.

Drafting of the manuscript: AHM, FP, and SD.

Critical revision of the manuscript for important intellectual content: AHM, AG, FP, FWR, AP, CS, MH, BZ, JJS, and SD.

Statistical analysis: AHM, FP, and SD.

Administrative, technical, or material support: AG, FWR, AP, CS, MH, BZ, JJS, and SD.

Supervision: AG, FWR, AP, CS, MH, JJS, and SD.

Other: None.

Conflict of interests

AG received funding from MerckSerono, AstraZeneca, Genzyme, OrthoTrophix, and TissueGene for consultation; as well as from Boston Imaging Core Lab (BICL) as the president and stockholder. FWR received funding from BICL as chief executive officer (CEO) and stockholder. SD received funding from Toshiba Medical Systems for consultation; as well as grants from GERRAF, and Carestream Health for a cone-beam computed tomographic clinical trial. None of the authors have any competing personal or financial relationships that could influence results of this work. Other authors declare that they didn't have any competing interests.

Role of funding source

None.

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Supplementary data

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