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The association between MR T1ρ and T2 of cartilage and patient-reported outcomes after ACL injury and reconstruction

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SUMMARY

Objective: To determine if cartilage T1ρ and T2 relaxation time measures after ACL injury and prior to reconstruction (baseline) are associated with patient-reported outcomes at baseline, 6-months, and 1-year after surgery.
Design: Fifty-four ACL-injured participants were scanned in both knees at baseline using 3T MR T1ρ and T2 mapping. Participants also completed Knee-injury and Osteoarthritis Outcome Score (KOOS) and Marx activity level questionnaires at baseline, 6-months, and 1-year after reconstruction. The difference between cartilage T1ρ or T2 of the injured and contralateral knee (side-to-side difference, SSD) was calculated to account for physiological variations among patients. Linear regression models were built to evaluate the association between the baseline SSD T1ρ or T2 and KOOS or Marx at all time points.
Results: Higher baseline SSD T1ρ posterolateral tibia (pLT) was associated with worse KOOS in all subscales except symptoms at baseline, worse KOOS pain at 6-months, and worse KOOS in all subscales except sports function at 1-year. Higher baseline SSD T2 femoral trochlea (TrF) was associated with worse KOOS activities of daily living (ADL) at 1-year. Higher baseline SSD T1ρ pLT was associated with lower Marx activity level at 1-year. More severe cartilage lesions, as assessed by Whole-Organ MRI Scoring (WORMS), was significantly associated with worse KOOS pain at 6-months and 1-year.
Conclusion: T1ρ and T2 of cartilage after ACL injury were associated with KOOS after injury and both KOOS and Marx after reconstruction. Such associations may help clinicians stratify outcomes post-injury, and thus, improve patient management.

Introduction

Anterior cruciate ligament (ACL) tears are prevalent and serious knee injuries that often involve concomitant damage to the cartilage[1]. In acute injuries, the most severe chondral damage is observed in the lateral compartment, where the pivot shift and transchondral impaction occurs[2–6]. The reported incidence of cartilage lesions ranges from 16% to 88% in ACL-injured knees, and such lesions have been shown to be a risk factor for osteoarthritis (OA) development 5–15 years after ACL injury[7–11].

In the current literature, the reported effects of cartilage injury and patient-reported outcomes after ACL reconstruction (ACLR) are inconsistent. Several recent cohort studies have shown that full-thickness cartilage lesions result in worse patient-reported outcome measures two- and six-year after ACLR, whereas other studies did not find such significant associations[12–16]. Since the short-term success of ACLR has been largely predicated on a patient's time to return to activity, level of pain, and quality of life (QOL), it has become increasingly important to identify sensitive measures of cartilage damage that can potentially predict patient outcomes[17].

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Standard magnetic resonance imaging (MRI) is an accurate, noninvasive means to detect morphological changes associated with cartilage breakdown, but is limited from evaluating early degenerative changes of the cartilage matrix[18–20]. Recent advances in quantitative MRI, such as T1ρ and T2, have been used to assess the biochemical matrix depletion of the cartilage in ACL-deficient and reconstructed knees[8,21,22]. However, to date, there has been little to no investigation on determining the relationship between these cartilage imaging techniques and patient-reported outcomes after ACLR[23]. Determining such a relationship may help clinicians provide more accurate functional expectations to patients prior to surgery.

The objective of this study was to determine if MR T1ρ and T2 measures in knee cartilage after ACL injury are associated with patient-reported outcome measures at baseline, 6-months, and 1-year after reconstruction. We hypothesize that increased cartilage T1ρ and T2 of the lateral compartment after ACL injury would associate with worse post-surgical outcomes and activity levels.

Materials and methods

Study participants

This prospective study was conducted after obtaining approval from our Institutional Review Board. Fifty-four participants with unilateral ACL injuries were consented and enrolled. Patients with concomitant ligamentous injuries, history of inflammatory or primary OA, or previous knee surgery were excluded from the baseline cohort. Patients were excluded from follow-up if they chose to decline ACLR. All ACLRs were performed by one of three board-certified, fellowship-trained orthopaedic surgeons. All patients underwent the standard postoperative rehabilitation protocol.

Of the 54 participants who had bilateral knee MR scans at baseline (after injury but before reconstruction), 51 completed the validated patient-reported outcomes surveys [Knee Injury and Osteoarthritis Outcome Score (KOOS) and Marx activity rating scale][24,25]. One MR scan of the contralateral uninjured knee was confounded by excessive motion artifact and was omitted, as it was not possible to obtain accurate T1ρ and T2 measurements. Forty-six patients completed only KOOS at the 6-month follow-up, while 42 patients completed both questionnaires at the 1-year follow-up.

Patient-reported outcome questionnaires

The KOOS survey assesses five categories: pain, symptoms, activities of daily living (ADL), sport and recreation function, and knee-related QOL. The scale ranges from 0 to 100, with 0 being the worst and 100 being the best. The Marx activity rating scale surveys subjects regarding their level of physical activity, specifically inquiring about the frequency of various physical actions (running, cutting, decelerating, and pivoting) during the subject's healthiest and most active state in the past year. The scale ranges from 0 to 16, with 0 and 16 being the least and most active, respectively.

Magnetic resonance image acquisition

All images were acquired using a 3T MRI scanner (GE Milwaukee, WI) with an eight-channel knee coil (Invivo Inc, Gainesville, FL). High-resolution, 3D fast spin-echo (CUBE) images were used to evaluate cartilage, ligamentous, and meniscal morphology. The imaging parameters included: repetition time (TR), 1500 ms; echo time (TE), 25 ms; echo train length, 32; matrix, 384 × 384; field of view (FOV), 16 cm; slice thickness, 1 mm; and acquisition time, 8 min 13 s. Sagittal T1ρ- and T2-weighted sequences were obtained using a previously developed method based on combined T1ρ and T2 acquisition techniques[26]. The imaging parameters included: TR/TE, 9 ms/3 ms; FOV, 14 cm; matrix, 256 × 128; slice thickness, 4 mm; views per segment, 64; spin-lock frequency, 500 Hz; T1ρ time of spin-lock: 0, 10, 40, 80 ms; T2 preparation TE: 0, 13.7, 27.3, 54.7 ms; and acquisition time, 9 min 37 s. Although the typical slice thickness of knee MRs range from 2.5 to 3 mm, the use of 4 mm was to keep the MRI examination within clinically acceptable time constraints while still being able to cover the entire knee.

Image post-processing

After image acquisition, the CUBE images of the injured knee were registered and down-sampled in the sagittal direction to match the images of the first T1ρ image. Cartilage was segmented semi-automatically on CUBE into six compartments [lateral femoral condyle (LF), lateral tibia (LT), medial femoral condyle (MF), medial tibia (MT), femoral trochlea (TrF), and patella (P)] using an in-house program developed with MATLAB (Mathworks, Natick, MA)[27,28]. Based on previous literature and the clinical assumption that the posterolateral tibia (pLT) is often injured during ACL disruption, the LT was further subdivided to include this region using the posterior horn of the lateral meniscus as an anatomical landmark (Fig. 1). Care was taken not to include the subchondral plate and synovial fluid in the segmentations.

Piecewise rigid registration was applied along both T1ρ and T2 echoes to account for non-rigid movement of the femur, tibia, and patella with respect to one another. An image mask for each bone was defined by the cartilage segmentations and used to constrain the registration. The T1ρ and T2 maps of each bone were subsequently reconstructed on a pixel-by-pixel basis using a two-parameter, monoexponential fitting algorithm. Additionally, all T1ρ and T2 echoes of the contralateral knee were registered to first T1ρ echo of the injured knee to assure that the same anatomical regions of cartilage were being compared in the analysis. The registration was accomplished using an intensity-based multi-resolution pyramidal approach[29,30]. Mean T1ρ and T2 values were calculated for each cartilage compartment after transferring the segmentations from CUBE onto the maps.

After recruitment of 23 participants, the 3T HDx Long Bore MR scanner was replaced with a 3T MR750 Wide Bore unit. In order to account for potential differences in T1ρ and T2 values from using different MR systems, phantoms and human subjects were scanned on both units within a 4-month period: 9 individuals for T1ρ [average time between scans, 49.5 (range, 9–114) days] and 5 individuals for T2 [average time between scans, 13.6 (range, 9–18) days]. A decrease in T1ρ and T2 was observed between the old Long Bore system and the new Wide Bore system, with the measurements being highly correlated ($R^2 = 0.95$ and $R^2 = 0.92$ for T1ρ and T2, respectively) (see Supplemental Fig. S1). A linear regression model was established to adjust T1ρ and T2 values as follows:

$$T1\rho_{new} = 0.94\,T1\rho_{old} + 0.10$$

$$T2_{new} = 0.98\,T2_{old} + 0.64$$

where the subscripts *old* and *new* signify the values of the old and new systems, respectively.

Clinical MR assessment

All images were evaluated by two board-certified, fellowship-trained musculoskeletal radiologists each with over 10 years of experience. A modified Whole-Organ MRI Scoring (WORMS) system was used to assess the lateral and medial menisci as follows: 0, intact menisci; 1, intact menisci with at least one region with

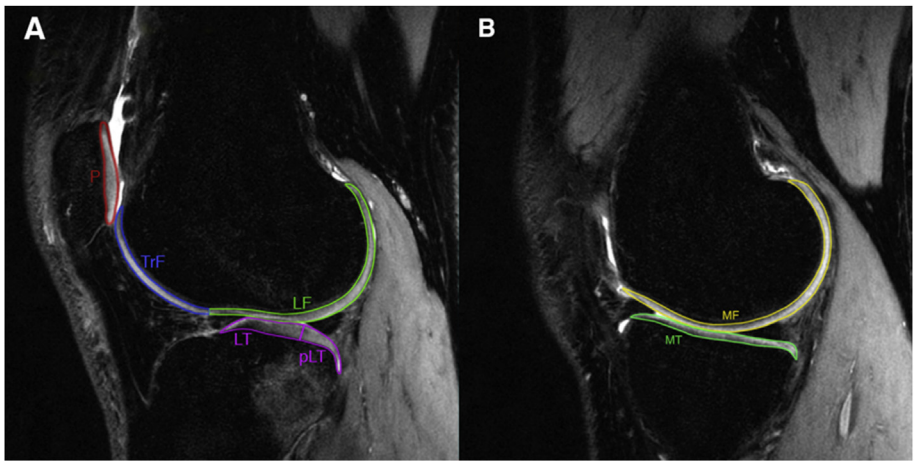

Fig. 1. The CUBE image demonstrates the delineation of the cartilage overlying the (A) lateral and (B) medial compartments of the knee. LF, lateral femoral condyle; LT, lateral tibia; pLT, posterolateral tibia; P, patella; TrF, femoral trochlea; MF, medial femoral condyle; MT, medial tibia.

intra-substance abnormalities; 2, only one non-displaced tear in one region; 3, more than one non-displaced tear or one complex tear in the meniscus; 4, more than one displaced or complex tear with deformity in the meniscus; 5, maceration of only one region; and 6, maceration of more than one region. An unmodified eight-point WORMS scale was used to evaluate the cartilage overlying the medial and lateral femoral condyles and tibial plateaus, as well as the cartilage overlying the patella and trochlea[31]. Bone marrow edema-like lesions (BMEL) was assessed and quantified as absent (Grade 0), mild (Grade 1: diameter, $d < 5$ mm), moderate (Grade 2: 5 mm $< d < 20$ mm), or severe (Grade 3: $d > 20$ mm) over both the femoral condyles and the tibial plateaus.

Statistical analysis

Paired *t*-tests were used to compare T1ρ and T2 values between the injured and contralateral knees for each cartilage compartment. Linear regression models were built to determine the relationship between cartilage T1ρ and T2 values at baseline and KOOS and Marx at baseline, 6-months, and 1-year. A side-to-side difference (SSD) in T1ρ or T2, defined as the difference between the relaxation time values in the injured and contralateral knee, was calculated to account for physiological variations among patients and used in all regression analyses. To reduce the number of included predictors and the degree of multiple testing, we first screened variables by testing if their relaxation times were significantly different between sides. Only SSDs that were statistically significant were included as independent variables in the regression models for predicting KOOS and Marx scores. The dependent variables consisted of the 5 subscales of KOOS and the Marx activity rating score at each time point. The regression models were adjusted for age, gender, BMI, WORMS for medial and lateral menisci, total BMEL, and total cartilage lesions. For the 6-month and 1-year follow-up, lateral meniscectomy at the time of ACLR (categorized as yes or no) and baseline KOOS and Marx were also included in the adjustments. Medial meniscectomy was not included in the follow-up analyses since only two participants had undergone surgical treatment. All statistical analyses were performed using SPSS Statistics version 22.0.0 (IBM, Armonk, NY). To account for multiple comparisons made between baseline T1ρ and T2 of ACL-injured and contralateral knees in seven compartments, Bonferroni correction was applied and the significance level was set to 0.007. For the regression models, the significance level was 0.05.

Results

Baseline patient and clinical characteristics

Fifty-four patients were enrolled (31 men, 23 women), with a mean age of 29.6 years (range, 15–50 years) and average BMI of 24.4 ± 3.5 kg/m^2 (Table I(a)). The average time between injury and MRI was 61.5 ± 49.5 days. Of the initial cohort, 52 patients underwent ACLR using hamstring autograft ($n = 36$) or soft tissue allograft ($n = 16$). The clinical characteristics of the analyzed cohort are provided in Table I(b). Based on MR evaluation, lateral meniscal injury (WORMS ≥2) was noted in the ACL-deficient knee of 24 (44%) subjects, with 10 undergoing debridement and three undergoing repairs. Medial meniscal injury (WORMS ≥2) was observed in 20 (37%) subjects, with two undergoing partial meniscectomy and one undergoing repair. Thirty-five (65%) patients also sustained a MRI-detectable cartilage injury in their ACL-ruptured knee, most frequently observed over the LT ($n = 20$). Forty-two (78%) patients had BMEL in at least one compartment, with the LF and LT being most affected ($n = 27$ and n = 42, respectively).

Patient-reported outcome scores

The baseline and follow-up outcome scores for KOOS and Marx are presented in Table II. From baseline to 6-months following reconstruction, KOOS in the pain, ADL, and sports subscales significantly improved ($P = 0.005$, <0.001, and 0.006, respectively).

Table I(a)
Baseline patient characteristics

Characteristic	
Sex ($n = 54$)*	
Male	31 (57%)
Female	23 (43%)
Age (years)†	29.6 ± 8.4
BMI (kg/m^2)†	24.4 ± 3.5
Time from injury to MRI (days)†	61.5 ± 49.5
Time from injury to surgery (days)†	76.3 ± 54.5
ACL Graft ($n = 52$)*	
Hamstring autograft	36 (69%)
Posterior tibialis allograft	14 (27%)
Hamstring allograft	2 (4%)

* Data expressed as count (percentage %).
† Data expressed as mean ± standard deviation.

Table I(b)
Baseline clinical characteristics as assessed by WORMS*

Characteristic		Characteristic	
Medial meniscus		Lateral meniscus	
Normal	29 (54%)	Normal	21 (39%)
Grade 1	5 (9%)	Grade 1	9 (17%)
Grade 2	10 (18%)	Grade 2	20 (37%)
Grade 3	2 (4%)	Grade 3	1 (2%)
Grade 4	7 (13%)	Grade 4	3 (5%)
Grade 5	1 (2%)	Grade 5	0 (0%)
Grade 6	0 (0%)	Grade 6	0 (0%)
MF cartilage lesion		LF cartilage lesion	
Normal	49 (90%)	Normal	46 (85%)
Grade 1	1 (2%)	Grade 1	3 (6%)
Grade 2	2 (4%)	Grade 2	4 (7%)
Grade 2.5	0 (0%)	Grade 2.5	1 (2%)
Grade 3	2 (4%)	Grade 3	0 (0%)
Grade ≥4	0 (0%)	Grade ≥4	0 (0%)
MT cartilage lesion		LT cartilage lesion	
Normal	46 (85%)	Normal	34 (62%)
Grade 1	5 (9%)	Grade 1	10 (19%)
Grade 2	3 (6%)	Grade 2	10 (19%)
Grade 2.5	0 (0%)	Grade 2.5	0 (0%)
Grade ≥3	0 (0%)	Grade ≥3	0 (0%)
Patellar cartilage lesion		Trochlear cartilage lesion	
Normal	41 (75%)	Normal	44 (81%)
Grade 1	3 (6%)	Grade 1	2 (4%)
Grade 2	3 (6%)	Grade 2	4 (7%)
Grade 2.5	0 (0%)	Grade 2.5	0 (0%)
Grade 3	7 (13%)	Grade 3	3 (6%)
Grade 4	0 (0%)	Grade 4	0 (0%)
Grade 5	0 (0%)	Grade 5	1 (2%)
Grade 6	0 (0%)	Grade 6	0 (0%)
MF bone marrow edema		LF bone marrow edema	
Normal	50 (92%)	Normal	27 (50%)
Grade 1	1 (2%)	Grade 1	1 (2%)
Grade 2	3 (6%)	Grade 2	13 (24%)
Grade 3	0 (0%)	Grade 3	13 (24%)
MT bone marrow edema		LT bone marrow edema	
Normal	46 (85%)	Normal	12 (22%)
Grade 1	5 (9%)	Grade 1	0 (0%)
Grade 2	3 (6%)	Grade 2	17 (31%)
Grade 3	0 (0%)	Grade 3	25 (47%)

WORMS, Whole-Organ MRI Scoring; MF, medial femoral condyle; LF, lateral femoral condyle; MT, medial tibial plateau; LT, lateral tibial plateau.
* Data expressed as count (percentage %).

At the 1-year follow-up, patients had reported significantly higher KOOS scores in all categories than at 6-months (all $P < 0.001$). The Marx activity level of patients at 1-year post-reconstruction was less than that prior to injury, but this finding was not significant ($P = 0.21$).

Cartilage T1ρ and T2 after ACL injury

At baseline, mean T1ρ and T2 values were significantly elevated in the cartilage of the injured knee overlying the pLT with respect to the contralateral knee (both $P < 0.0001$) (Fig. 2) (Table III). The T2 cartilage value of both the LT and TrF were also significantly higher in ACL-deficient knees compared to that of the uninjured knees ($P = 0.002$ and $P < 0.0001$, respectively).

Summary of significant predictors of KOOS and Marx at each time point

Table IV displays the significant associations identified for each individual outcome after linear regression. Baseline SSD T2 LT and pLT were not included in the model, as they are highly correlated with baseline SSD T1ρ pLT ($P < 0.001$). At baseline, higher SSD T1ρ pLT was significantly associated with lower KOOS in all subscales except symptoms ($P = 0.073$).

At 6-months post-reconstruction, higher baseline SSD T1ρ pLT was associated with worse KOOS pain ($P = 0.050$). Regarding WORMS, more severe cartilage lesions in the entire knee were significantly associated with worse KOOS outcomes in pain and ADL subscales ($P = 0.030$ and $P = 0.008$, respectively). The baseline outcome score for KOOS ADL was significantly associated with the 6-month score.

At 1-year follow-up, higher baseline SSD T1ρ pLT was significantly associated with worse KOOS in all subscales except sports ($P = 0.098$). Higher baseline SSD T2 TrF was significantly associated with worse 1-year KOOS ADL scores ($P = 0.032$). More severe articular cartilage injuries, as assessed by WORMS at baseline, were significantly associated with worse 1-year KOOS in the pain subscale ($P = 0.030$). For Marx at 1-year following surgery, only higher baseline SSD T1ρ pLT was associated with lower activity levels ($P = 0.013$) (Fig. 3).

Table V shows the change in patient-reported outcomes at all time points due to increases in the significant predictors from the lower to upper quartile. Clinically meaningful changes in a KOOS subscale and Marx activity level were estimated to be 8 and 2 points, respectively. At baseline, the effect of increasing the SSD T1ρ pLT was associated with clinically meaningful decreases in KOOS scores. At the 6-month follow-up, the effect of increasing the WORMS for total cartilage lesions was associated with clinically worse outcomes in KOOS pain. At 1-year follow-up, the effect of increasing the baseline SSD T1ρ pLT was associated with clinically relevant decreases in the KOOS QOL subscale and Marx activity level.

Discussion

In the present study, quantitative T1ρ and T2 mapping were used to determine the association between cartilage damage at the time of ACL injury and patient-reported outcomes after injury and post-reconstruction. Our results revealed that patients with higher baseline T1ρ in the pLT of the ACL-injured knee compared to the contralateral knee reported significantly worse outcomes at the time of injury and at 1-year post-reconstruction. To the best of our knowledge, this the first study to demonstrate that cartilage MR relaxation times can predict patient-reported outcomes after ACLR.

Table II
Patient-reported outcome scores over time*

Outcome	Baseline ($n = 51$)	6-month follow-up ($n = 46$)	1-year follow-up ($n = 42$)
KOOS			
Pain	74.4 ± 18.0	83.5 ± 12.4	86.4 ± 11.1
Symptoms	68.6 ± 19.4	74.4 ± 15.4	79.9 ± 13.1
ADL	81.9 ± 18.4	92.0 ± 9.4	94.6 ± 6.7
Sports	55.1 ± 27.7	68.9 ± 20.1	78.0 ± 17.8
QOL	43.4 ± 24.5	52.3 ± 19.3	62.4 ± 19.3
Marx activity	11.2 ± 3.9	–	10.2 ± 3.8

KOOS, Knee-injury and Osteoarthritis Outcome Score; ADL, activity of daily living; QOL, knee-related quality of life.
* Data expressed as mean ± standard deviation.

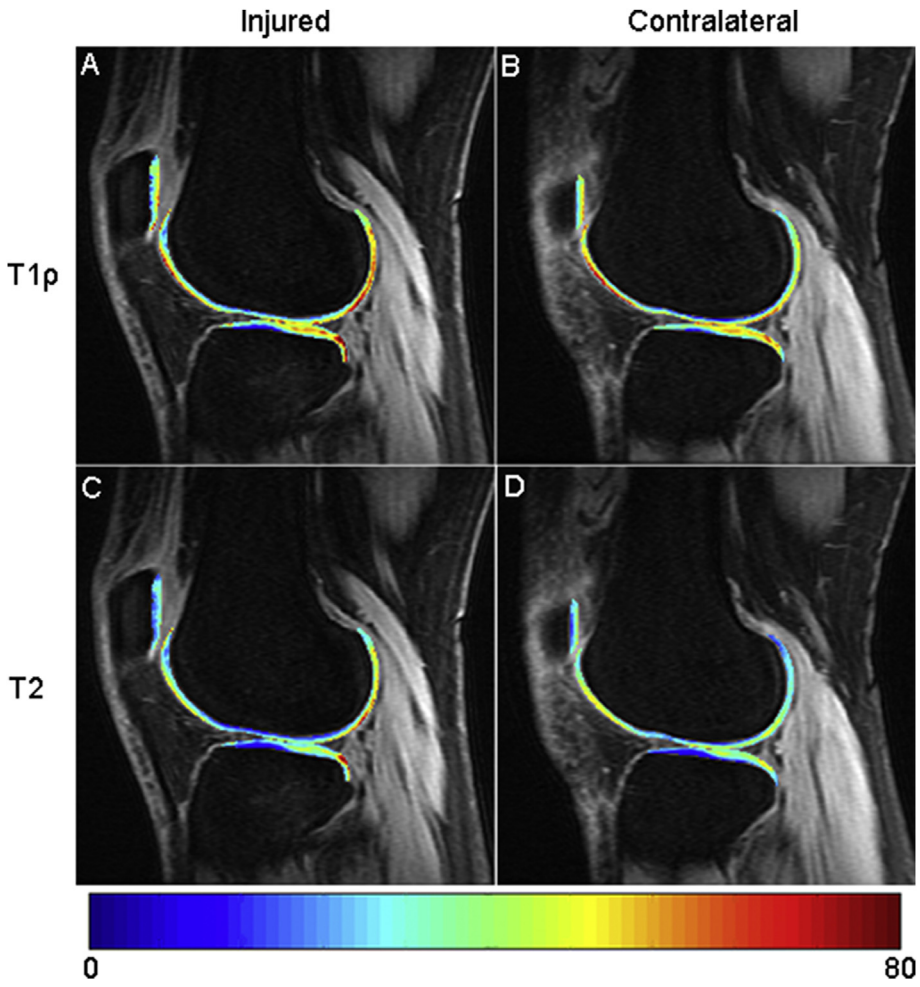

Fig. 2. Sagittal (A) T1ρ and (C) T2 maps of the ACL-ruptured knee show prolonged T1ρ and T2 relaxation times over the posterolateral tibial plateau and posterolateral femoral condyle compared to the (B, D) contralateral knee.

Table III
Baseline T1ρ and T2 (ms) of ACL-injured and contralateral knees*

	MF	LF	MT	LT	P	TrF	pLT
T1ρ							
Injured	38.9 ± 2.7	39.1 ± 2.5	35.5 ± 3.0	34.8 ± 2.8	38.9 ± 3.3	40.5 ± 2.7	41.9 ± 4.25
Contralateral	38.9 ± 3.1	38.4 ± 2.5	35.8 ± 3.0	34.3 ± 3.1	39.3 ± 3.6	40.0 ± 2.7	39.1 ± 3.9
P-value	0.89	0.012	0.48	0.14	0.28	0.093	**<0.0001**
SSD†	0.048 (−1.3, 1.0)	0.72 (−0.3, 2.3)	−0.34 (−2.6, 1.7)	0.529 (−1.3, 1.9)	−0.38 (−2.2, 1.0)	0.52 (−0.6, 1.5)	2.85 (0.9, 5.6)
T2							
Injured	30.1 ± 2.2	29.7 ± 2.3	27.0 ± 2.8	25.5 ± 2.3	28.6 ± 3.0	31.3 ± 2.4	31.9 ± 3.5
Contralateral	29.9 ± 2.6	29.4 ± 2.0	26.9 ± 2.6	24.7 ± 2.5	28.5 ± 2.6	29.8 ± 2.1	29.3 ± 3.3
P-value	0.42	0.27	0.62	**0.002**	0.72	**<0.0001**	**<0.0001**
SSD†	0.19 (−0.8, 1.0)	0.30 (−0.9, 1.2)	0.17 (−1.0, 2.1)	0.84 (−0.5, 2.0)	0.10 (−1.1, 1.1)	1.5 (0.5, 2.2)	2.5 (0.8, 4.8)

* Data is expressed as mean ± standard deviation. MF, medial femoral condyle; LF, lateral femoral condyle; MT, medial tibia; LT, lateral tibia; P, patella; TrF, femoral trochlea; pLT, posterolateral tibia. Bold denotes significance.
† Data is expressed as mean (interquartile range).

At baseline, T1ρ and T2 measurements were significantly elevated in the pLT of the ACL-deficient knee compared to the contralateral knee. BMELs were also most frequently noted in the lateral compartment of the injured knee. These findings are consistent with our previous studies, which compared ACL-injured knees to knees from a healthy control cohort, and reports from other groups, suggesting that most of the damage is dealt to the lateral compartment during anterior subluxation of the knee[8,21,22]. Thus, the worse baseline KOOS scores reported by patients with higher T1ρ in the pLT of the injured knee compared to the contralateral knee may be related to the severity of the cartilage damage experienced during injury. Furthermore, clinical morphological factors presumably related to severity of injury such as BMEL size, depth of cartilage lesions, and meniscal tears were not associated with KOOS at the time of ACLR. A prior prospective study likewise demonstrated that these factors were not significantly associated with KOOS pain or symptoms at baseline[6]. These findings suggest that the compositional changes to the cartilage matrix at the time of injury are better indicators of knee pain and function than morphological changes at baseline.

Table IV
Significant predictors of each outcome at baseline, 6-month, and 1-year follow-up*

Outcome	Baseline SSD T1ρ pLT			Baseline SSD T2 TrF			WORMS Medial Meniscus			WORMS Lateral Meniscus		
	β	SE	*P*-value	β	SE	*P*-value	β	SE	*P*-value	β	SE	*P*-value
Baseline ($n = 51$)												
KOOS												
Pain	**−0.38**	**0.14**	**0.008**	−0.04	0.14	0.773	−0.12	0.15	0.426	−0.02	0.14	0.882
Symptoms	−0.26	0.14	0.073	0.07	0.14	0.635	0.15	0.16	0.333	−0.22	0.15	0.136
ADL	**−0.38**	**0.13**	**0.006**	−0.06	0.13	0.668	−0.04	0.15	0.776	−0.10	0.14	0.488
Sports	**−0.37**	**0.16**	**0.022**	0.03	0.16	0.833	0.04	0.18	0.825	−0.15	0.17	0.379
QOL	**−0.33**	**0.15**	**0.034**	0.17	0.15	0.274	0.09	0.17	0.583	−0.05	0.16	0.747
6-month follow-up ($n = 46$)												
KOOS												
Pain	**−0.34**	**0.16**	**0.050**	0.04	0.16	0.816	−0.04	0.21	0.837	−0.15	0.21	0.495
Symptoms	−0.27	0.16	0.105	0.06	0.17	0.728	0.09	0.21	0.667	−0.05	0.22	0.827
ADL	−0.04	0.16	0.820	−0.14	0.15	0.362	−0.11	0.19	0.568	−0.17	0.20	0.415
Sports	−0.14	0.18	0.435	0.16	0.18	0.371	0.06	0.22	0.805	−0.22	0.23	0.352
QOL	−0.10	0.15	0.538	0.28	0.17	0.114	−0.05	0.20	0.806	−0.01	0.20	0.979
1-year follow-up ($n = 42$)												
KOOS												
Pain	**−0.45**	**0.15**	**0.006**	−0.07	0.15	0.639	−0.04	0.18	0.831	−0.15	0.17	0.384
Symptoms	**−0.36**	**0.16**	**0.027**	−0.09	0.17	0.606	0.08	0.20	0.698	−0.11	0.19	0.559
ADL	**−0.30**	**0.14**	**0.046**	**−0.33**	**0.15**	**0.032**	−0.23	0.18	0.210	−0.07	0.17	0.680
Sports	−0.28	0.16	0.098	−0.07	0.17	0.697	0.12	0.20	0.534	0.09	0.19	0.648
QOL	**−0.50**	**0.17**	**0.006**	0.06	0.19	0.737	−0.01	0.22	0.983	0.10	0.20	0.620
Marx	**−0.47**	**0.17**	**0.013**	0.07	0.22	0.717	0.21	0.21	0.341	0.06	0.23	0.807

Outcome	WORMS Total BMEL			WORMS Total Cartilage Lesion			Lateral Meniscectomy			Baseline KOOS or Marx Score		
	β	SE	*P*-value	β	SE	*P*-value	β	SE	*P*-value	β	SE	*P*-value
Baseline ($n = 51$)												
KOOS												
Pain	0.17	0.14	0.224	−0.22	0.14	0.133	–	–	–	–	–	–
Symptoms	0.00	0.14	0.983	−0.30	0.15	0.052	–	–	–	–	–	–
ADL	0.22	0.13	0.107	−0.27	0.14	0.060	–	–	–	–	–	–
Sports	0.18	0.16	0.255	0.06	0.17	0.714	–	–	–	–	–	–
QOL	0.00	0.15	0.999	−0.18	0.16	0.271	–	–	–	–	–	–
6-month follow-up ($n = 46$)												
KOOS												
Pain	0.10	0.19	0.596	**−0.41**	**0.18**	**0.030**	−0.03	0.24	0.892	0.15	0.16	0.379
Symptoms	0.24	0.19	0.215	−0.21	0.19	0.280	−0.10	0.24	0.672	0.26	0.18	0.160
ADL	−0.04	0.18	0.841	**−0.49**	**0.17**	**0.009**	−0.10	0.23	0.660	**0.38**	**0.16**	**0.027**
Sports	0.25	0.20	0.231	−0.36	0.19	0.070	0.09	0.26	0.743	0.36	0.17	0.046
QOL	0.07	0.18	0.712	−0.33	0.17	0.062	−0.24	0.23	0.310	0.21	0.16	0.190
1-year follow-up ($n = 42$)												
KOOS												
Pain	0.10	0.17	0.541	**−0.36**	**0.16**	**0.033**	0.12	0.20	0.543	0.08	0.15	0.614
Symptoms	0.28	0.18	0.121	−0.24	0.18	0.185	0.11	0.21	0.590	0.27	0.16	0.094
ADL	0.08	0.16	0.641	−0.18	0.15	0.251	−0.03	0.19	0.861	0.25	0.16	0.125
Sports	0.09	0.18	0.603	−0.08	0.17	0.644	−0.17	0.21	0.424	0.27	0.15	0.077
QOL	0.02	0.20	0.930	−0.09	0.19	0.643	−0.06	0.23	0.795	0.04	0.16	0.820
Marx	−0.21	0.21	0.337	0.30	0.19	0.123	0.07	0.23	0.807	0.18	0.21	0.430

SSD, side-to-side difference; pLT, posterolateral tibia; TrF, femoral trochlea; WORMS, Whole-Organ MRI Scoring; BMEL, bone marrow edema-like lesions; β, standardized regression coefficient; SE, standard error; KOOS, Knee-injury and Osteoarthritis Outcome Score; ADL, activities of daily living; QOL, knee-related quality of life. Bold denotes statistical significance.

* Regression analyses adjusted for age, gender, and BMI.

Although our previous quantitative MR studies on ACL-ruptured knees only identified differences in the tibiofemoral joint after injury, the current study establishes that T2 was significantly higher in the TrF of the ACL-injured knee compared to the contralateral knee at baseline. Frobell *et al.* previously documented cartilage thinning in the TrF of the ACL-injured knee within the first year, suggesting that the thinning may be related to development of patellofemoral arthritis[32,33]. Furthermore, Potter *et al.* reported increased risk of cartilage loss in the patellofemoral joint 7–11 years after ACL injury[8]. Additional studies using quantitative MRI will hopefully elucidate the long-term outcomes of the chondral degeneration to the patellofemoral joint after ACL injury.

At 6-month follow-up, higher baseline SSD T1ρ of the pLT predicted worse outcomes in KOOS pain, while more severe cartilage lesions in the entire knee, as assessed by WORMS, predicted worse outcomes in both KOOS pain and ADL subscales. However, at 1-year follow-up, our data demonstrated that higher baseline SSD T1ρ of the pLT predicted worse outcomes for KOOS in most subscales and Marx activity level, while increased severity of cartilage lesions of the entire knee only predicted worse outcomes for KOOS pain. These results suggest that the initial cartilage damage in the pLT, as assessed by T1ρ, is superior to the severity of cartilage loss in predicting the patient's final outcome after postoperative rehabilitation. In addition, neither the severity of meniscal tears nor excision of the lateral meniscus was significantly associated with patient-reported outcomes at 6-months or 1-year follow-up. This finding is supported by Norwegian and Swedish national ACL study that failed to identify significant associations between meniscal lesions and KOOS in any subscale at 2-year follow-up[12].

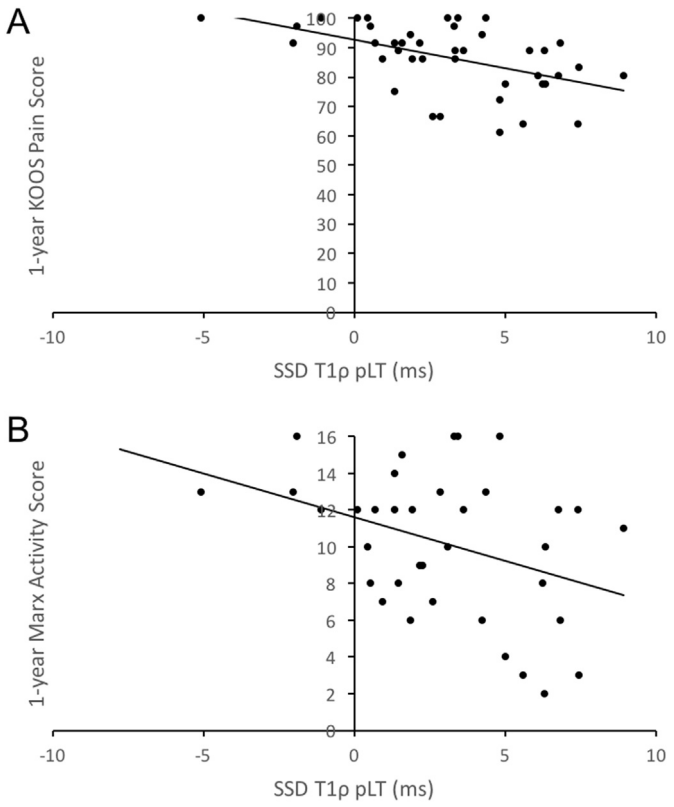

Fig. 3. Relationship between SSD T1ρ pLT and (A) 1-year KOOS Pain Score and (B) 1-year Marx Activity Score. SSD, side-to-side difference; pLT, posterolateral tibia; KOOS, Knee-Injury and Osteoarthritis Outcome Score.

Although these findings were statistically significant, their clinical significance can be debated. Roos *et al.* previously suggested that a difference of 8 points in a KOOS subscale may represent a clinically significant change following ACLR[24]. In regards to Marx activity level, the minimal clinical important difference was previously estimated to be 2 points[34]. The results of this study show that the effect of increasing the WORMS for cartilage lesions in the entire knee from the lower to upper quartile (3.8 points) decreased 6-month KOOS pain by 8.5 points. The clinical significance of this finding, however, was not observed at 1-year follow-up. For baseline SSD T1ρ of the pLT, an increase from the lower to upper quartile (4.7 ms) decreased 1-year KOOS knee-related QOL by 12.6 points and Marx activity level by 2.3 points. Thus, increased damage to the posterolateral tibial cartilage during ACL injury may influence clinically meaningful decreases in patient knee-related QOL and may be a potential factor as to why most patients do not return to pre-injury activity levels 1-year post-reconstruction.

In contrast to the results aforementioned, a recent cohort study involving 62 participants showed no significant correlations between cartilage T2 relaxation times and International Knee Documentation Committee and Tegner Lysholm Scoring Scale outcomes after ACLR[23]. However, possible differences in the study population, different follow-up periods, and use of different patient-reported outcome measures make it difficult to compare the findings and might explain the discrepancies in the reported results from the previous and the present studies. Moreover, the previous study recruited only male subjects and limited its analyses to the global cartilage compartments and cartilage-on-cartilage weight-bearing regions. Our analysis was more specific in that we included the pLT, an area often severely damaged during ACL injury, and the SSD in relaxation times.

The baseline KOOS scores from the present cohort are comparable to what has been reported by another comprehensive cohort in the United States (Multicenter Orthopaedic Outcomes Network,

Table V
Change in outcome measures at all time points from increasing the predictors from lower to upper quartile*

Outcomes	Baseline SSD T1ρ pLT (0.9, 5.6)†		Baseline SSD T2 TrF (0.5, 2.2)†		Total WORMS Cartilage Lesion (0.0, 3.8)†	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
Baseline ($n = 51$)						
KOOS						
Pain	**−8.92**	**−15.4 to −2.5**	−0.57	−4.5 to 3.4	−6.58	−14.8 to 1.6
Symptoms	−6.58	−13.5 to 0.4	1.08	−3.2 to 5.3	−9.57	−19.1 to 0.0
ADL	**−9.12**	**−15.2 to −3.0**	−0.88	−4.6 to 2.8	−8.25	−16.6 to 0.1
Sports	**−13.36**	**−24.7 to −2.0**	0.66	−6.2 to 7.6	2.76	−12.6 to 18.1
QOL	**−10.54**	**−19.9 to −1.2**	3.31	−2.4 to 9.0	−7.32	−20.1 to 5.4
6-month follow-up ($n = 46$)						
KOOS						
Pain	−5.50	−10.6 to −0.4	0.39	−2.7 to 3.5	**−8.45**	**−15.7 to −1.2**
Symptoms	−5.42	−11.7 to 0.9	0.73	−3.3 to 4.8	−5.37	−14.9 to 4.2
ADL	−0.49	−4.3 to 3.4	−1.05	−3.2 to 1.2	−7.65	−12.8 to −2.4
Sports	−3.67	−12.9 to 5.6	2.56	−3.1 to 8.2	−12.02	−24.5 to 0.4
QOL	−2.52	−9.9 to 4.9	4.29	−0.8 to 9.4	−10.58	−21.2 to 0.1
1-year follow-up ($n = 42$)						
KOOS						
Pain	−6.51	−10.8 to −2.3	−0.62	−3.2 to 2.0	−6.64	−12.4 to −0.9
Symptoms	−6.15	−11.5 to −0.8	−0.94	−4.4 to 2.5	−5.22	−12.9 to 2.5
ADL	−2.62	−5.0 to −0.2	−1.76	−3.3 to −0.2	−2.00	−5.3 to 1.3
Sports	−6.50	−13.8 to 0.8	−0.99	−5.7 to 3.7	−2.37	−12.2 to 7.5
QOL	**−12.60**	**−21.0 to −4.2**	0.92	−4.8 to 6.6	−2.88	−14.8 to 9.1
Marx	**−2.33**	**−4.0 to −0.7**	0.21	−1.1 to 1.5	1.89	−0.5 to 4.2

* SSD, side-to-side difference; pLT, posterolateral tibia; TrF, femoral trochlea; WORMS, Whole-Organ MRI Scoring; CI, confidence interval; KOOS, Knee-Injury and Osteoarthritis Outcome Score; ADL, activities of daily living; QOL, knee-related quality-of-life. Bold denotes clinically meaningful changes.
† Interquartile range.

MOON)[34,35]. Similarly, there is no clinically meaningful difference in baseline KOOS between our cohort and patients from the Danish, Swedish, and Norwegian national registries except for sports recreation and function and knee-related QOL[12,36,37]. The differences in these KOOS subscales between cohorts may be due to the longer times from injury to surgery in the national registries. However, the change in KOOS scores from baseline to 1-year follow-up in this study is comparable to those reported in the Danish ACL Reconstruction Registry[37]. In regards to activity levels, the results of this study, indicating that most participants (54%) do not return to their pre-injury activity levels after surgery, are corroborated by findings from previous reports[35,38–41].

In this study, the SSD T1ρ and T2 values of the pLT were significantly correlated ($r = 0.41$, $P < 0.001$). Consequently, T2 of pLT was excluded from the regression models to avoid multicollinearity. In an effort to compare the association between T1ρ and KOOS vs T2 and KOOS, we ran similar regression models using the SSD T2 of the pLT as the only quantitative MR measure. It was observed that T2 of the pLT is significantly associated with baseline KOOS except for symptoms and QOL ($P = 0.461$ and 0.080, respectively). These findings are similar to that of T1ρ; however, no significant associations are observed between T2 of the pLT and KOOS at 6-months and 1-year. These results suggest that although T1ρ and T2 may provide correlated image contrast after acute ACL injury, T1ρ may be more predictive of longitudinal patient-reported outcomes than that of T2. This finding is also corroborated by previous studies that have shown that T1ρ is more sensitive than T2 in detecting changes in proteoglycan concentration, and suggested that the cartilage matrix after acute ACL injury primarily involves loss of proteoglycan rather than significant damage to the collagen network[42–45]. Furthermore, Zarins *et al.* identified stronger associations between T1ρ and self-reported outcomes for pain, function, and stiffness in patients with OA than with T2[46]. Despite of all this, it should be noted that T1ρ imaging is currently used as a research prototype sequence with limited availability while T2 imaging is a product sequence available on all major vendors. The spin-lock strength of T1ρ imaging is also limited by the amount of energy allowed to be deposited to the tissue (measured by specific absorption rate, SAR). For clinical application at 3T, a spin-lock frequency of 500 Hz is normally used.

The primary limitation of the present study is the relatively small sample size of 42 patients at 1-year follow-up. As such, our models could not provide a more detailed analysis of the injuries involving BMEL, meniscal tears, and cartilage damage by compartment. In the current analysis, the WORMS scores of these potential morphological predictors were summed over the entire knee. Despite using a cumulative score, more severe cartilage lesions in the entire knee after injury, as assessed by WORMS, were almost significantly associated with worse baseline and 6-months KOOS in several subscales. To achieve a power of 80% with a two-sided significance level of 0.05, the sample size required for testing if WORMS total cartilage lesions predict 6-month KOOS in the sports subscale, for example, would be 52 based on the findings of this study. Therefore, cohorts with larger sample sizes are warranted to further investigate these relationships. Another weakness is the use of subjective questionnaires as the only outcome measure. The current assessments for evaluating the success of an ACLR also include the clinical stability and functional performance of the knee. Furthermore, the methods of this study rely on the use of bilateral knee MRs, which are currently not practical in a clinical setting. Finally, it is unknown how the associations between MR relaxation times and outcomes after ACLR will change with longer follow-ups. A planned 3-year follow-up will further clarify this.

Despite these limitations, the results from this study suggest that quantitative MRI provides a non-invasive, sensitive measure of cartilage damage that can potentially help clinicians predict the functional outcome of patients after ACLR. Our models inform us that a more severe injury to the cartilage matrix, especially in the pLT, are associated with worse patient-reported outcomes including pain, knee-related QOL, and activity level 1-year post-reconstruction.

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Supplementary data

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Competing interest statement

The authors involved in this study do not have any competing interests to disclose.

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