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SCIENTIFIC ARTICLE

Subchondral insufficiency fracture of the knee: grading, risk factors, and outcome

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Abstract

Objective To propose an magnetic resonance imaging (MRI) grading system for subchondral insufficiency fracture of the knee (SIFK) to predict outcome and assess risk factors.

Materials and methods A total of 50 SIFK patients were retrospectively reviewed utilizing two MRI examinations approximately a year apart and compared them with 51 control subjects. A grading system was introduced that classifies lesions as low- vs high-grade. Lesion location 3D dimensions, extent of bone marrow edema (BME), location of meniscal tears and associated extrusion, degree of chondrosis and among other parameters were stratified according to lesion grade and compared with follow-up examinations. Statistical analyses were performed (Pearson's correlation, binary logistic regression, and Chi-squared analysis).

Results The majority of SIFK lesions were low-grade (LG; 78%) and most of them (70%) were observed in the medial femoral condyle. Predictor variables comparing low-grade and high-grade SIFK lesions included meniscal tear ($p = 0.01$), degree of extrusion ($p < 0.003$), chondrosis ($p = 0.01$), medial chondrosis grade ($p = 0.001$), medial femoral condyle ($p = 0.01$), surface collapse ($p < 0.0001$), marrow edema improvement ($p < 0.0001$), first MRI anteroposterior dimension ($p = 0.001$), transverse dimension ($p < 0.001$), and ellipsoid volume ($p = 0.02$). Predictor variables found to be significantly different between controls and patients were meniscal tear ($p = 0.024$), location of the medial meniscal tear ($p < 0.0001$), degree of extrusion ($p < 0.0001$), chondrosis ($p < 0.0001$), joint effusion ($p < 0.0001$), Baker's cyst ($p < 0.0001$), knee lock ($p = 0.03$) and buckle ($p = 0.01$), and history of trauma ($p = 0.01$).

Conclusion A SIFK grading system for MRI is introduced. Surrogate markers of high-grade lesions include medial meniscus posterior root tears with associated moderate to severe extrusion, high-grade chondrosis, larger lesion sizes (anteroposterior/transverse), and articular surface collapse. Improvement of BME on follow-up was highly predictive of low-grade disease.

Keywords Insufficiency fracture of the knee · Meniscus · Bone marrow edema · Chondrosis · Spontaneous osteonecrosis of the knee

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Abbreviations

BME	Bone marrow edema
MMPRT	Medial meniscal tears at the posterior root attachment
MRI	Magnetic resonance imaging
SIFK	Subchondral insufficiency fracture of the knee
SONK	Spontaneous osteonecrosis of the knee

Introduction

Subchondral insufficiency fracture of the knee (SIFK) typically presents as a subchondral plate fracture surrounded by perifocal “flame-like” marrow edema, which can extend along and beyond the adjacent epiphysis. It results when a weakened subchondral bone plate is exposed to abnormal forces owing to absent overlying cartilage or inadequate meniscal protective property [1]. Since its description by Ahlbäck et al. [2], this entity has been reported to involve the weight-bearing articular aspect of the medial femoral condyle in elderly women, frequently presenting with severe, atraumatic knee pain of sudden onset. Little to no osteonecrosis has been identified on histological studies [2, 3] proving incorrect Ahlbäck’s original views that this lesion was due to osteonecrosis by excluding other possible etiologies such as arthritis, infection, trauma, osteochondritis dissecans, and malignancy. For this reason, the original term spontaneous osteonecrosis of the knee is now considered a misnomer; the entity has recently been categorized along the spectrum of SIFK.

Clinically, SIFK patients typically present with acute atraumatic pain and swelling/effusion and when focal articular collapse is present, this may be apparent on radiographs [4, 5]. The relevance of improving our understanding about this condition lies in establishing ways to treat the affected patients, as the clinical outcome of SIFK varies. The lesion may either heal with conservative management or undergo progression with articular collapse. It remains unclear by imaging which patients will progress to frank subchondral osteonecrosis and which will progress to resolution or lessened clinical disease burden. The prognosis of this disease process has been shown to depend on factors such as lesion size [6], location [7] and laterality of the meniscal tear [8, 9], and degree of meniscal extrusion [4]. Although more advanced SIFK stages typically present as a radiolucency or flattening of the affected condyle [2], radiography shows limited characterization of early lesions. For this reason, magnetic resonance imaging (MRI) has surfaced as the gold standard for characterizing this entity.

Only a few studies have evaluated the prognostic value of the location, size, and morphology of SIFK on MRI. We seek to further define this entity and identify MRI characteristics that may predict disease progression. Our main objective is to introduce an MRI-based grading system for SIFK to predict outcome and assess associated factors based on the grading system.

Materials and methods

Participants

This is an institutional review board-approved, Health Insurance Portability and Accountability Act-compliant retrospective study. An initial search for knee MRIs acquired between October 2012 and December 2015 in our radiology picture archiving and communication system yielded a total of 727 examinations (Fig. 1). After applying the inclusion and exclusion criteria, a total of 50 patients were identified with SIFK by MRI. Patient hospital electronic records were accessed to obtain demographic data and medical history in addition to information regarding knee pain and the presence of associated restricted ambulation. Patient MRI characteristics were compared with those of 51 age-, gender-, and body mass index (BMI)-matched controls, all of whom presented with acute unilateral knee pain (matching the side of the symptomatic comparison), with no evidence of SIFK on MRI (Table 1).

Inclusion criteria

Subjects included in the study met the following criteria: age ≥ 18 years; patients with an initial/baseline MRI with findings consistent with SIFK and a follow-up MRI examination within a year; patients with clinical symptoms of SIFK such as sudden pain in the affected side with tenderness, some degree of restricted range of motion, and no history of major trauma (Fig. 1). SIFK patients were treated with toe-touch weight-bearing restriction after their first MRI examination. This type of restriction requires that when the patient stands or walks, the foot only touches the floor for balance without placing any body weight on the affected leg.

Exclusion criteria

Subjects were excluded from the study on the following basis: history of recent (<3 months) surgical intervention in the symptomatic knee or infection, chronic knee pain (> 1 year), high-energy trauma (defined as trauma associated with fracture or high-grade contusion) prior to presentation or in the period between the two MRIs, and comorbidities such as alcoholism, chronic steroid use, sickle cell disease, arthropathies, or chronic renal disease (Fig. 1).

Outcome measures

The outcomes of the patients included were defined based on MRI findings at follow-up as either worsened/progressed or improved/resolved.

MRI protocol

Magnetic resonance imaging was performed using a 1.5-Tesla scanner (Siemens Medical Systems, Erlangen, Germany) with a phased array knee coil. Images from four pulse sequences were used in the assessment of SIFK features: sagittal fat-saturated, proton density-weighted, turbo spin echo images (repetition time 3,610 ms; echo time 40 ms; slice thickness

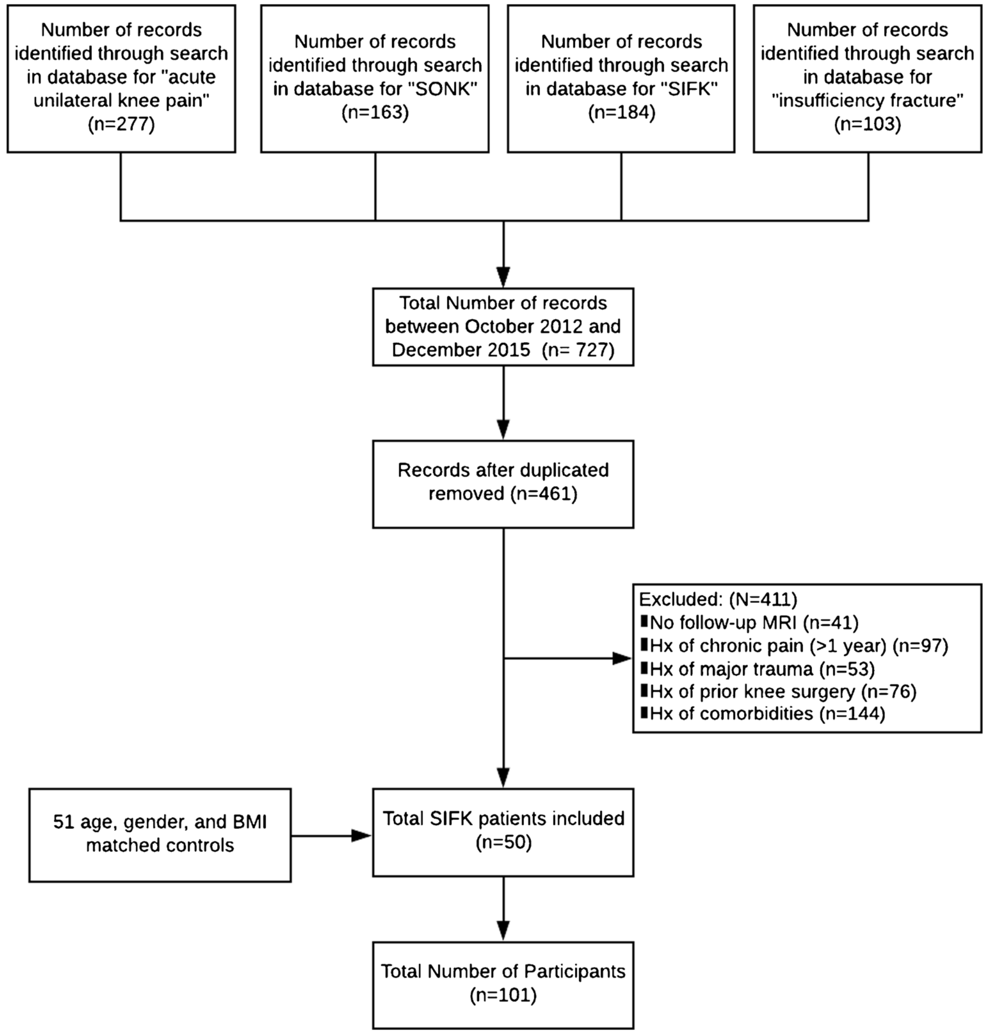

Fig. 1 Flow diagram of patient selection between October 2012 and December 2015. *SONK* spontaneous osteonecrosis of the knee, *SIFK* subchondral insufficiency fracture of the knee, *MRI* magnetic resonance imaging, *Hx* history, *BMI* body mass index

3.5 mm; interslice gap 0 mm; echo train length 7; field of view 140 mm × 140 mm; matrix 256 × 256) and axial, coronal, and sagittal fat-saturated, T2-weighted spin echo images (repetition time > 2,000 ms; echo time 70–80 ms; slice thickness 3.5 mm; interslice gap 0 mm; field of view 140 mm × 140 mm; matrix 256 × 256), and coronal T1-weighted spin echo images without fat saturation (repetition time 500 ms; echo time 9.8 ms; slice thickness 3.5 mm; interslice gap 0 mm; field of view 140 mm × 140 mm; matrix 256 × 256).

Proposed SIFK grading system based on MRI findings

Three MSK fellowship trained radiologists with more than 25 years of combined post-fellowship experience graded the MRI images. The grading was done blindly and determined based on consensus. The following SIFK grading system was proposed based on the experience of the most common presentations of these lesions observed by the radiologists, where types 1 and 2 were considered as LG and types 3 and 4 as high-grade (HG) lesions (Fig. 2). Subchondral fractures were defined as T1-T2 hypointense signal intensity changes, usually in the form of a line paralleling the articular surface.

- Type 1: Presence of bone marrow signal abnormality of the subchondral plate with associated thickening and surrounding intense marrow edema (osteitis) in the absence of a visible subchondral fracture.
- Type 2: Subchondral fracture in the absence of cystic or osteonecrotic changes.
- Type 3: Subchondral fracture accompanied by cystic changes.
- Type 4: Subchondral fracture in the presence of subchondral collapse and overlying articular surface step off.

SIFK lesion

The SIFK lesion location was defined in the medial and lateral tibiofemoral compartments using the coronal (medial, central,

Table 1 Comparisons of demographic data, physical findings, and incidence of trauma between patients and control subjects

		Patients	Controls	*p* value*
Age (years)		51.5 ± 15.7 (range: 12–89)	50.61 ± 16.25 (range: 13–87)	0.784
Gender	Male	62% (31/50)	49% (25/51)	0.978
	Female	38% (19/50)	51% (26/51)	
BMI		29.9 ± 5.9 (range: 14.6–48.7)	29.9 ± 7.7 (range: 16.3–36.6)	0.189
History of trauma		66% (33/49)	41.2% (21/51)	0.012
Medial collateral knee stabilizers injury	MCL	9.1% (3/33)	33% (7/21)	0.025
	MPFL	0%	0%	
Time interval between trauma and first MRI (months)		2.4 ± 2.73	2.97 ± 8.71	0.660
Physical findings on presentation	Pop	42% (21/50)	41.2% (21/51)	0.933
	Lock	34% (17/50)	15.7% (8/51)	0.033
	Buckle	52% (26/50)	25.5% (13/51)	0.006
Time interval between first and second MRI (months)		5.06 ± 3.344	–	–

BMI body mass index, *MCL* medial collateral ligament, *MPFL* medial patellofemoral ligament, *MRI* magnetic resonance imaging

*Please note that significant *p* values (<0.05) are highlighted in bold

lateral) and sagittal (anterior, middle, posterior) planes. On T1-weighted images, lesion size was documented as a percentage with respect to the total articular surface in the affected location (lesion size/affected femoral condyle or tibial plateau articular surface on both coronal and sagittal planes), as shown in Fig. 3. Additionally, a lesional elliptical volume (mm^3) was calculated by measuring the anteroposterior (AP; in the sagittal plane), transverse (TR; in the coronal plane), and craniocaudal dimensions (CC; in the coronal plane) using the following formula: volume = 4/3 x (πabc) with a = AP

	Low Grade		High Grade	
	Grade 1	Grade 2	Grade 3	Grade 4
Contusion of subchondrate plate	+	+	+	+
Subchondral fracture		+	+	+
Subchondral cystic changes			+	+
Early osteonecrosis +/- subchondral collapse				+

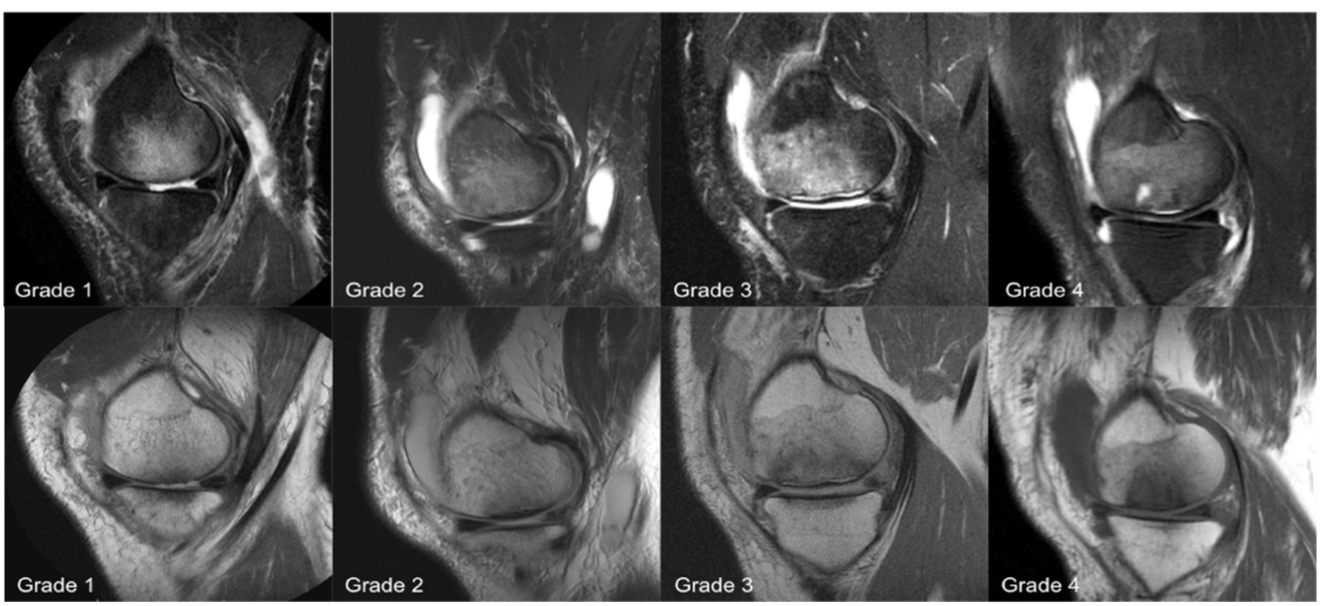

Fig. 2 Illustration of types 1 through 4 in a table format (*top*) showing partial articular surface collapse in the advanced stage 4 with equivalent T2- and T1-weighted MRI (*bottom*), with the presence of a subchondral fracture in type 2, subchondral cystic changes in type 3, and collapse in type 4

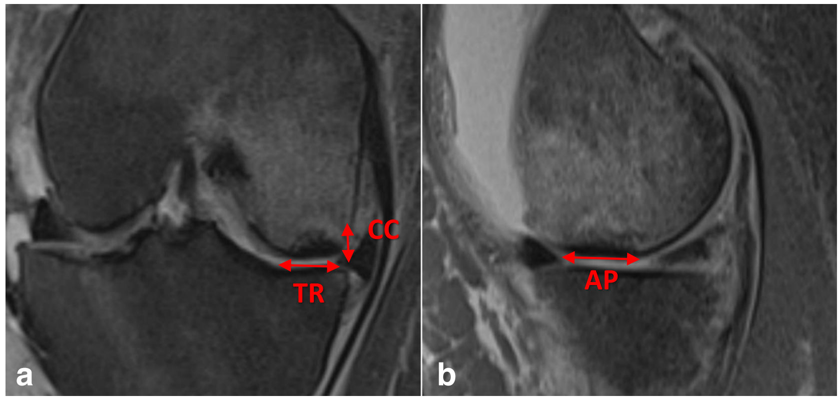

Fig. 3 **a** Transverse (*TR*) and craniocaudal (*CC*) measurements of a SIFK lesion on coronal view and **b** anteroposterior (*AP*) measurement of the same lesion on sagittal view located in the medial femoral condyle

dimension; B = TR dimension; C = CC dimension in millimeters [6]. Focal surface collapse was described as contour depression on the femoral or tibial joint surface.

Bone marrow edema, joint effusion, and soft-tissue edema

On MRI, BME was described as an area of low signal on T1-weighted images and high signal on T2-weighted imaging. Follow-up of BME change on imaging described either a reduction by 50–75% or 90–100% vs an increase by 0–50% or > 50% with respect to the total surface area of the femoral condyle or tibial plateau affected. On the initial MRI, the femoral condyle and tibial plateau were divided into three zones (anterior, central, and posterior) and the bone marrow edema distribution present was graded with respect to the area it occupied in each of these zones (grade 1: < 25%; grade 2: 25–50%, grade 3:>50–75%, grade 4 > 75%). A point system was assigned to each grade by annotating 1 through 4; therefore, if a scan showed edema >75%, that scan would receive a score of 4. Lastly, a qualitative assessment of the joint effusion (small, moderate, or large) and soft-tissue edema (adjacent and non-adjacent) was recorded.

Meniscal tears and extrusions

Meniscal tears (medial or lateral) with or without extrusions were identified on the coronal and sagittal fat-suppressed T2-weighted sequences. Meniscal tear location was described with respect to the anterior or posterior horns or meniscal body with or without root attachment involvement. Meniscal extrusion measurement was determined as the distance between the outer margins of the tibial plateau and the mid-central aspect of the meniscal body and was classified as mild (< 3 mm), moderate (3–5 mm), and severe (> 5 mm), as proposed in the literature [4, 10, 11].

Chondrosis

The International Cartilage Repair Society grading system was used to evaluate the extent of chondrosis [12] as follows: grade 0—normal cartilage; grade 1—signal intensity alterations with an intact surface of the articular cartilage compared with the surrounding normal cartilage; grade 2—partial thickness chondral defect (<50% of the total cartilage thickness); grade 3—chondral defect or fissuring involving >50%; and grade 4—full thickness defect with exposed subchondral bone. Chondrosis location was described as being in the medial or lateral knee compartments.

Medial collateral ligament complex

To evaluate if SIFK was seen in the setting of high-energy trauma, the integrity of medial collateral and medial patellofemoral ligaments was assessed (grade 1 sprain with superficial or surrounding fluid, grade 2 as partial-thickness and grade 3 as full-thickness tears). The medial collateral ligament complex was evaluated specifically because the medial femoral condyle/medial knee compartment is the most common SIFK location.

Statistical analysis

Pearson's correlation coefficient was computed to evaluate the correlation of SIFK grade, participant, gender, history of trauma, presence of clinical signs (pop, lock, buckle), meniscal tears and extrusions, chondrosis, surface collapse, bone marrow and soft-tissue edema, joint effusion, Baker's cysts, and MRI measurements. A binary logistic regression analysis was used to predict participant category based on clinical assessment measures. Furthermore, another binary logistic regression was used to determine whether the factors associated with pathogenesis and progression of SIFK (i.e., meniscal tears and location, degree of extrusion, presence of chondrosis and grade of chondrosis, location in knee, surface collapse, soft-tissue edema, marrow edema improvement, and MRI AP, TR, CC, volume, and measurements) would be able to predict LG or HG lesions. Additionally, an ROC analysis was performed to determine the sensitivity, specificity, and threshold cut-offs for first MRI measurements in discriminating LG and HG SIFK, in addition to the presence or absence of bone edema improvements. All analyses were performed in SPSS version 24 (IBM, Armonk, NY, USA). Statistical significance level was 0.05.

Results

Patients vs controls

The binary logistic regression model for predicting participant category was found to be significant based on the omnibus test of model coefficients ($p < 0.0001$). The Nagelkerke R square value was 0.826, indicating that the predictor variables explained 82.6% of the variation in the participant category. The model goodness-of-fit was assessed using the Hosmer–Lemeshow test and was found to be significant ($p = 0.976$) and the model correctly predicted participant category in 91.1% of the cases. The predictor variables found to be significant in the model were meniscal tear ($p = 0.024$), location of medial meniscal tear ($p < 0.0001$), degree of extrusion ($p < 0.0001$), chondrosis ($p < 0.0001$), joint effusion ($p < 0.0001$), Baker's cyst ($p < 0.0001$), knee lock ($p = 0.03$) and buckle ($p = 0.01$), and history of trauma ($p = 0.01$).

Overall, meniscal tears were located medially in 66% of the patients (33 out of 50), laterally in 10% (5 out of 50), and concurrently medially and laterally in 4% (2 out of 50). In contrast, 47.1% of the controls (24 out of 51) had medial meniscal tears, 2% (1 out of 51) had lateral meniscal tears, and 11.8% (6 out of 51) demonstrated both medial and lateral meniscal tears ($p = 0.024$; Chi-squared). Medial meniscal tears involving the posterior root attachment (MMPRT) were seen in 58% of the patients (29 out of 50) compared with 13.7% (22 out of 51) in the control participants ($p = 0.000$; Chi-squared; Fig. 4; see Table 3). As for meniscal extrusion, 32% of patients (16 out of 50) had no meniscal extrusion and 62% (17 out of 50) had moderate to severe extrusion (3–5 mm and > 5 mm) as opposed to 58% (30 out of 51) of controls who did not have meniscal extrusion and 27.5% (14 out of 51) who had mild extrusion (<3 mm) ($p = 0.000$; Chi squared; see Table 3).

Furthermore, chondrosis in patients was detected medially in 62% (31 out of 50) of the cases and laterally in 16% (8 out of 50; see Table 3). Twenty-two percent of patients (11 out of 50) showed no signs of chondrosis vs 51% among controls (26 out of 51) ($p = 0.000$; Chi-squared). As for the degree of medial compartment chondrosis, no significant difference was seen between patients and controls ($p = 0.094$; Chi-squared; see Table 3). Additionally, SIFK patients had moderate sized joint effusions in 40% (20 out of 50) of cases, in contrast to 56.9% of control participants (29 out of 51) who did not have any joint effusion ($p = 0.00$; Chi-squared) as shown in Table 3. Lastly, 66% of patients (33 out of 49) reported minor trauma ($p = 0.012$; Chi-squared) to the affected knee (Table 1). A third (33.3%) of the controls (7 out of 21) showed signs of grade 1 MCL sprain vs 9.1% of the patients (3 out of 33) ($p = 0.025$; Chi-squared). The mean time between the reported trauma and the first MRI was 2.4 ± 2.73 months in our patient population ($p = 0.660$; *t* test).

Knee popping was found to be almost equal in our groups: 42% of the patients (21 out of 50) vs 41.2% of the controls (21 out of 51) ($p = 0.933$; Chi-squared). However, in our patient population, incidence of locking (34%; 17 out of 50; $p = 0.033$; Chi-squared) and buckling (52%; 26 out of 50; $p = 0.01$; Chi-squared) of the symptomatic knee was significantly higher. Eight out of 51 controls (15.7%) reported knee locking and 13 out of 51 (25.5%) reported buckling.

High-grade vs low-grade lesions

The binary logistic regression model for predicting SIFK grade was found to be significant based on the omnibus test of model coefficients ($p < 0.01$). The Nagelkerke R square value was 0.99, indicating that the predictor variables explained 99.99% of the variation in the participant category. The model goodness-of-fit was assessed using Hosmer–

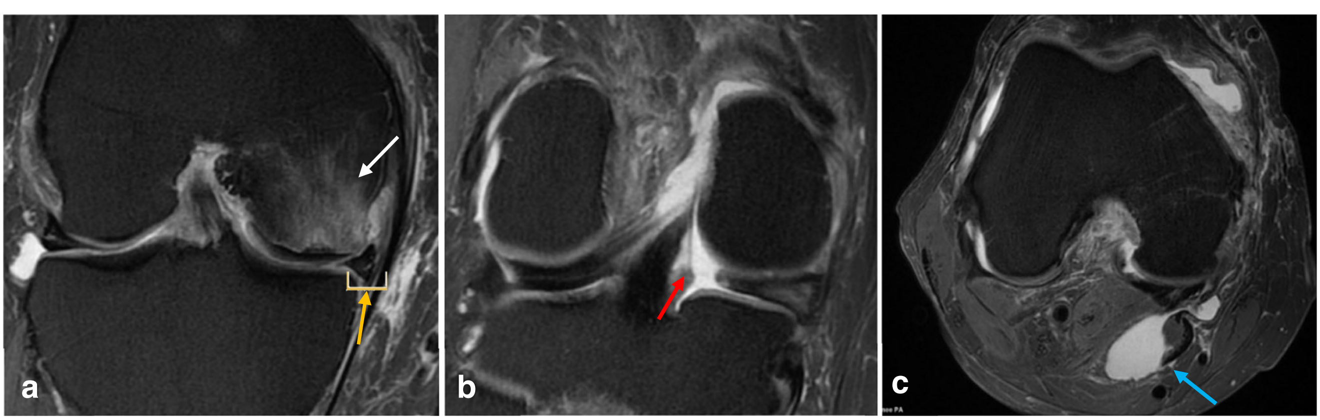

Fig. 4 **a**, **b** Coronal T2-weighted views of a high-grade (HG) lesion in the medial femoral condyle (*white arrow*). See associated posterior medial meniscal root radial tear (*red arrow*) and meniscal body extrusion (*yellow arrow*). **c** Axial view of the same knee showing a Baker's cyst (*blue arrow*)

Lemeshow test and was found to be significant ($p > 0.99$) and the model correctly predicting participant category in 99.99% of the cases. The predictor variables found to be significant in the logistic model were meniscal tear ($p = 0.01$), degree of medial meniscal tears extrusion ($p = 0.01$), location ($p = 0.013$) and degree of chondrosis ($p = 0.008$), medial chondrosis grade ($p = 0.001$), medial femoral condyle ($p = 0.01$), bone marrow edema improvement ($p < 0.0001$), surface collapse ($p < 0.0001$), first MRI AP dimension ($p = 0.001$), first MRI TR dimension ($p < 0.001$), and ellipsoid volume ($p = 0.02$).

Type 1 SIFK was seen in 42% (21 out of 50), type 2 in 36% (18 out of 50), type 3 in 12% (6 out of 50), and type 4 in 10% of patients (5 out of 50; Table 2). The most common location for SIFK lesions was the medial femoral condyle, which was seen in 70% of patients (35 out of 50), followed by the lateral femoral condyle (12%; 6 out of 50), the lateral tibial plateau (12%; 6 out of 50), and lastly the medial tibial plateau (6%; 3 out of 50; Table 2). 100% of HG lesions (11 out of 11) were located in the medial femoral condyle as opposed to 61.5% (24 out of 39) LG lesions ($p = 0.014$; Chi-squared).

Predictor variables found to be significant in the logistic regression model include the presence of meniscal tear ($p = 0.012$; Chi-squared) and degree of medial meniscal extrusion ($p = 0.01$; Chi-squared). Ninety-one percent (10 out of 11) of patients with HG SIFK (types 3 and 4) had MMPRT and associated meniscal extrusion compared with 49% (19 out of 39) in patients with LG SIFK and specifically 63.6% (7/11) of HG lesions were seen in conjunction with severe meniscal extrusion (>5 mm). On the other hand, 41% LG lesions (16/39) exhibited meniscal tears without meniscal extrusion with 35.9% (14 out of 39) demonstrating moderate extrusion (see Table 4).

Location of chondrosis was also observed to be a significant factor ($p = 0.01$; Chi-squared) in the logistic analysis. All HG lesion patients showed some degree of chondrosis in the medial knee compartment (100%; 11 out of 11; Fig. 5). LG lesions were seen in association with medial compartment chondrosis in only 51.3% of the cases (20 out of 39). HG lesions were associated with grade 4 medial compartment chondrosis in 45.5% (5 out of 11) in contrast to 48.7% of LG lesions (19 out of 39), which were not associated with degenerative cartilage disease ($p = 0.008$; Chi-squared; see Table 4). Chondrosis grade was a significant differentiating factor between LG and HG lesions ($p = 0.008$; Chi-square).

In the sagittal plane, the femoral and tibial condyles were divided into three zones (anterior, central, and posterior) and the bone marrow edema distribution present on the initial MRI was graded with respect to the area it occupied in each of these zones on the initial MRI scans (grade 1: < 25%; grade 2: 25–50%, grade 3:>50–75%, grade 4 > 75%). Mean scores were 1.7 for the LG lesions (types 1 and 2) and 3.4 for the HG lesions (types 3 and 4), $p < 0.001$. Improvement of BME was found to be another important predictive variable ($p < 0.0001$). Although the majority of patients had substantial BME (affecting more than 25% of the femoral condyle or tibial plateau involved), only LG SIFK had substantial BME improvement (ranging from a 50% decrease to resolution) in 92.7% of cases (38 out of 41; Chi-squared test; Fig. 5). Only 2.6% of edema linked to LG lesions (1 out of 39) progressed

Table 2 Comparisons of demographic data and lesion characteristics between low-grade (LG) and high-grade (HG) subchondral insufficiency fractures of the knee (SIFK) patients

		LG	HG	*p* value*
Age (years)		49.9 ± 16	57.2 ± 13.6	0.174
Gender (%)	Male:female	64.1% 35.9%	54.5% 45.5%	0.564
BMI		29.8 ± 5.88	30.0 ± 6.21	0.913
Lesion grade		39/50 78%	11/50 22%	
Lesion location	Medial femoral condyle	24/39 61.5%	11/11100%	**0.014**
Mean lesion dimension	Anteroposterior (mm)	10.78 ± 3.77	16.78 ± 7.88	**0.032**
	Transverse (mm)	8.83 ± 3.02	13.14 ± 3.13	**0.001**
	Craniocaudal (mm)	2.27 ± 2.68	3.45 ± 2.72	0.203
	Maximum (mm)	11.63 ± 3.44	18.82 ± 5.67	**0.000**
	Sum (mm)	21.87 ± 6.82	33.37 ± 8.54	**0.000**
	Ellipsoid V (mm^3)	1133 ± 2122	2948 ± 2598	**0.021**
	First MRI mean surface area (%)			
	Coronal	4.036 ± 4.11	3.95 ± 3.56	0.943
	Sagittal	2.26 ± 0.36	1.79 ± 0.54	0.381
	Second MRI mean surface area (%)			
	Coronal	1.45 ± 2.64	10.23 ± 6.30	**0.001**
	Sagittal	1.02 ± 2.33	7.86 ± 3.43	**0.000**

*Please note that significant *p* values (<0.05) are highlighted in bold

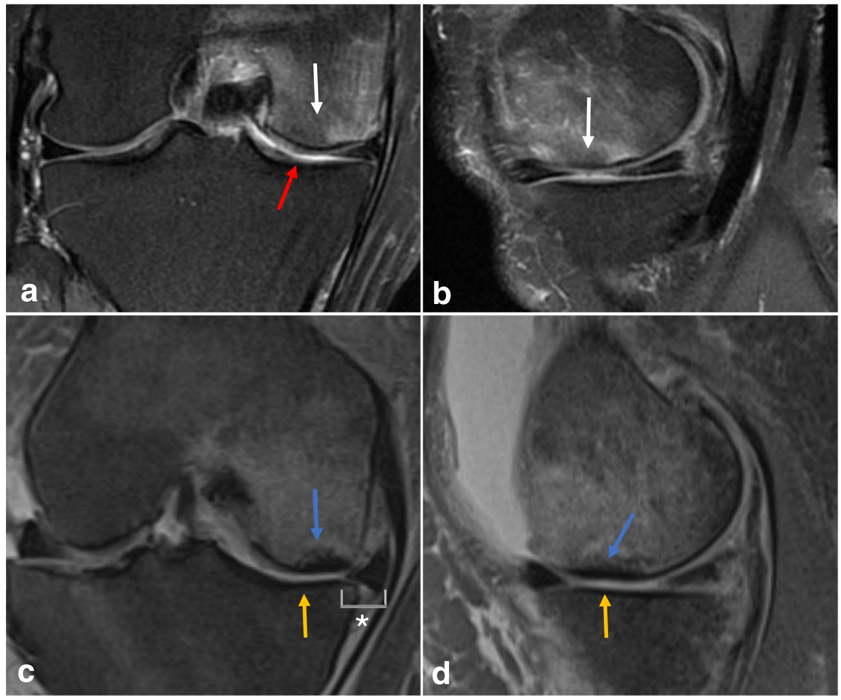

Fig. 5 **a** Coronal and **b** sagittal T2-weighted images showing a low-grade (LG) SIFK lesion (*white arrows*) associated with grade 2 chondrosis (*red arrow*) as per modified Outerbridge classification. **c** Coronal and **d** sagittal images of a HG SIFK lesion (*blue arrows*) associated with grade 3–4 chondrosis (*yellow arrows*). Please note the marked medial meniscal extrusion seen in the setting of an HG lesion (*asterisk*)

by 0–50%. In contrast, 89% of HG SIFK patients (8 out of 9) on the initial MRI showed no decrease in BME on follow-up imaging (Fig. 6). Five out of 11 (45.5%) and 3 of 11 HG lesions (27.3%) exhibited an increase in BME by 0–50% and greater than 50% respectively (see Table 4). None of the LG lesions was associated with articular surface collapse, a finding that was found in all HG lesions ($p < 0.0001$; Chi-squared test).

There was no significant difference between knee joint effusion in LG and HG SIFK lesions ($p = 0.067$; Chi-squared test; see Table 4). As for the presence of Baker's cysts, 52% of patients had small cysts (26 out of 50) and 18% were found to have a moderate-sized cyst; Fig. 4; Table 3). In contrast, 70.6% of controls (36 out of 51) did not have a cyst ($p < 0.0001$; Chi-squared test). Perilesional soft-tissue edema was seen in all the cases. Twenty-seven out of 39 of LG SIFK (69.2%) had adjacent soft-tissue edema and only 17.9% (7 out of 39) displayed non-adjacent edema in comparison with 54.5% of HG lesions that were associated with extending non-adjacent perilesional soft-tissue edema (Fig. 7; Table 4).

Lesion size

In comparison with LG lesions, HG lesions had larger AP (mean values of 16.78 ± 7.88 [HG] vs 10.78 ± 3.77 [LG], $p = 0.032$; ***t*** test) and TR dimensions (13.14 ± 3.13 [HG] vs 8.83 ± 3.02 [LG], $p = 0.001$; ***t*** test). In fact, HG lesions had larger means of maximum lesion dimensions (18.82 ± 5.67 vs 11.63 ± 3.44; $p = 0.00$; ***t*** test) and sum of dimensions (33.37 ± 8.54 vs 21.87 ± 6.82; $p = 0.000$; ***t*** test). The mean of ellipsoid volumes of SIFK lesions was significantly greater in HG than those of LG lesions (2,948 ± 2,598 mm^3 vs 1,133 ± 2,122 mm^3; $p = 0.021$; ***t*** test). Lastly, the mean percentage surface area on the coronal ($p = 0.947$) and sagittal ($p = 0.381$) planes on the initial MRI examinations were not significantly different among the LG and HG lesions. However, on follow-up MRI, the mean % surface area of HG lesions was greater than that of LG lesions on the coronal plane (10.23 ± 6.30 vs 1.45 ± 2.64; $p = 0.001$; ***t*** test) and on the sagittal plane (7.86 ± 3.43 vs 1.02 ± 2.35; $p = 0.000$; ***t*** test); Table 2.

Receiver operating characteristic analysis

Receiver operating characteristic (ROC) analysis showed that higher first MRI AP dimension values were significant in differentiating HG SIFK from LG SIFK ($p = 0.03$; area under the curve [AUC] = 0.71; 95% confidence interval: 0.49–0.93). A cut-off value of 16.5 mm for AP dimension yielded a specificity of 92.3% and sensitivity of 63.6%. Higher first MRI TR dimension values were also significant in differentiating HG SIFK from LG SIFK ($p < 0.0001$; AUC = 0.85; 95% confidence interval: 0.75–0.96). A cut-off value of 10.5 mm for TR dimension yielded a specificity of 76.9% and a sensitivity of 81.8%. ROC analysis also revealed that larger first MRI ellipsoid volume was significant in differentiating HG SIFK from LG SIFK ($p = 0.004$; AUC = 0.79; 95% confidence interval: 0.6–0.97). A cut-off value of 237.72 mm^3 for ellipsoid volume yielded a specificity of 84.6% and a sensitivity of 81.8%. ROC analysis showed that higher first MRI TR

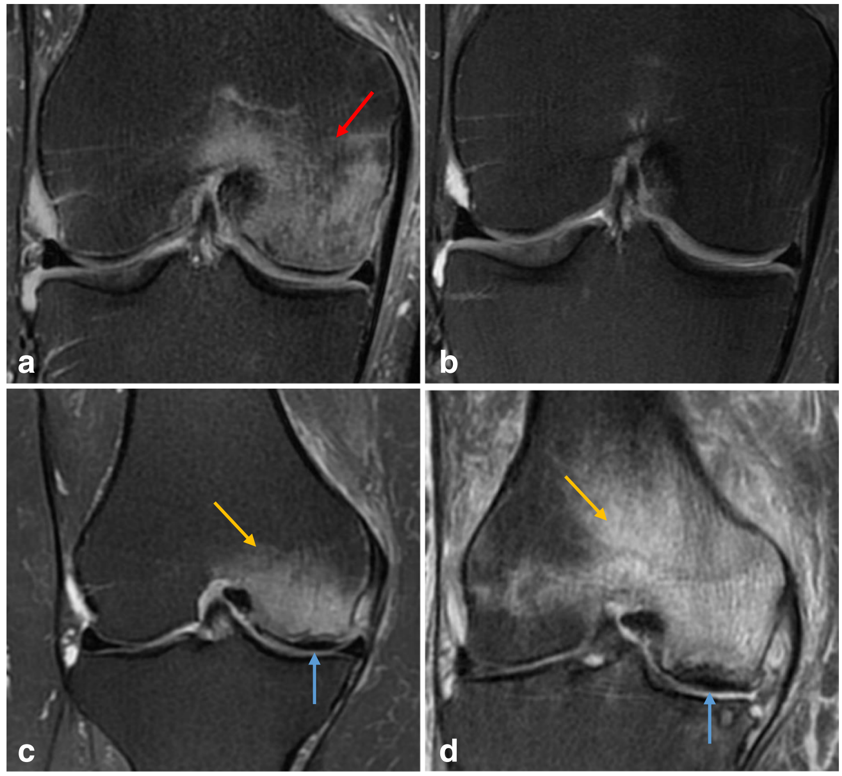

Fig. 6 **a** Coronal T2-weighted image of a type 1 lesion present in the medial femoral condyle with associated bone marrow edema (BME) taken on 15 November 2013 (*red arrow*), whereas **b** is a coronal follow-up MRI of the same knee on 16 April 2013 showing resolution of BME. **c** Coronal T2-weighted image of a type 3 lesion (*blue arrow*) present in the medial femoral condyle with associated BME (*yellow arrow*) taken on 7 March 2014 and **d** is a coronal follow-up MRI of same knee on 30 August 2014 showing an increase in BME (*yellow arrow*) and lesion size

dimension was significant in differentiating no bone edema improvement from improvement ($p < 0.0001$; AUC = 0.89; 95% confidence interval: 0.80–0.99). A cut-off value of 10.5 mm for TR dimension yielded a specificity of 75.6% and sensitivity of 88.9%.

Discussion

Subchondral insufficiency fracture of the knee has been previously described to be more common among female patients who are 60 years of age or older [13]; however, our patient demographics reveal a higher incidence of younger (mean age of approximately 52 years) males being affected. We hypothesize that at a lower mean age, males might be more likely to be affected than females, perhaps because of greater physical demand on the knees, and because at a more advanced age, osteoporosis is four times more common in women than in men, and female patients present more commonly with osteoporosis-related complications [14]. In addition, a similar BMI (30) was found between LG vs HG lesions and BMI was not found to be an independent variable implicated in disease progression, which may also be related to the younger patient population.

The clinical outcome of SIFK varies and there is controversy regarding which imaging findings in SIFK patients predict irreversible lesions, i.e., those that progress regardless of conservative therapy and that may ultimately necessitate joint replacement. A detailed assessment of the associated changes in the form of a grading system would allow differentiation between early irreversible lesions and lesions that resolve with conservative treatment. We found that a cutoff of 26 mm for the mean sum of the lesion dimensions (i.e., AP, TR and depth dimensions) was the most reliable predictor (sensitivity of 91%) of forecasting a bad prognosis and that individual AP and TR dimensions of or greater than 16.5 and 10.5 mm respectively also predicted disease progression and a negative outcome. Lesion size as a prognostic indicator has been discussed in the literature, although not at length. Lotke et al. proposed that a lesion depth of over 4 mm on the TR plane and a length in the AP direction of over 14 mm on T2-weighted images was predictive of a poor prognosis [15]. Norman and Baker showed that lesions with a width greater than 50% of the femoral condyle were associated with worse outcomes [16]. Similarly, Aglietti et al. established that a ratio of <40% (percentage of the maximum TR width of the affected condyle) was an indicator of a more favorable outcome [13]. In the landmark paper by Yamamoto et al., a review of pathological specimens demonstrated that a subchondral insufficiency fracture represents the primary etiology that may result in osteonecrosis confined to the fracture area [17], attesting to the importance of localizing and providing details of this fracture, including lesion dimensions and degree of overlying articular surface collapse. Our study incorporates the lesion size criteria as part of our grading

Table 4 Comparison of imaging findings associated with SIFK disease progression between patients with LG and HG lesions

		LG		HG		*p* value*
Location of medial meniscal tears	Posterior horn with root attachment	19/39	48.7	10/11	91	***p* = 0.012**
	Posterior horn without root attachment	3/39	7.7	0/11	0	
	Anterior horn	1/39	2.6	1/11	9.1	
	Meniscal body	1/39	2.6	0/11	0	
Degree of medial meniscal tear extrusion	None	16/39	41	0/11	0	***p* = 0.01**
	Mild (< 3 mm)	2/39	5.1	1/11	9.1	
	Moderate (3–5 mm)	14/39	35.9	3/11	27.3	
	Severe (> 5 mm)	7/39	17.9	7/11	63.6	
Location of chondrosis	Medial	20/39	51.3	11/11	100	***p* = 0.013**
	Lateral	8/39	20.5	0/11	0	
	Both	11/39	28.2	0/11	0	
Degree of chondrosis	None	19/39	48.7	0/11	0	***p* = 0. 008**
	Grade I	0/39	0	0/11	0	
	Grade II	11/39	28.2	3/11	27.3	
	Grade III	4/39	10.3	3/11	27.3	
	Grade IV	5/39	12.8	5/11	45.5	
Bone marrow evolution	Decreased by 100–90%	28/39	71.8	0/11	0	***p* = 0.000**
	Decreased by 75–50%	10/39	25.6	3/11	27.3	
	Increased by 0–50%	1/39	2.6	5/11	45.5	
	Increased by >50%	0/39	0	3/11	27.3	
Articular surface collapse		0/39	0	8/8	100	***p* = 0.000**
Perilesional soft-tissue edema	None	5/39	12.8	0/11	0	
	Adjacent	27/39	69.2	5/11	45.5	
	Non-adjacent	7/39	17.9	6/11	54.57	
Joint effusion	None	8/39	20.5	0/11	0	*p* = 0.067
	Small	13/39	33	1/11	9.1	
	Moderate	13/39	33	7/11	63.6	
	Large	5/39	12.8	3/11	27	
Baker's cyst	None	12/39	30.8	3/11	27.3	*p* = 0.974
	Small	20/39	51.3	6/11	54.5	
	Moderate	7/39	17.8	0/11	0	
	Large	0/39	0	2/11	18.18	

*Please note that significant *p* values (<0.05) are highlighted in bold

system, which we consider a critical step in predicting which lesions will likely not perform well.

The medial femoral condyle was found to be the most common location for SIFK [3, 5, 18, 19]. Its vulnerability to osteonecrosis was explained by Reddy and Fredericks' cadaveric study [20], which demonstrated that the medical femoral condyle has a limited intraosseous blood supply, with apparent watershed areas, as opposed to the lateral femoral condyle. The incidence of this lesion in places other than the medial femoral condyle is reported by our study and in the literature [21, 22]. The lateral femoral condyle and the lateral tibial plateau were found to be the second most common location of SIFK. A distinguishing factor differentiating LG vs HG lesions is the extent of marrow edema surrounding the lesion on the initial MRI, reaching 75–100% of the surface area in HG lesions. Adding to the significance of understanding the lesion morphology in connection with evolution, we found that the absence of subchondral changes (e.g., cystic changes, osteonecrosis or collapse) among LG lesions is 100% predictive of reversibility [22]. We also found that most of the lesions were LG lesions (78%), which went on to undergo significant improvement/reduction of BME with toe-touch weight-bearing restrictions. One hypothesis is that in LG lesions secondary trabeculae might be affected to a lesser extent, and hence more support is expected from the longitudinal trabeculae. Furthermore, all HG SIFK lesions in our study were associated with subchondral collapse, a negative prognostic factor that has been reported to contribute to disease progression [16]. Our results demonstrate that most of our LG lesions showed complete resolution of BME at about 5 months by weight-bearing restriction. It is important that

Table 3 Comparison of imaging findings associated with onset of SIFK between patient and control subjects

		Patients		Controls		*p* value*
		n	%	*n*	%	
Meniscal tears	Medial	**33/50**	**66**	**24/51**	**47.1**	**0.024**
	Lateral	5/50	10	1/51	2	
	Both	2/50	4	6/51	11.8	
Location of medial meniscal tears	Posterior horn with root attachment	29/50	58	7/51	13.7	**0.000**
	Posterior horn without root attachment	3/50	6	22/51	43.1	
	Anterior horn	2/50	4	0/51	0	
	Meniscal body	1/50	2	1/51	2	
Degree of medial meniscal tear extrusion	No extrusion	16/50	32	30/51	58	**0.000**
	Mild (< 3 mm)	3/50	6	14/51	27.5	
	Moderate (3–5 mm)	17/50	34	7/51	13.7	
	Severe (> 5 mm)	14/50	28	0/51	0	
Location of lateral meniscal tears	Posterior horn with root attachment	0/50	0	0/51	0	0.506
	Posterior horn without root attachment	0/50	0	1/51	2	
	Anterior horn	0/50	0	0/51	0	
	Meniscal body	7/50	14	5/51	9.8	
Degree of lateral meniscal tear extrusion	No extrusion	0/50	0	44/51	86.3	**0.003**
	Mild (< 3 mm)	0/50	0	4/51	7.8	
	Moderate (3–5 mm)	0/50	0	3/51	5.9	
	Severe (> 5 mm)	2/50	4	0/51	0	
Location of chondrosis	Medial	31/50	62	16/51	31.4	**0.000**
	Lateral	11/50	16	0/51	0	
	Both	0/50	0	9/51	17.6	
Degree of medial chondrosis	No chondrosis	19/50	38	26/51	50	0.094
	Grade I	0/50	0	4/51	7.8	
	Grade II	14/50	28	7/51	13.7	
	Grade III	7/50	14	7/51	13.7	
	Grade IV	10/50	20	7/51	13.7	
Degree of lateral chondrosis	No chondrosis	42/50	84	42/51	82.4	0.136
	Grade I	0/50	0	4/51	7.8	
	Grade II	4/50	8	4/51	7.8	
	Grade III	1/50	2	1/51	2	
	Grade IV	3/50	6	0/51	0	
Joint effusion	Small	14/50	28	12/51	23.5	**0.000**
	Moderate	20/50	40	9/51	17.6	
	Large	8/50	16	1/51	2	
Baker's cyst	Small	26/50	52	12/51	23.5	**0.000**
	Moderate	9/50	18	2/51	3.9	
	Large	0/50	0	1/51	2	

*Please note that significant *p* values (<0.05) are highlighted in bold

patients and treating physicians are cognizant that it takes some time for this healing process to take place.

Association with meniscal tears, particularly medial meniscus root tears, supports the theory of mechanical stress and chronic microtrauma as the etiology of SIFK [8, 10, 23]. Comparing SIFK patients with controls, 58% of affected subjects showed MMPRT vs controls, where most meniscal tears were present medially in the posterior horn, only without posterior root attachment involvement. We support the concept of the MMPRT being a precipitant of SIFK, as kinematic alterations secondary to the inability to withstand hoop strain increase contact pressures and axial loading across the articular surfaces [4]. This in turn leads to several degrees of meniscal extrusion, allowing for contact and forces to dissipate across the subchondral plate, and as the degree of extrusion increases so does the severity of the lesion, as suggested in the results. It was also found that the degree of meniscal extrusion is predictive of the lesion type: 64% of HG lesions were seen in

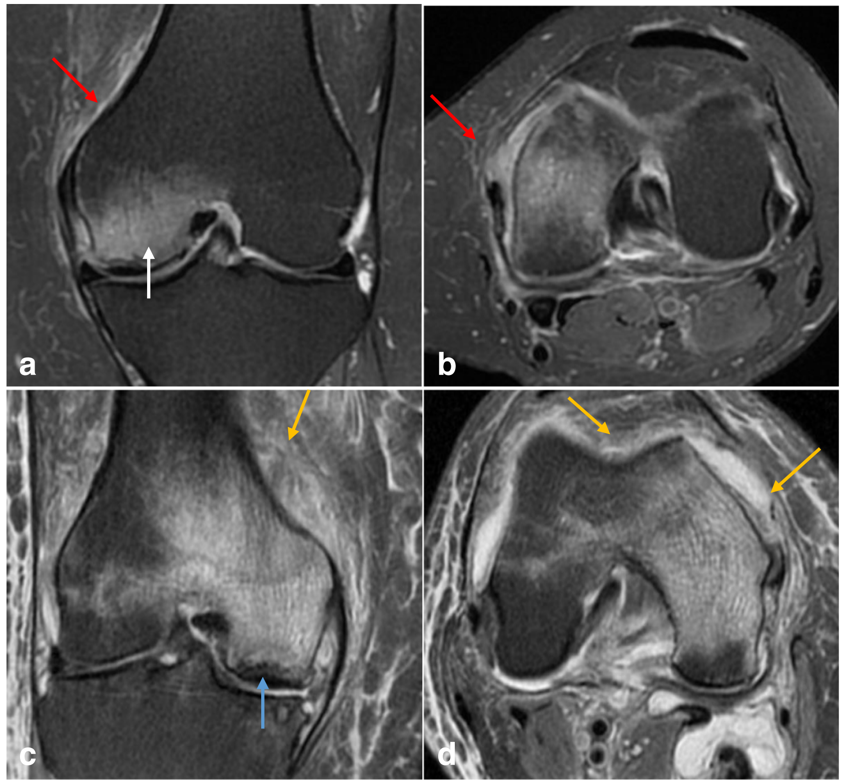

Fig. 7 **a** Coronal and **b** axial T2-weighted images showing a LG SIFK lesion (*white arrow*) associated with surrounding soft tissue edema (*red arrow*) just adjacent to the lesion. On the other hand, **c** Coronal and **d** sagittal images of a HG SIFK lesion (*blue arrow*) associated with adjacent and extending perilesional soft-tissue edema (*yellow arrows*)

association with severe meniscal extrusion (>5 mm) vs 18% in LG lesions ($p = 0.01$).

With regard to chondrosis, 69% of patients with HG lesions showed higher degrees of chondrosis (grades 3 and 4). Seventy-seven percent of LG lesions have lower degrees of chondrosis (grade 2 or less). Association between chondrosis and SIFK has not been reported before. Subchondral insufficiency fractures appear to occur in association with altered bony structure, local metabolism, and hemodynamic instability, inducing a direct metabolic reaction that ensures articular cartilage degradation [24]. In addition, we hypothesize that as the grade of the lesions increases, the degree of articular inflammation and synovitis is also likely to increase. This is suggested by the 90.6% of HG lesions associated with moderate and large joint effusions vs 53.3% of LG lesions presenting with small or no effusions. There was a significant prevalence of Baker's cysts in SIFK patients, which has been previously reported in association with medial meniscal tear (shown by Artul et al. [25]). The extent of the perilesional soft-tissue edema appears to predict lesion grade, with HG SIFK patients presenting with edema that exists adjacent to the lesion, with regional extension vs LG SIFK, where the soft-tissue edema was only seen adjacent to the lesion ($p = 0.01$). Last, we observed specific physical knee findings, such as locking and buckling, to be predominantly present among the SIFK patients.

One limitation to our study is that our SIFK population had a lower mean age (51 years) than that usually described in the literature [5, 6, 19, 26–28]. One explanation for this finding may be that our demographics are based on MRI evaluation, which allows early onset detection, rather than on radiographical imaging. Another limitation is the lack of pathological correlation and bone density measurements. The patients who had the MRI examinations did not undergo a dual-energy X-ray absorptiometry scan prior to or around the time of the MRI. One reason might be that the patients with SIKF in our study were younger than the age at which most patients are checked for quality of bone density. We defined grade 1 as marrow edema in the absence of any visible fracture line. This is a topic of great debate. It is possible that a microscopic fracture might be present or that the resolution of MRI does not allow for detection of a miniscule line.

It is important to assess for associated cartilage loss and, in the knee, meniscal pathology, which can contribute to an unfavorable prognosis for SIFK healing. LG lesions are considered a reversible condition and weight-bearing limitations result in disease resolution or significant improvement. On the other hand, HG lesions may be treated by medication or surgery [29] and to circumvent a prolonged recovery time, early diagnosis using MRI followed by appropriate targeted treatment should be emphasized [13]. There are various potential surgical options, including arthroscopy, osteochondral allografting, and bone grafting directed at preserving the joint [29–33]. Arthroplasty represents the final treatment option. In contrast to HG lesions, treatment is usually focused on preventing articular surface collapse and secondary osteoarthritis [34]. Medical therapy including statins, anticoagulation, and prostacyclin may be given in conjunction with bisphosphonates contingent on the etiology of the osteonecrosis [19]. Regardless of non-operative treatment possibilities, operative intervention is often required [29].

To our knowledge, no grading system has been introduced to stage the disease progression of SIFK with applications related to clinical prognosis and outcome. Surrogate markers of HG lesions include MMPRT with associated moderate to severe extrusion, HG chondrosis, articular surface collapse, and a greater degree of perilesional soft-tissue edema. On the other hand, BME-associated LG SIFK substantially improves or resolves. Lesion dimensions (AP 16.5 mm, TR 10.5 mm, mean sum of dimensions greater than 26 mm) offer a way of stratifying which patients are more likely to develop a worse prognosis.

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