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KOOS Pain as a Marker for Significant Knee Pain Two and Six Years after Primary ACL Reconstruction: A Multicenter Orthopaedic Outcomes Network (MOON) Prospective Longitudinal Cohort Study

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Abstract

Objective—The prevalence of radiographic osteoarthritis (OA) after anterior cruciate ligament reconstruction (ACLR) approaches 50%, yet the prevalence of significant knee pain is unknown. We applied three different models of Knee injury and Osteoarthritis Outcome Score (KOOS) thresholds for significant knee pain to an ACLR cohort to identify prevalence and risk factors.

Design—Multicenter Orthopaedic Outcomes Network (MOON) prospective cohort patients with a unilateral primary ACLR and normal contralateral knee were assessed at 2 and 6 years. Independent variables included patient demographics, validated Patient Reported Outcomes (PRO; Marx activity score, KOOS), and surgical characteristics. Models included: (1) KOOS criteria for a painful knee = quality of life subscale <87.5 and ≥2 of: $KOOS_{pain}$ <86.1, $KOOS_{symptoms}$ <85.7, $KOOS_{ADL}$ <86.8, or $KOOS_{sports/rec}$ <85.0; (2) $KOOS_{pain}$ subscale score ≤72 (≥2 standard deviations below population mean); (3) 10-point $KOOS_{pain}$ drop from 2 to 6 years. Proportional odds models (alpha≤0.05) were used.

Results—1,761 patients of median age 23 years, median BMI 24.8 kg/m2 and 56% male met inclusion, with 87% (1530/1761) and 86% (1506/1761) follow-up at 2 and 6 years, respectively. At 6 years, n=592 (39%), n=131 (9%) and n=169 (12%) met criteria for models #1 through #3,

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respectively. The most consistent and strongest independent risk factor at both time-points was subsequent ipsilateral knee surgery. Low 2-year Marx activity score increased the odds of a painful knee at 6 years.

Conclusions—Significant knee pain is prevalent after ACLR; with those who undergo subsequent ipsilateral surgery at greatest risk. The relationship between pain and structural OA warrants further study.

Keywords

Symptomatic osteoarthritis; Anterior cruciate ligament reconstruction; Knee Injury and Osteoarthritis Outcome Score (KOOS); Knee pain

INTRODUCTION

Anterior Cruciate Ligament (ACL) reconstruction (ACLR) is the most effective and reproducible treatment for ACL injured patients who want to return to cutting and pivoting sports[1,2,3]. More than half of patients undergoing ACLR will have concomitant pathology, including injuries to the articular cartilage in more than 20%, lateral meniscal tears in up to 46% and medial meniscal tears in 38% [4].

An ACL tear is a known risk factor for the development of osteoarthritis (OA)[5]. Intermediate and long-term follow-up of ACLR patients has demonstrated a high prevalence of radiographic findings consistent with post-traumatic OA[6,7,8]. Which factors, including concomitant pathology, the original injury, surgical techniques, or other as yet unidentified factors, are most responsible for the development of radiographic changes is unknown. A systematic review of studies including patients 5- to 10- years after ACLR[6], found radiographic joint space narrowing in 0–13% of patients with intact menisci, and 21–48% in those who had undergone either meniscectomy or repair. The meniscal status was also demonstrated to be important in a systematic review of non-reconstructed ACL injured patients[7]. Most studies, however, are limited by poor follow-up and significant heterogeneity in the classification systems utilized to describe radiographic OA.

Although the definitions can be challenging[9,10], a systematic review in 2011 demonstrated a relationship between structural OA and symptomatic OA among high quality studies[11]. Studies using Osteoarthritis Initiative (OAI) data have yielded further insight. Oak et al.[12] found a correlation between joint space narrowing at study entry, and greater progression of narrowing over the course of the study, with worse patient reported outcomes (PRO) at 4 years. Others have found weak correlations between PRO and MRI confirmation of joint space narrowing[13], but these correlations were highest for the knee pain subscale of the Knee injury and Osteoarthritis Outcome Score (KOOS).

A consensus expert panel developed a definition of patients with a symptomatic knee significant enough to seek medical attention. This definition, based on threshold levels of KOOS subscale scores[14], was based on the long-term follow-up of patients who previously underwent isolated partial meniscectomy with intact cruciate ligaments. Other criteria for clinically significant knee pain that have been developed based on PRO, include the KOOS

Minimally Clinically Important Difference (MCID) of 8–10 points[15], and the Osteoarthritis Research Society International (OARSI) Standing Committee criteria for interventions of osteoarthritis of the knee ("OARSI responder criteria") of 20 points[16,17].

Given that many patients who undergo ACLR develop radiographic OA, the main objective of this study was to identify the prevalence of significant knee pain by PRO after ACLR, using published definitions and cut-offs for either symptomatic OA or clinically significant knee pain. The second objective was to identify risk factors for developing a painful knee from patient, injury, and surgical characteristics 6 years following an ACL reconstruction.

METHODS

Study design

Longitudinal prospective cohort (prognostic): The Multicenter Orthopaedic Outcomes Network (MOON) cohort[18]. MOON is a prospective, longitudinal, multicenter cohort study based in the United States, and designed to examine short and long-term prognosis after ACL reconstruction using validated patient-reported outcomes. MOON was also designed to generate hypotheses surrounding novel methods for improving outcomes after ACL injury.

Data sources

Participants completed a 13-page questionnaire providing patient demographics, a description of their injury, sports participation history, comorbidities and past medical history. Each participant also completed validated general and knee specific instruments, including the Knee injury and Osteoarthritis Outcome Score (KOOS)[19] and the Marx activity rating scale[20]. Contained within the KOOS is the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) [21]. All were completed within 2 weeks of the surgery date.

Surgeons completed a standardized questionnaire, which included detailed information regarding surgical technique, graft choice, and concomitant meniscal and articular cartilage pathology and treatment. The inter-rater reliability of grading systems for articular cartilage (modified Outerbridge) and meniscal lesions were previously validated among participating surgeons and found to be high[22, 23]. Meniscal pathology was classified by size, location, partial versus complete tears and treatment (not treated, repaired, resection and extent of resection).

Cohort design

All patients (n=2222) who had undergone a unilateral primary ACLR at a participating MOON institution (Vanderbilt University, The Ohio State University, Washington University at St. Louis, University of Iowa, the Cleveland Clinic, and the Hospital for Special Surgery) between 2002 and 2005 were eligible for inclusion into this study. All patients provided informed consent from their respective institution. A prior exclusion criteria included previous contralateral ACL reconstruction, simultaneous bilateral ACL reconstruction, ACL repair, or a revision ACL reconstruction as the index (enrollment) event. ACL revision patients report worse PRO than primary ACL reconstruction patients[4,27–9], and so were excluded. ACL repair is an atypical treatment and was excluded. Patients with a contralateral ACL reconstruction prior to initial enrollment into the MOON cohort, or performed concurrently, were excluded on the basis that this study's objective included understanding how a subsequent contralateral reconstruction would influence PRO for significant knee pain. No patients were excluded from analysis due to incomplete baseline data (all n=2222 completed baseline PRO).

Outcomes - Definitions of a 'painful or symptomatic knee'

We utilized previously published definitions of KOOS thresholds for a symptomatic knee as described in the introduction. We built three models, as follows:

1. **Model #1.** The primary model was defined as the operational definition of Englund et al.[14] ("Englund model") to distinguish patients with sufficient knee symptoms to seek medical care. The Englund model is defined as having a KOOS knee-related quality of life (QoL) subscale ≤ 87.5 AND two or more of the other subscales: KOOS pain ≤ 86.1, KOOS symptoms ≤ 85.7, KOOS activities of daily living (ADL) ≤ 86.8, or KOOS sports and recreation ("sport/rec") ≤85.0.

2. **Model #2.** The KOOS knee pain subscale has been shown to have the highest correlation with structural OA changes[13], and is a direct measure of knee pain. Therefore, we defined a secondary model for significant knee pain as a KOOS pain subscale two standard deviations lower than the reported normal mean value in athletic populations with a history of (any) knee ligament injury. This value was 92.3 ± 10.0 [24], which translated into a cut-off score of ≤72 points ("KOOS pain ≤72 model"). This definition also qualified as a 20-point change, consistent with OARSI responder criteria for effective interventions in OA[16].

3. **Model #3.** The reported Minimal Clinically Important Difference (MCID) for the KOOS pain subscale is 6.1 points in athletes after ACL reconstruction[25], to between 8 and 10 points for patients with OA[15, 26]. To utilize a more conservative estimate of the MCID, we selected a drop of 10 points in the KOOS pain subscale from 2 years to 6 years follow-up as an additional secondary definition of patients with a painful knee after ACL reconstruction ("KOOS pain MCID model"). This model attempted to identify patients who had a clinically significant worsening of knee pain.

Model variables

Variables included all those from the original MOON cohort. They included patient demographics (age, sex, body mass index [BMI], smoking status, education level, main sport played at the time of injury, enrollment year), validated PRO (KOOS, WOMAC, Marx activity), surgical characteristics (graft type, meniscal pathology/treatment, articular cartilage pathology), and incidence of subsequent surgery on either knee (Table 1). The Marx score is a measure of the frequency and intensity of cutting and pivoting sports. The inclusion of variables in our models was based on substantive knowledge of the clinical or epidemiological association between them and patient reported outcomes after ACL reconstruction surgery. These relationships have been established by our own work with this cohort[4,7,18,27] and have been derived from literature review[18]. They extend to include baseline PRO scores, patient demographic factors and surgical variables.

Statistical analysis

To describe our patient sample, we summarized continuous variables as percentiles (i.e., 25th, 50th, and 75th) with their mean and standard deviation, and categorical variables with frequencies and percentages. Multivariable regression analyses were constructed to examine which baseline risk factors were independently associated with each outcome variable. An a priori determined list of variables to be included in all models were given by: age, gender, BMI, smoking status, education level, main sport played the last 2 years, baseline KOOS, WOMAC, and Marx activity levels, graft type, previous meniscal pathology, current meniscal pathology/treatment, previous articular cartilage pathology, current articular cartilage pathology, subsequent surgery on the ipsilateral and contralateral knee, and enrollment year. We assumed independence of all covariates because we compared between subjects and not within, and when fitting the multivariable regression models, we measured each covariate's independent adjusted association with the outcome. For binary outcome variables a multivariable logistic regression model was fit to the data, parameter estimates were exponentiated to obtain odds ratios (OR) and 95% confidence intervals (CI), based on a dichotomous outcome (yes/no). We did not assume a linear relationship between continuous covariates (independent variables) and each outcome in order to avoid underestimating the true relationship, instead utilized a restricted cubic regression splines technique that assumes smooth relationships (i.e., they are linearly related to the log odds). To avoid case-wise deletion of records with missing covariates, we employed multiple imputation via predictive mean matching. All model assumptions (as listed above) were met. Statistical analysis was performed using open source R statistical software (www.r-project.org; Version 3.0.3).

Post hoc analysis

Preliminary findings demonstrated that a low Marx activity score at 2 years increased the odds of reporting a painful knee in both the Englund and KOOS pain ≤72 models. Therefore, in order to further understand the interaction of pain and activity, we performed a post hoc analysis to identify the proportion of patients reporting a high level of sport/activity-related knee pain, and to understand which factors modified that outcome. This model utilized responses from a 5-point Likert question on the IKDC: "What is the highest level of activity that you can perform without significant knee pain?" Patients were classified based on their answer to this question as high activity tolerance ("very strenuous activities" or "strenuous activities" or "moderate activities") or low activity tolerance ("light activities" or "no described activities"). Models were built for this outcome (**Model #4**: "Activity tolerance model") at 6 years based on the response to the question at 2 years.

After determining that subsequent ipsilateral surgery was a risk factor, we performed a second post-hoc analysis to identify the number of patients who underwent a second surgery within 1 and 3 months prior to the 2- and 6-year time-points. This was performed due to concern that recent surgery may be the cause of higher reported pain. Furthermore, we reanalyzed each of the 4 models after excluding the patients with surgery within 3 months of the 2- and 6-year time-points.

RESULTS

Figure 1 illustrates the cohort inclusion/exclusion criteria. There were 1761 subjects who fit the inclusion criteria and were included in this analysis. The median age of our cohort was 23 years, median BMI 24.8 kg/m^2 and the cohort was 56% male. Patient follow-up was obtained on 87% (1530/1761) and 86% (1506/1761) at 2 and 6 years, respectively. The proportion of patients who met each of the three model criteria was calculated (see Table 3). At 2 years, n=46 patients fit both the Englund and KOOS pain ≤72 points models, out of a total n=141 possible patients (32.6%). At 6 years, n=67 patients fit all four models, out of a total n=131 possible (51%). Full baseline demographics are supplied in Table 2 alongside the list of model variables and levels.

Table 3 depicts the significant independent risk factors identified in each model. Subsequent ipsilateral surgery was the most consistent and strongest predictor of increased symptoms at both 2 and 6 years post-ACL reconstruction (broken down by type in Figure 2). Subsequent surgeries were common, occurring at a rate of 16% (239/1530) at 2 years and 21.5% (324/1506) at 6 years. The majority of subsequent surgeries other than total knee replacement took place more than a year prior to the 6 year outcome measurement. The mean time to revision ACLR was 2.4 ± 1.9 years, total knee replacement 5.3 ± 2.2 years and other arthroscopic surgical procedures 2.1 ± 1.9 years. Revision ACLR was the single most common subsequent procedure. The vast majority of subsequent procedures took place remote from sampled time-points: only 1.3% (3/239) and 0% (0/324) of patients had a subsequent surgery within one month of filling out the KOOS forms at 2 years and 6 years, respectively. Furthermore, only 3.8% (9/239) and 1.2% (4/324) of patients had a subsequent surgery within 3 months of filling out the KOOS forms at 2 years and 6 years, respectively. When all 4 models were re-run with patients who had undergone subsequent surgery within 3 months removed, no changes were noted in the significance or magnitude of any statistically significant risk factors. One risk factor in model #4 which previously approached significance then became significant (current vs. never smoker: OR 1.82 (1.02, 3.27); p=0.043).

Other independent risk factors that were found to be significant (although inconsistent) of increased symptoms at 2 and/or 6 years post-ACL reconstruction included higher BMI, smokers, less years of education, lower baseline KOOS ADL and higher baseline KOOS sports/rec subscale scores, and lower 2-year Marx activity levels (for predicting the 6-year models).

Potential prognostic factors that did not alter the risk of reporting a painful knee or having significant activity-related pain included age, pre-operative/baseline activity level, pre-operative WOMAC (pain, stiffness) or KOOS (symptoms, pain, and quality of life) baseline scores, graft type, medial meniscal pathology/treatment, and subsequent contralateral knee surgery. The grade of chondral damage at initial arthroscopy was an inconsistent predictor in the patellofemoral, medial and lateral compartments. In general, when chondral damage influenced the odds of reporting either a painful knee or significant activity-related pain, the tendency was for the effect to be driven by grade 3/4 change.

DISCUSSION

The prevalence of significant patient-reported knee pain 6 years after ACLR was high, including 39% by the Englund definition, 9% for KOOS pain score ≤72 (drop ≥20 points) and 12% for KOOS pain MCID definition (drop ≥10 points). A similar proportion of patients (11%) reported significant activity-related knee pain at 6 years. This study is the first to apply these definitions to characterize this patient population and represents an important first step in identifying at-risk patients for the development of significant knee pain after ACLR.

The most consistent risk factor across all definitions of significant knee pain also carried the largest impact – subsequent ipsilateral knee surgery. We utilized interactions of age and subsequent surgery in our statistical modeling because of our previous findings[4] that demonstrated younger age increased the risk of subsequent surgery at 2 and 6 year follow-up. This limited the degrees of freedom we could use to identify which of the subsequent procedures had the most influence. At 6 years, ipsilateral re-operation was dominated by revision ACLR, further meniscus/articular cartilage surgery and surgical interventions for stiffness. Revision ACLR has been associated with worse PRO[4,27,28,29], and subsequent meniscal or articular cartilage surgery is a recognized risk for radiographic OA changes in ACL reconstructed patients[6]. The identification of subsequent surgery as a risk factor for reporting a painful knee was also a robust enough finding that it held even with the removal of patients who had surgery within 3 months of the 2- and 6-year time-points from statistical analysis. That contralateral knee surgery did not increase the odds of reporting a painful knee, places further importance on subsequent surgeries as a marker for additional trauma or joint degeneration as a driver of poor outcomes. Better resolution of the type of procedure in subsequent investigations will be helpful, as some are potentially preventable through improved surgical technique, timing of surgery, or rehabilitation.

Many ACLR patients exhibited activity-related knee pain in follow-up. We assessed this using model #4, and determined that 11% of patients met these criteria. This included approximately half who also met criteria for models #2 and #3 – both KOOS pain models. KOOS pain assesses both activity-related and non-activity related pain and contains the questions from the validated hip and knee osteoarthritis tool – Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[15]. Furthermore, we noted that a low Marx score at 2 years increased the odds of a patient meeting the Englund criteria (model #1), KOOS pain ≤72 criteria (model #2), and IKDC activity-related pain threshold (model #4). Whether simply being less active is a risk factor for reporting significant knee pain, or whether patients already developing significant knee pain become less active, is not known.

There is no consensus definition for symptomatic OA or significant knee pain using Patient Reported Outcomes. This is further complicated by the heterogeneity of diagnoses/ definitions reported in the literature. While we found the prevalence of significant knee pain was high, it varied considerably based on our definitions. The Englund et al.[14] criteria were the least stringent, but also the broadest including pain, symptoms and quality of life reporting. The KOOS pain threshold in that model was 86 points, which corresponded to the 25th percentile of KOOS pain scores in the MOON cohort [4]. Accordingly, this model identified the most patients. Few cues are available from the literature for prevalence of pain based on the Englund model in similar patients, with only two small published studies. In a cohort of 84 female soccer players with an ACL injury treated with either rehabilitation or surgery[30], 75% met the Englund criteria at 15 years follow-up. In contrast, 51% met criteria for knee OA on radiographs, and 42% met both. In a purely non-operative cohort[31] of 67 ACL injured patients, the 15-year KOOS pain scores were all 85 points or greater.

The 20-point drop in KOOS pain score that we selected corresponded to the OARSI responder criteria[16] and 2 standard deviations below the mean of KOOS scores of athletes with a history of knee ligament injury[24]. Even fewer comparative studies exist in the literature for this definition. Paradowski et al.[17] applied the OARSI responder criteria, developed for use in OA interventional studies to identify therapies that produce significant knee pain reduction, to identify mild OA patients with significantly increased knee symptoms post-meniscectomy. Those with radiographic changes had a larger drop in KOOS pain score (11 points), and by six years they determined that 7% of patients had a ≥20 point KOOS pain drop. Another study of older, post-meniscectomy patients with intact ligaments demonstrated a mean baseline KOOS pain of 84 points[32], but with high individual variation. Seven years later the same patients reported a further 6 point drop in KOOS pain on average which was worse in females and those with radiographic changes.

A 20-point KOOS pain drop that is 2 standard deviations below population norms[24] should theoretically include only 2.5% of our cohort. In fact, however, the distribution of KOOS pain was skewed to the left at 6 years with more than 9% of patients having a score below this cut-off. This finding offers both clinical and statistical significance and reinforces the role of subsequent injury, joint degeneration, or concomitant pathology at the primary reconstruction in the identification of patients at-risk for high levels of self-reported knee pain. Furthermore, a significant proportion of these patients reported high levels of activity-related pain according to our IKDC model #4 definition.

Limitations

There are some challenges in comparing our cohort with previous studies that have attempted to develop and characterize the prevalence of significant knee pain. Prior studies have examined patients with a different primary surgical intervention – namely meniscectomy[14, 17, 32, 33]. The etiology of meniscal tears in those cohorts included both traumatic and atraumatic mechanisms, whereas our cohort had sustained a traumatic rupture of the ACL. Secondly, the meniscectomy cohorts have an older mean age than our cohort (mean age typically 46–56 years, compared to mean age <30 years at follow-up in our study). How a degenerative process and traumatic process modify the risk of developing knee OA is unknown.

Loss to follow-up in our study was 13% (2 year) or 14% (6 year). Although there is no consensus on the introduction of bias based on follow-up, most estimates suggest that <5% loss will have no effect, while >20% may pose serious threats to validity[34]. Yet the direction and approximate magnitude of some covariates, such as socioeconomic markers, do not change with attrition approaching even 50% [35,36]. MOON investigators go to considerable length to contact enrolled patients, including repeated mailings and phone calls. As noted in Table 3, the proportion of males lost to follow-up was slightly higher (63% vs 56%), and some minor differences were seen for BMI and smoking status. We don't think this will have had a large effect on the study conclusions, as sex was not associated with outcome, smoking was inconsistently associated with only a couple outcomes and BMI was only a predictor in model #1.

Our study was not designed to identify the best definition for a symptomatic knee. Accordingly, we utilized various definitions, each with advantages and disadvantages as well as mixed support in the literature. The agreement between models was reasonable at 6 years after ACLR, as exemplified by identifying approximately half of the patients (n=67) from the most stringent model (KOOS pain ≤72; n=131) in the remaining models. The identification of which outcomes (pain, function, or ADL) remain most important to post-ACLR patients, and the establishment of cut-off scores using the PASS (Patient Acceptable Symptomatic State) concept for ACLR will be important steps in further defining this subset of patients.

Finally, we did not have radiographs available in follow-up of these patients to correlate structural change with symptomatic findings, as has been done in smaller series post isolated meniscectomy[17,30,32,37,38]. The interaction of structural changes with symptoms is an important area for future research. This is heightened by the discordance between our study and systematic reviews of post-ACL reconstruction patients[6] that suggests meniscal pathology at the time of injury/surgery moderates radiographic OA risk. It would appear that while meniscal loss initiates joint space changes, it may be a weaker mediator of symptoms compared to other factors we have identified such as chondral damage and subsequent injury/surgery. There is some support for this notion based upon weak associations demonstrated between joint space narrowing and poor PRO in Osteoarthritis Initiative cohort studies[12, 13]. A second explanation is that the follow-up in our study is not yet long enough for meniscal status at the time of surgery to have the same influence on PRO. Exploring these interactions in future work is of critical importance to define the patients truly at-risk for clinically relevant OA after ACL reconstruction.

Summary

Significant knee pain and symptoms is prevalent among 9–39% of first-time ACL reconstruction patients at 6 years. Patient-reported pain is affected to some degree by demographic factors and higher grades of concurrent cartilage damage at the index procedure, however, those who undergo second surgeries (e.g., revision, repeat arthroscopy) are at greatest risk. Whether this patient report of significant knee pain relates to structural arthritic changes requires further study.

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AUTHOR CONTRIBUTIONS

Factor	Contributor
Study design/conception	DW, LJH, KPS
Acquisition of data	LJH
Analysis and interpretation of data	DW, LJH, SN, KPS
Drafting of manuscript	DW
Critical revision for intellectual content	DW, LJH, KPS
Final approval	DW, LJH, KPS
Provision of study materials or patients	AA, JTA, WRD, CCK, RM, ECM, RDP, KPS, MLW, BRW, RWW
Statistical expertise	SN
Obtaining of funding	KPS
Administrative, technical or logistic support	?
Collection and assembly of data	AA, JTA, WRD, LJH, CCK, RM, ECM, RDP, KPS, MLW, BRW, RWW

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COMPETING INTEREST STATEMENT

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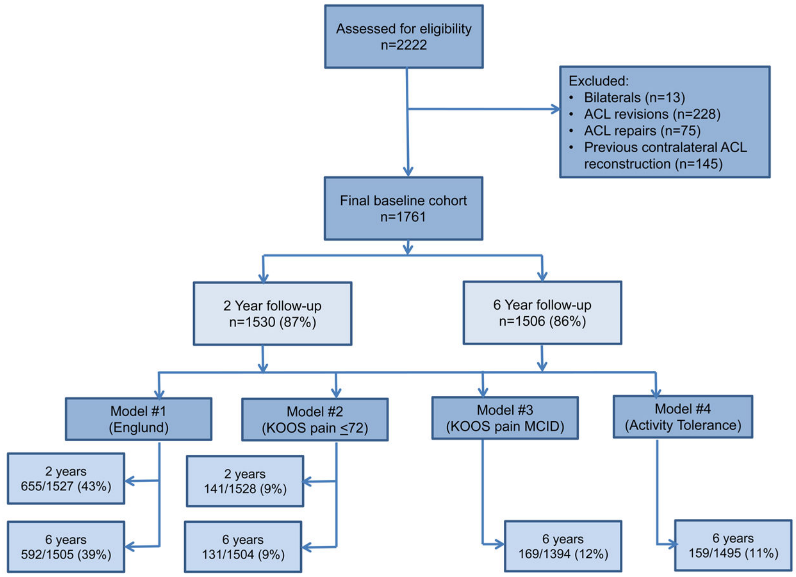

Figure 1.
Flowchart showing the inclusion of participants in the study.

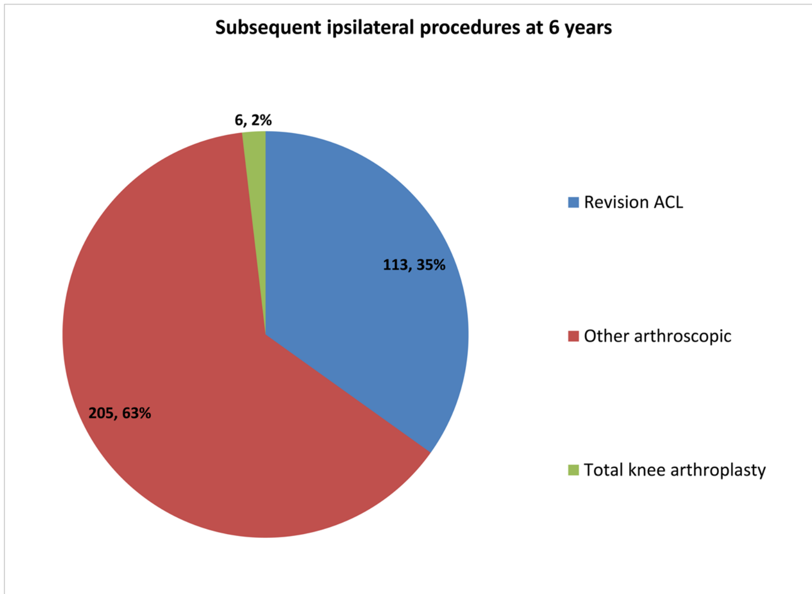

Figure 2.

Subsequent ipsilateral surgical procedures at 6 years ("Other arthroscopic" includes hardware removal, meniscal and articular cartilage surgery, infection, arthrolysis/ manipulation).

Table 1

List of Modeling Variables

	Category	Levels
Baseline Outcome Scores	KOOS (5 subscales); WOMAC (pain, stiffness subscales)	continuous
Patient Demographics	Age (years)	continuous
	Gender	male, female
	BMI	continuous
	Smoking status	never, quit, current
	Education level (years)	1 – 16 (continuous)
	Baseline activity level (Marx)	continuous
	Main sport played last 2 yrs	basketball, football, soccer, other, none
Surgical Variables	Graft type	Autograft (BTB), autograft (soft tissue), allograft (BTB), allograft (soft tissue)
	Meniscal pathology	
	* previous	no, yes
	* medial	normal, no tx for tear, repair, excised, other
	* lateral	normal, no tx for tear, repair, excised, other
	Articular cartilage pathology	
	* previous	no, yes
	* medial femoral condyle (MFC)	normal/grade 1, grade 2, grade 3, grade 4
	* lateral femoral condyle (LFC)	normal/grade 1, grade 2, grade 3, grade 4
	* medial tibial plateau (MTP)	normal/grade 1, grade 2, grades 3/4
	* lateral tibial plateau (LTP)	normal/grade 1, grade 2, grades 3/4
	* patella	normal/grade 1, grade 2, grades 3/4
	* trochlea	normal/grade 1, grade 2, grades 3/4
Miscellaneous Variables	Year of surgery (enrollment)	2002, 2003, 2004, 2005
	Subsequent ipsilateral surgery	no, arthroscopic procedure, revision ACL reconstruction, total knee arthroplasty (TKA)
	Subsequent contralateral surgery	no, arthroscopic procedure, ACL reconstruction, total knee arthroplasty (TKA)

Table 2

Baseline data for the included cohort and the patients lost to follow-up

Category	Variable (N)	Level	Overall Cohort (n=1761) n (%) or median (25th–75th)	Lost to Follow-up @ 2 yrs (n=231) n (%) or median (25th–75th)	Lost to Follow-up @ 6 yrs (n=255) n (%) or median (25th–75th)
Patient demographics	Sex	Male	980 (56%)	146 (63%)	169 (66%)
		Female	781 (44%)	85 (37%)	86 (34%)
	Age	Continuous	23 years (17–35)	22 years (17–30)	22 years (17–32)
	BMI	Continuous	24.8 kg/m^2 (22.3–27.9)	25.4 kg/m^2 (22.9–29.2)	26.4 kg/m^2 (23.2–29.9)
	Smoking status	Current	167 (10%)	32 (15%)	44 (18%)
		Quit smoking (>6 months)	172 (10%)	15 (7%)	16 (6%)
		Never smoker	1354 (80%)	171 (78%)	186 (76%)
	Education level	Continuous	14.0 years (11.0–16.0)	13.0 years (11.0–16.0)	12.0 years (10.0–16.0)
	Main sport	Basketball	393 (23%)	61 (27%)	69 (27%)
		Football	191 (11%)	38 (17%)	35 (14%)
		Soccer	230 (13%)	17 (7%)	20 (8%)
		Other	793 (46%)	99 (43%)	106 (42%)
		None	134 (8%)	14 (6%)	22 (9%)
Patient Reported Outcomes (PRO)	Marx activity	Baseline	12 (8–16)	13 (9–16)	13 (8–16)
		2 Years	9 (4–13)	N/A	8 (1–12)
	KOOS symptoms	Baseline	68 (57–82)	68 (50–79)	68 (50–82)
	KOOS pain	Baseline	75 (64–89)	69 (58–86)	72 (58–86)
	KOOS ADL	Baseline	88 (74–96)	83 (68–94)	82 (65–94)
	KOOS Sports & rec	Baseline	50 (30–75)	50 (25–75)	50 (25–75)
	KOOS QoL	Baseline	38 (25–50)	31 (19–50)	31 (19–44)
	WOMAC stiffness	Baseline	75 (62–88)	75 (50–88)	75 (50–88)
	WOMAC pain	Baseline	90 (75–95)	85 (70–95)	85 (65–95)
Surgical/Injury factors	Previous meniscal pathology	No	1632 (93%)	210 (91%)	230 (90%)
		Yes	129 (7%)	21 (9%)	25 (10%)
	Previous articular cartilage pathology	No	1739 (99%)	228 (99%)	249 (98%)

Category	Variable (N)	Level	Overall Cohort (n=1761) n (%) or median (25^{th}–75^{th})	Lost to Follow-up @ 2 yrs (n=231) n (%) or median (25^{th}–75^{th})	Lost to Follow-up @ 6 yrs (n=255) n (%) or median (25^{th}–75^{th})
		Yes	22 (1%)	3 (1%)	6 (2%)
	Graft type	Allograft (BTB)	121 (7%)	16 (7%)	27 (11%)
		Allograft (soft tissue)	299 (17%)	39 (17%)	35 (14%)
		Autograft (BTB)	832 (47%)	116 (51%)	120 (47%)
		Autograft (soft tissue)	509 (29%)	60 (26%)	73 (29%)
	Medial meniscus treatment	Normal/none	1106 (63%)	149 (65%)	173 (68%)
		Tear/no treatment	94 (5%)	10 (4%)	10 (4%)
		Repair	229 (13%)	39 (17%)	35 (14%)
		Partial excision	317 (18%)	33 (14%)	37 (15%)
		Other	15 (1%)	0 (0%)	0 (0%)
	Lateral meniscus treatment	Normal/none	927 (53%)	118 (51%)	127 (50%)
		Tear/no treatment	197 (11%)	25 (11%)	25 (10%)
		Repair	128 (7%)	16 (7%)	22 (9%)
		Partial excision	497 (28%)	72 (31%)	80 (31%)
		Other	12 (1%)	0 (0%)	1 (<1%)
	Medial femoral condyle	Normal/grade 1	1381 (78%)	189 (82%)	202 (79%)
		Grade 2	225 (13%)	30 (13%)	31 (12%)
		Grade 3	117 (7%)	8 (3%)	15 (6%)
		Grade 4	38 (2%)	4 (2%)	7 (3%)
	Lateral femoral condyle	Normal/grade 1	1498 (85%)	197 (85%)	209 (82%)
		Grade 2	186 (11%)	24 (10%)	32 (13%)
		Grade 3	59 (3%)	10 (4%)	11 (4%)
		Grade 4	18 (1%)	0 (0%)	3 (1%)
	Medial tibial plateau	Normal/grade 1	1694 (96%)	228 (99%)	250 (99%)
		Grade 2	45 (3%)	1 (<1%)	1 (<1%)
		Grades 3–4	22 (1%)	0 (0%)	0 (0%)
	Lateral tibial plateau	Normal/grade 1	1611 (91%)	215 (94%)	230 (92%)
		Grade 2	122 (7%)	13 (6%)	20 (8%)

Category	Variable (N)	Level	Overall Cohort (n=1761) n (%) or median (25^{th}–75^{th})	Lost to Follow-up @ 2 yrs (n=231) n (%) or median (25^{th}–75^{th})	Lost to Follow-up @ 6 yrs (n=255) n (%) or median (25^{th}–75^{th})
		Grades 3–4	28 (2%)	0 (0%)	0 (0%)
	Patella	Normal/grade 1	1470 (83%)	199 (90%)	213 (88%)
		Grade 2	181 (10%)	21 (10%)	29 (12%)
		Grades 3–4	110 (6%)	0 (0%)	0 (0%)
	Trochlea	Normal/grade 1	1641 (93%)	219 (96%)	238 (96%)
		Grade 2	82 (5%)	10 (4%)	11 (4%)
		Grades 3–4	38 (2%)	0 (0%)	0 (0%)

Table 3

Summary of Independent Variables [reported as Odds Ratios (95% CI); bolded and p-value included when significant]

	Category	Variable Comparison	Variable (worse outcome, if significant)	Model 1 (Englund)		Model 2 (KOOS Pain ≤ 72)		Model 3 (KOOS Pain MCID)	Model 4 (Activity Tolerance)
				2 Years	6 Years	2 Years	6 Years	6 Years	6 Years
Number of patients who satisfied criteria for each model				655/1527 (43%)	592/1505 (39%)	141/1528 (9%)	131/1504 (9%)	169/1394 (12%)	159/1495 (11%)
Baseline Outcome Scores	KOOS	Symptoms		0.90 (0.69, 1.18)	0.83 (0.69, 1.09)	0.78 (0.45, 1.36)	0.81 (0.45, 1.49)	0.91 (0.59, 1.40)	1.27 (0.78, 2.07)
		Pain		0.66 (0.40, 1.07)	0.78 (0.46, 1.32)	0.48 (0.17, 1.36)	0.87 (0.32, 2.37)	1.45 (0.66, 3.18)	1.00 (0.40, 2.51)
		ADL	ADL (low)	**0.53 (0.36, 0.79) p<0.001**	**0.67* (0.45, 0.99) p=0.117**	0.78 (0.37, 1.62)	0.89 (0.42, 1.89)	1.13 (0.61, 2.07)	0.67 (0.32, 1.41)
		Sports/Rec	Sports/Rec (high)	1.04 (0.82, 1.32)	1.01 (0.77, 1.33)	**1.63 (1.13, 2.34) p=0.016**	0.78 (0.53, 1.16)	0.90 (0.63, 1.30)	0.88 (0.60, 1.29)
		Quality of Life		0.90 (0.76, 1.06)	0.97 (0.82, 1.15)	0.96 (0.73, 1.27)	1.00 (0.73, 1.36)	0.82 (0.64, 1.04)	0.79 (0.60, 1.04)
	WOMAC	Pain		1.18 (0.77, 1.81)	1.09 (0.69, 1.72)	0.68 (0.31, 1.47)	0.46 (0.20, 1.05)	0.63 (0.29, 1.35)	1.03 (0.50, 2.13)
		Stiffness		0.92 (0.74, 1.15)	0.92 (0.72, 1.16)	1.06 (0.70, 1.59)	1.57 (1.00, 2.47)	1.07 (0.73, 1.58)	0.92 (0.62, 1.36)
Patient Characteristics	Age (yrs)	Age		0.91 (0.55, 1.51)	0.76 (0.42, 1.37)	1.65 (0.73, 3.71)	1.21 (0.48, 3.05)	0.96 (0.42, 2.17)	1.43 (0.62, 3.28)
	Gender	Females : Males	Males	1.10 (0.86, 1.40)	1.00 (0.75, 1.33)	0.85 (0.54, 1.34)	0.90 (0.54, 1.51)	**0.67 (0.47, 0.96) p=0.028**	1.46 (0.89, 2.39)
	BMI	BMI	Higher BMI	**1.24 (1.01, 1.53) p=0.004**	**1.28* (1.01, 1.61) p=0.071**	**1.52 (1.04, 2.20) p=0.003**	1.30 (0.84, 2.02)	1.00 (0.71, 1.39)	1.27 (0.89, 1.83)
	Smoking status	Current : Never	Current (compared to never)	1.45 (0.96, 2.19)	1.22 (0.81, 1.85)	1.59 (0.92, 2.75)	**2.83 (1.46, 5.49) p=0.002**	1.13 (0.62, 2.08)	1.78 (1.00, 3.18)
		Quit : Never	Quitting (compared to never)	**1.66 (1.12, 2.45) p=0.011**	0.84 (0.54, 1.32)	0.96 (0.50, 1.83)	**1.96 (1.02, 3.75) p=0.042**	0.59 (0.32, 1.12)	1.03 (0.57, 1.89)
	Education (years)	Years of education	Less education years	1.04 (0.77, 1.41)	0.80 (0.56, 1.14)	0.63 (0.38, 1.03)	**0.43 (0.23, 0.79) p=0.022**	0.72 (0.44, 1.16)	**0.61* (0.39, 0.98) p=0.126**
	Baseline activity level (Marx)	Marx activity score		1.31 (0.92, 1.87)	1.16 (0.80, 1.69)	1.38 (0.72, 2.65)	1.39 (0.66, 2.92)	0.93 (0.53, 1.63)	1.26 (0.60, 2.67)
	2 Year activity level (Marx)	Marx activity score	Low score (low activity)		**0.62 (0.48, 0.82) p=0.001**		**0.53 (0.33, 0.86) p=0.032**	0.91 (0.64, 1.31)	**0.41 (0.26, 0.63) p<0.001**
Surgical Factors	Previous meniscal pathology	Yes : No	No (compared to 'yes')	1.48 (0.91, 2.39)	1.23 (0.76, 1.98)	1.11 (0.57, 2.16)	1.13 (0.51, 2.52)	**0.43 (0.19, 0.97) p=0.041**	1.78 (0.90, 3.51)
	Previous articular cartilage pathology	Yes : No		3.98 (0.95, 16.73)	0.70 (0.20, 2.50)	2.50 (0.70, 8.86)	1.79 (0.46, 6.93)	0.53 (0.08, 3.55)	3.47 (0.58, 20.63)
	Current Meniscal pathology								
	* medial	Repair : Normal		1.34 (0.94, 1.90)	1.11 (0.79, 1.55)	1.53 (0.90, 2.60)	1.61 (0.91, 2.86)	0.96 (0.59, 1.59)	1.21 (0.65, 2.25)
	* lateral	No tear for treatment : Normal	Normal (compared to no tx for tear)	**0.59 (0.39, 0.89) p=0.012**	0.74 (0.50, 1.10)	0.97 (0.50, 1.89)	0.62 (0.28, 1.40)	0.93 (0.52, 1.67)	1.22 (0.65, 2.30)

	Category	Variable Comparison	Variable (worse outcome, if significant)	Model 1 (Englund)		Model 2 (KOOS Pain ≤ 72)		Model 3 (KOOS Pain MCID)	Model 4 (Activity Tolerance)
				2 Years	6 Years	2 Years	6 Years	6 Years	6 Years
	Current Articular cartilage pathology								
	* medial femoral condyle (MFC)	Grade 4 : Normal/grade 1	Grade 4 (compared with normal/grade 1)	1.62 (0.69, 3.76)	1.43 (0.65, 3.14)	1.07 (0.35, 3.32)	1.28 (0.46, 3.61)	1.42 (0.50, 3.98)	**2.67 (1.05, 6.80) p=0.040**
	* lateral femoral condyle (LFC)	Grade 2 : Normal/grade 1	Normal/grade 1 (compared to grade 2)	0.70 (0.47, 1.05)	0.73 (0.48, 1.09)	0.75 (0.36, 1.57)	**0.34 (0.14, 0.82) p=0.016**	0.83 (0.46, 1.49)	1.01 (0.53, 1.92)
		Grade 3 : Normal/grade 1	Grade 3 (compared with normal/grade 1)	1.78 (0.85, 3.73)	**2.58 (1.21, 5.50) p=0.014**	1.40 (0.54, 3.62)	1.37 (0.44, 4.29)	1.89 (0.83, 4.32)	1.56 (0.47, 5.19)
	* medial tibial plateau (MTP)	Grades 3/4 : Normal/ grade 1	Grades 3/4 (compared with normal/grade 1)	0.73 (0.24, 2.27)	2.98 (0.93, 9.50)	1.26 (0.35, 4.53)	3.20 (0.76, 13.48)	**4.20 (1.33, 13.25) p=0.015**	0.86 (0.17, 4.25)
	* lateral tibial plateau (LTP)	Grade 2 : Normal/grade 1	Normal/grade 1 (compared to grade 2)	0.91 (0.57, 1.46)	**0.46 (0.26, 0.82) p=0.008**	0.41 (0.15, 1.14)	1.24 (0.53, 2.93)	1.15 (0.60, 2.22)	0.56 (0.24, 1.35)
	* patella	Grade 2 : Normal/grade 1	Grade 2 (compared with normal/grade 1)	0.95 (0.63, 1.42)	**1.65 (1.06, 2.58) p=0.028**	1.81 (0.96, 3.39)	1.59 (0.74, 3.43)	1.30 (0.66, 2.59)	**3.06 (1.68, 5.56) p<0.001**
		Grades 3/4 : Normal/ grade 1	Grades 3/4 (compared with normal/grade 1)	**1.71 (1.04, 2.80) p=0.033**	1.55 (0.94, 2.55)	1.28 (0.60, 2.70)	2.29 (0.92, 5.68)	**2.10 (1.09, 4.03) p=0.026**	**2.14 (1.07, 4.30) p=0.032**
	* trochlea	Grade 2 : Normal/grade 1	Normal/grade 1 (compared to grade 2)	0.93 (0.52, 1.67)	0.96 (0.54, 1.73)	0.88 (0.37, 2.10)	0.44 (0.14, 1.37)	0.57 (0.22, 1.48)	**0.31 (0.12, 0.82) p=0.017**
Subsequent Surgery	Ipsilateral knee	Yes : No	yes (compared to 'no')	**2.31 (1.35, 3.96) p<0.001**	**2.66 (1.77, 4.01) p<0.001**	**2.20 (1.07, 4.55) p<0.001**	**3.41 (1.72, 6.75) p<0.001**	**1.94* (1.11, 3.39) p=0.060**	**3.03 (1.59, 5.79) p<0.001**
	Contralateral knee	Yes : No		0.62 (0.27, 1.41)	0.92 (0.50, 1.68)	0.23 (0.03, 1.88)	0.90 (0.29, 2.76)	1.55 (0.54, 4.45)	0.47 (0.14, 1.64)

Key:

Significant values are depicted in bold

Gray shading indicates outcome is counterintuitive to what one would think

*Although odds ratio did not cross 1, indicating significance, the p value did not reach 0.05 level of significance.

For Continuous variables, where the Odds ratio < 1.0 --- variables are inversely related.

For Categorical variables, where the Odds ratio > 1.0 --- 1st variable listed is worse than 2nd variable listed

For Categorical variables, where the Odds ratio < 1.0 --- 2nd variable listed is worse than 1st variable listed