Winner of the Systematic Review Award

High Rates of Osteoarthritis Develop After Anterior Cruciate Ligament Surgery

CME

An Analysis of 4108 Patients

Mark E. Cinque,* MD, Grant J. Dornan,* MSC, Jorge Chahla,* MD, PhD, Gilbert Moatshe,*† MD, and Robert F. LaPrade,*‡§ MD, PhD
Investigation performed at the Steadman Philippon Research Institute, Vail, Colorado, USA

Background: Posttraumatic osteoarthritis (PTOA) after anterior cruciate ligament (ACL) reconstruction ultimately translates into a large economic effect on the health care system owing to the young ages of this population.

Purpose/Hypothesis: The purposes were to perform a meta-analysis to determine the prevalence of osteoarthritis after an ACL reconstruction, examining the effects of length of time after surgery, preoperative time interval from injury to surgery, and patient age at the time of surgery. It was hypothesized that the prevalence of PTOA increased with time from surgery and that increased time from injury to surgery and age were also risk factors for the development of PTOA.

Study Design: Meta-analysis.

Methods: A meta-analysis of the prevalence of radiographic PTOA after ACL reconstruction was performed of studies with a minimum of 5 years' follow-up, with a level of evidence of 1, 2, or 3. The presence of osteoarthritis was defined according to knee radiographs evaluated with classification based on Kellgren and Lawrence, Ahlbäck, International Knee Documentation Committee, or the Osteoarthritis Research Society International. Metaregression models quantified the relationship between radiographic PTOA prevalence and the mean time from injury to surgery, mean patient age at time of surgery, and mean postoperative follow-up time.

Results: Thirty-eight studies (4108 patients) were included. Longer postsurgical follow-up time was significantly positively associated with a higher proportion of PTOA development. The model-estimated proportion of PTOA (95% CI) at 5, 10, and 20 years after surgery was 11.3% (6.4%-19.1%), 20.6% (14.9%-27.7%), and 51.6% (29.1%-73.5%), respectively. Increased chronicity of the ACL tear before surgery and increased patient age were also associated with a higher likelihood of PTOA development.

Conclusion: The prevalence of osteoarthritis after an ACL reconstruction significantly increased with time. Longer chronicity of ACL tear and older age at the time of surgery were significantly positively correlated with the development of osteoarthritis. A timely referral and treatment of symptomatic patients are vital to diminish the occurrence of PTOA.

Keywords: anterior cruciate ligament; anterior cruciate ligament reconstruction; osteoarthritis; osteoarthritis after anterior cruciate reconstruction

Osteoarthritis (OA) is the most prevalent musculoskeletal disease, affecting 51.8 million adults in the United States,[37] and it has been reported to account for up to 18% of all health care visits.[58] This health care utilization translates into an annual cost of $461.5 billion to the economy secondary to lost wages and the costs of treatment.[19] Notably, health care costs attributed to OA constitute twice the costs devoted to chronic heart and lung disease.[37]

As of 2006, an estimated 12% of cases of symptomatic OA in the United States were identified as posttraumatic OA (PTOA), totaling 5.6 million cases annually.[54] One of the most common but often overlooked causes of OA is the development of PTOA after anterior cruciate ligament (ACL) tears.[30,31] This is worrisome because most patients who sustain ACL tears are young and otherwise free of risk factors for developing OA.[16]

While ACL reconstruction (ACLR) is primarily performed to restore joint stability, secondary benefits of the procedure include the restoration of normal joint kinematics and decreased stresses on the menisci and chondral surfaces as compared with an ACL-deficient knee.[22,31] However, the development of PTOA after ACLR is still prevalent.[40,41]

§Address correspondence to Robert F. LaPrade, MD, PhD, Steadman Philippon Research Institute, The Steadman Clinic, 181 West Meadow Drive, Suite 400, Vail, CO 81657, USA (email: drlaprade@sprivail.org).
*Steadman Philippon Research Institute, Vail, Colorado, USA.
†Oslo University Hospital, Oslo, Norway.
‡The Steadman Clinic, Vail, Colorado, USA.

One or more of the authors has declared the following potential conflict of interest or source of funding: R.F.L. is a consultant for and receives royalties from Arthrex, Ossur, and Smith & Nephew.

The American Journal of Sports Medicine
2018;46(8):2011–2019
DOI: 10.1177/0363546517730072

TABLE 1
Equivalence Table for Radiographic Osteoarthritis Scoring Scales[a]

Knee	Kellgren-Lawrence	Ahlbäck	IKDC	OARSI-JSN
Normal	Grade 0	Grade 0	A: No or doubtful changes in the knee joint	1
Minimal OA	Grade 1	Grade 0	B: Small osteophytes, slight sclerosis, flattening of femoral condyles	2
OA	Grade 2	Grade 1	C: Joint space narrowing <50%	>2
	Grade 3	Grade 2		
	Grade 4	Grade 3	D: Joint space narrowing between 50% and 100%	
		Grade 4		
		Grade 5		

[a]Modified from Claes et al.[9] IKDC, International Knee Documentation Committee; OA, osteoarthritis; OARSI-JSN, Osteoarthritis Research Society International–joint space narrowing.

It is important to determine factors associated with and risk factors for the development of OA and to employ measures to modify modifiable factors. The effects of patient-specific factors, including meniscal pathology, meniscectomy, and focal articular cartilage pathology, have been demonstrated to be associated with the development of PTOA. The effects of (1) the interval between ACL tear and surgery, (2) age at surgery, and (3) time from surgery on the development of PTOA after ACLR are unclear. Therefore, the purposes of this study were to perform a meta-analysis to determine the prevalence of OA after an ACLR, examining the effects of length of time after surgery, preoperative time from injury to surgery, and patient age at the time of surgery. It was hypothesized that the prevalence of PTOA increased with time from surgery and that increased time from injury to surgery and age were also risk factors for the development of PTOA.

METHODS

Article Identification and Selection

This study was conducted in accordance with the 2009 PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-analyses).[35] A systematic review of the literature regarding the existing evidence for the development of OA after an ACLR was performed with the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, PubMed (1980-2016), and MEDLINE (1980-2016). The queries were performed in December 2016. Registration of this systematic review was performed in February 2017 with the PROSPERO international prospective register of systematic reviews (CRD42017056903).

The literature search strategy inclusion criteria were as follows: radiographic evaluation for OA after ACLRs in studies with a mean follow-up of at least 5 years and with a level of evidence of 1, 2, or 3. Cadaveric studies, animal studies, basic science articles, editorial articles, surveys, and non-English studies were excluded.

Three investigators trained in orthopaedic surgery (R.F.L., J.C., G.M.) independently reviewed the abstracts from all identified articles. If necessary, full-text articles were obtained for review to allow further assessment of inclusion and exclusion criteria. Additionally, all references from the included studies were reviewed and reconciled to verify that no relevant articles were missing from the systematic review. A modified version of the Coleman methodology score (mCMS) was used to assess the quality of methodology of each included study. The 2-part mCMS grades studies based on 10 criteria: part A—study size, mean follow-up, number of different surgical procedures, type of study, description of surgical procedure, postoperative rehabilitation, inclusion of patients' radiographic outcomes; part B—outcome criteria, procedure for assessing clinical outcomes, and description of participant selection process. The maximum score of the mCMS is 100, which indicates that a study largely avoids chance, biases, and confounding factors.

Data Collection

The level of evidence of the studies was assigned according to the classification specified by Wright et al.[63] Patient demographics, mean follow-up length, mean time from injury to surgery, radiographic OA scores, and the total number of patients with OA were extracted and recorded. For continuous variables (eg, age, timing of surgery, follow-up length), the mean and range were collected if reported. There were 4 radiographic OA scoring scales used in these studies: Kellgren and Lawrence, Ahlbäck, the International Knee Documentation Committee, and the Osteoarthritis Research Society International–joint space narrowing. As described by Claes et al,[9] we used each radiographic grading system to develop an equivalence table to create a standard cutoff for the presence of OA (Table 1).

Data Processing

For studies that reported rates of PTOA at multiple time points, only the furthest follow-up time point from surgery was used for the analysis. Weighted means were computed when studies reported continuous variable summaries in multiple groups. For the 2 studies that reported the interval between injury and surgery as a maximum amount of time from injury to surgery,[38,46] we imputed the maximum number of months as the preoperative interval between injury

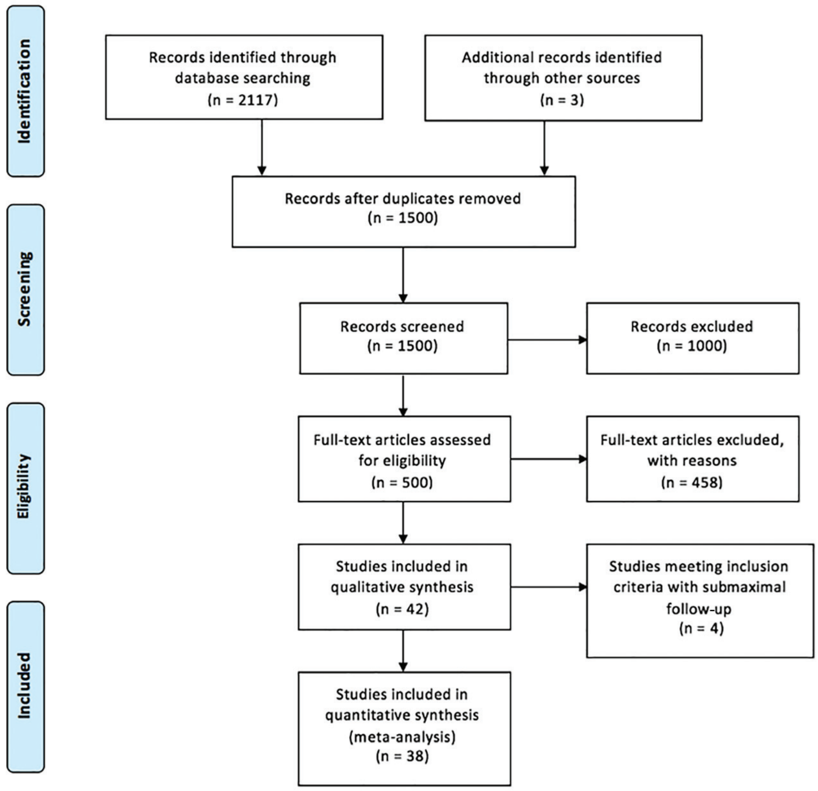

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) flowchart of the study selection criteria.

and surgery. To be included in the final analysis, patients were required to have undergone any type of ACLR surgery.

Quantitative Synthesis

The primary aim of this study was to synthesize the best available evidence to quantify the risk of developing PTOA after ACLR. Specifically, we aimed to correlate the proportion of patients who developed PTOA in each study with several covariates that were hypothesized a priori to affect the likelihood of developing PTOA. First, a naïve (nonmoderated) meta-analysis was conducted to estimate the overall rate of PTOA among all studies. Second, meta-regression was performed to test for the linear effects of mean length of follow-up, mean patient age at surgery, and mean time from injury to surgery in months on the log-odds of PTOA. Additionally, a subgroup meta-analysis was performed to test whether the proportion of PTOA differed by study level of evidence (1-3). All models utilized logit (log-odds) transformed proportions. To allow for generalizability of our results beyond the set of included studies, all metaregressions and subgroup meta-analyses utilized mixed effects models.[20] Residual heterogeneity was estimated with the DerSimonian-Laird method, reported with the I^2 statistic, and presented with 95% confidence intervals. Metaregression results were visualized by plotting fitted values with 95% confidence regions across the range of observed covariate values. Evidence for publication bias was assessed with funnel plots, and symmetry was tested with the rank correlation test. When asymmetry was found in nonmoderated models, the rank-based trim-and-fill method proposed by Duval and Tweedie, which aims to augment the data to reduce asymmetry, was reported as a sensitivity analysis.[13] Model assumptions and fit were assessed via residual diagnostics. The statistical software R (v 3.3.2) was used to produce all analyses and results figures (R Foundation for Statistical Computing, with additional packages meta, metafor, and ggplot2).[50,60,63]

RESULTS

Study Selection

Thirty-eight studies were identified after application of inclusion and exclusion criteria: 9 level 1 studies, 21 level 2 studies, and 8 level 3 studies. Methodological quality assessment of the included studies resulted in a mean mCMS score of 65.82 (range, 57-75). Seventeen studies compared bone–patellar tendon–bone reconstruction autografts with hamstring reconstruction autografts; 5 compared nonoperative and operative treatment; 3 compared single- and double-bundle reconstruction; and 13 were classified as “other.” Four studies fell into the “other” category because there was not at least 1 additional study

TABLE 2
Bibliometric and Demographic Data for the Included Studies[a]

First Author	Study Year	Level of Evidence	Comparison	OA Scale	Total Patients	Mean Age, y	Mean Follow-up, y	Mean Time to Surgery, mo	OA Percentage
O'Neill[39]	2001	1	BTB AUTO vs hamstring AUTO	IKDC	225	27.0	8.5	20.1	12
Pinczewski[43]	2002	2	BTB AUTO vs hamstring AUTO	IKDC	105	24.6	5	NR	3
Drogset[12]	2002	1	Other	Ahlbäck	68	26.0	8	42.0	50
Fithian[15]	2005	2	OP vs NONOP	IKDC	208	39.0	6.6	NR	18
Roe[46]	2005	2	BTB AUTO vs hamstring AUTO	IKDC	104	24.5	7	10.0	3
Sajovic[49]	2006	1	BTB AUTO vs hamstring AUTO	IKDC	52	37.0	11	24.0	27
Matsumoto[32]	2006	1	BTB AUTO vs hamstring AUTO	Kellgren-Lawrence	72	23.7	7.25	11.4	8
Zaffagnini[65]	2006	1	BTB AUTO vs hamstring AUTO	Kellgren-Lawrence	50	30.5	5	8.0	2
Pinczewski[44]	2007	2	BTB AUTO vs hamstring AUTO	IKDC	128	24.5	10	3.0	2
Keays[25]	2007	2	BTB AUTO vs hamstring AUTO	JSN	56	27.0	6	35.1	48
Liden[29]	2008	2	BTB AUTO vs hamstring AUTO	Ahlbäck	113	29.4	76	15.4	28
Kessler[26]	2008	2	OP vs NONOP	Kellgren-Lawrence	109	30.7	11.1	NR	25
Neuman[38]	2008	2	Other	JSN	79	42.0	15.7	0.3	16
Ahlden[2]	2009	3	BTB AUTO vs hamstring AUTO	Ahlbäck	44	27.6	7.3	14.1	16
Meuffels[33]	2009	3	OP vs NONOP	Kellgren-Lawrence	50	37.6	10	6.0	24
Shelbourne[52]	2009	2	Other	IKDC	502	23.0	14.1	31.2	10
Holm[21]	2010	1	BTB AUTO vs hamstring AUTO	Kellgren-Lawrence	57	35.9	10.5	40.9	61
Øiestad[42]	2010	3	Other	IKDC	164	27.4	12.1	27.0	69
Øiestad[40]	2010	2	Other	Kellgren-Lawrence	181	39.6	12.4	28.0	73
Sajovic[48]	2011	2	BTB AUTO vs hamstring AUTO	IKDC	54	25.4	5	24.0	2
Mihelic[34]	2011	2	OP vs NONOP	IKDC	54	25.3	18.5	19.0	11
Ferretti[14]	2011	3	Other	Kellgren-Lawrence	80	35.0	5	3.1	0
Øiestad[41]	2011	3	Other	Kellgren-Lawrence	210	39.1	13.7	24.8	71
Leys[28]	2012	2	BTB AUTO vs hamstring AUTO	IKDC	94	24.5	15	3.0	9
Suomalainen[54]	2012	2	SB vs DB	Kellgren-Lawrence	65	32.3	5	12.0	3
Frobell[17]	2013	1	OP vs NONOP	Kellgren-Lawrence	121	26.0	5	2.5	11
Song[53]	2013	2	SB vs DB	Kellgren-Lawrence	112	33.1	5.5	7.9	10
Janssen[23]	2013	2	Other	Kellgren-Lawrence	86	31.2	10	58.8	73
Barenius[5]	2014	1	BTB AUTO vs hamstring AUTO	Kellgren-Lawrence	134	40.4	14.1	15.1	55
Bulgheroni[8]	2015	3	Other	Kellgren-Lawrence	34	44.7	9.55	26.3	29
Ruffilli[47]	2015	3	Other	IKDC	51	29.2	12.1	NR	12
Webster[61]	2016	2	BTB AUTO vs hamstring AUTO	Kellgren-Lawrence	38	41.6	15.25	NR	29
Thompson[56]	2016	2	BTB AUTO vs hamstring AUTO	IKDC	137	24.5	20	3.0	50
Björnsson[7]	2016	2	BTB AUTO vs hamstring AUTO	Kellgren-Lawrence	147	27.4	16.4	34.7	44
Karikis[24]	2016	1	SB vs DB	Ahlbäck	87	29.1	5.4	23.5	22
Bjorkman[6]	2016	2	Other	IKDC	47	NR	5	NR	4
Wellsandt[62]	2016	3	Other	Kellgren-Lawrence	22	34.7	5	2.8	32
Risberg[45]	2016	2	Other	Ahlbäck	168	45.2	17.8	26.4	42

with the same comparison groups. Comparisons in these studies included bone–patellar tendon–bone autograft reconstruction versus Kennedy augmentation,[12] accelerated versus delayed rehabilitation,[23] medial meniscus transplant with ACLR versus a collagen meniscus implant with ACLR and single- versus double-strand hamstring ACLR,[47] and screw versus pin femoral fixation.[6] The remaining 9 studies in the "other" group were prospective (prognostic) cohort studies. All patients in these 9 studies underwent ACLR. Figure 1 demonstrates the selection criteria of the studies found with our search.

Demographics

A total of 4108 patients were included in this review. The weighted mean age at surgery of the aggregate study population was 30.5 years old (range of reported means, 23-45.2 years old). Among the included studies, sex distribution was reported in 24 studies (64%), totaling 1248 men and 837 women. All studies reported on patients with a minimum 5-year postoperative follow-up duration, and the mean follow-up time ranged from 5 to 20 years among studies, with a median of 9.8 years. The average preoperative time from injury to surgery was reported in 32 studies, producing a weighted mean interval of 17.9 months (range of reported means, 0.3-58.8 months). The reported proportion of patients with OA ranged from 0% to 73% among included studies. Detailed information on the included studies is displayed in Table 2.

Meta-analysis for Unadjusted Proportion of OA

A nonmoderated random effects meta-analysis of all 38 studies estimated the overall weighted proportion of PTOA to be 21.1% (95% CI, 15.1%-28.6%). A high degree of between-study heterogeneity was observed (I^2 = 95.6%; 95% CI, 94.7%-96.4%). Moreover, the rank correlation test found significant funnel plot asymmetry (P = .010), indicating evidence for publication bias against small

TABLE 3
Results From 3 Metaregression Models[a]

Model	Parameter	Estimate	95% CI	*P* Value
1 (38 studies)	Intercept	−2.766	−3.766 to −1.765	<.001
	Mean follow-up time, y	0.142	0.052 to 0.231	.002
2 (32 studies)	Intercept	−2.392	−3.117 to −1.667	<.001
	Mean time from injury to surgery, mo	0.061	0.031 to 0.091	<.001
3 (37 studies)	Intercept	−3.852	−5.765 to −1.939	<.001
	Mean patient age at surgery, y	0.082	0.022 to 0.141	.007

[a]For each model, the intercept estimates the log-odds for the proportion of posttraumatic osteoarthritis (PTOA) when the covariate is set to zero. The second parameter estimated in each model represents the expected change in the log-odds of PTOA development for each 1-unit change in the covariate variable. For instance, the estimated change in log-odds from a mean 5-year follow-up to a mean 6-year follow-up was 0.142 (95% CI, 0.052-0.231).

Figure 2. Estimated metaregression relationship between proportion with osteoarthritis development and mean follow-up time (years). The dots represent individual studies. The shaded region represents a 95% confidence region for the curve. PTOA, posttraumatic osteoarthritis.

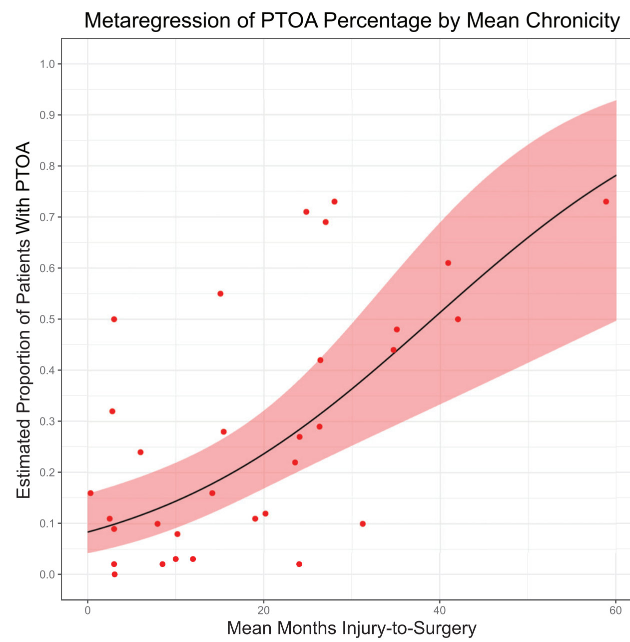

Figure 3. Estimated metaregression relationship between proportion with osteoarthritis development and mean time between injury and anterior cruciate ligament reconstruction (months). The dots represent individual studies. The shaded region represents the 95% confidence region for the curve. PTOA, posttraumatic osteoarthritis.

studies with a high PTOA prevalence. The trim-and-fill method, used as a sensitivity analysis in the face of potential publication bias, estimated a slightly higher overall proportion of PTOA (28.5%; 95% CI, 21.3%-37.0%). Subgroup meta-analysis found no significant difference in PTOA rates among studies with level of evidence 1, 2, or 3 (χ^2_2 = 1.42, *P* = .493).

Metaregression

A separate mixed effects metaregression model was built for each of 3 continuous covariates to test for a linear association between individual covariates and the log-odds of developing OA. These 3 models are summarized in Table 3 and visualized in Figures 2 to 4. Explicit formulation of these models, for clinical use to calculate the estimated risk of PTOA development, are available in the Appendix (available in the online version of this article).

Higher mean years of postsurgical follow-up time were significantly positively associated with a higher proportion of PTOA development (for 1 additional year of follow-up, an expected increase in log-odds of PTOA = 0.142, *P* = .002). The model-estimated proportion of PTOA (95% CI) at 5, 10, and 20 years after surgery was 11.3% (6.4%-

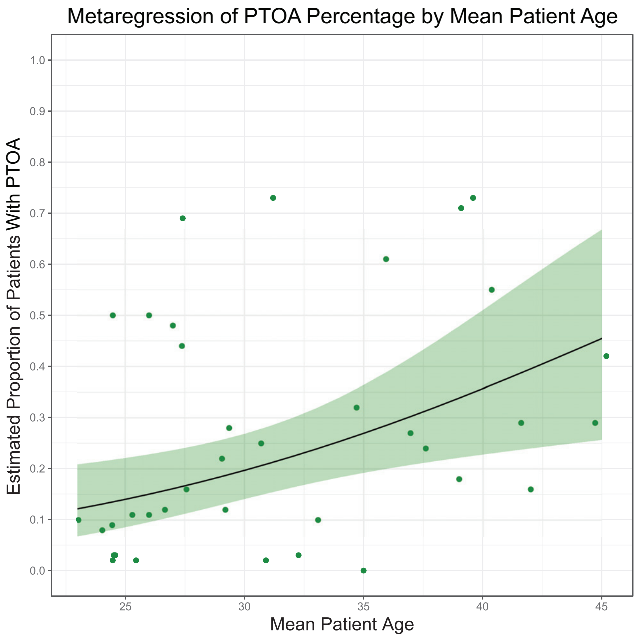

Figure 4. Estimated metaregression relationship between proportion with osteoarthritis development and mean patient age (years). The dots represent individual studies. The shaded region represents the 95% confidence region for the curve. PTOA, posttraumatic osteoarthritis.

19.1%), 20.6% (14.9%-27.7%), and 51.6% (29.1%-73.5%), respectively (Figure 2). The mean time from injury to surgery was reported in 32 studies, and model results were presented over the observed range of means among studies (0-60 months). Increased chronicity of the ACL tear before surgery was associated with a higher likelihood of PTOA development (for 1 additional month, an increase in log-odds of PTOA = 0.061, $P < .001$). The estimated PTOA proportion for a mean preoperative chronicity of 6, 18, and 36 months was 11.7% (6.8%-19.2%), 21.6% (15.2%-29.6%), and 45.3% (30.2%-61.3%), respectively (Figure 3). Finally, the mean patient age at surgery was also significantly positively associated with an increased likelihood of PTOA (for 1 additional year of age, increase in log-odds of PTOA = 0.082, $P = .007$) (Figure 4). The mean years of postsurgical follow-up was positively but not significantly correlated with mean patient age (rho = 0.22, $P = .164$) and mean time from injury to surgery (rho = 0.31, $P = .068$).

DISCUSSION

The most important finding of this study was that the proportion of patients who develop PTOA after ACLR significantly increased as the preoperative interval between the original injury and surgery, the patient's age, and the postoperative follow-up period increased. The likelihood of PTOA development at 5, 10, and 20 years postsurgery was 11.3%, 20.6%, and 51.6%, respectively. The proportion of patients with PTOA increased from 11.7% at 6 months' interval from injury to surgery to 21.6% at 18 months and 45.3% at 36 months. Finally, for every year increase in patient age at the time of surgery, a significant increase in the odds of PTOA was observed. The findings of this study were strengthened by the subanalysis of level of evidence, demonstrating no significant difference in PTOA rates based on the included studies' levels of evidence (1-3).

This meta-analysis identified 2 new risk factors for PTOA after ACLR surgery. First, as the preoperative interval between the ACL tear and ACLR increased, a significant increase in the development of PTOA was observed. Second, increased age at the time of surgery was recognized as a significant risk factor. These findings are important because much of the current literature has focused on other factors, such as meniscectomy, surgical technique, graft type, and previous sport participation and their effects on the development of PTOA after ACL injury.[9,57,59] Chronic knee instability attributed to an untreated ACL tear has been reported to be a risk factor for meniscal tears and chondral degeneration secondary to altered knee loading and biomechanics.[4] As a result, meniscal tears and chondral pathology are commonly seen in knees with the ACL reconstructed in the chronic phase (more than 6 to 8 weeks after injury).[10,27,51] These findings demonstrating increased rates of chondral and meniscal injuries in patients with untreated ACL tears, coupled with the findings of the current study demonstrating increased PTOA in patients with longer intervals from injury to surgery, highlight the need for early diagnosis, surgical treatment, and rehabilitation of those patients with symptomatic ACL tears. Furthermore, clinicians should have an appropriately lower threshold for referral to an orthopaedic specialist or for advanced imaging (magnetic resonance). Older patients undergoing ACLR have higher odds of developing PTOA,[51] and this information should be conveyed to older patients with an ACL tear before surgery.

Intra-articular injuries and their effect on PTOA development have been studied in the context of patients undergoing meniscectomy during an ACLR. A meta-analysis of 1554 patients at a minimum follow-up of 10 years (range, 10-24.5 years), evaluating the effect of meniscectomy on the prevalence of OA in ACL-reconstructed knees, suggested that the prevalence of OA was 16.4% in patients without meniscectomy and 50.4% in patients with meniscectomy, yielding a 3.54-higher odds of having OA when meniscectomy was performed concurrently with ACLR.[9] Moreover, van Meer et al[59] reported that medial meniscal injury/meniscectomy posed a high risk for the development of PTOA after an ACL tear, while a lateral meniscal tear/meniscectomy did not increase PTOA risk at a mean follow-up of 3.9 to 20 years in the included studies. These studies have helped shape clinical practice today, with more meniscal repairs now being performed to protect the knee joint.[1] However, these studies did not evaluate the timing of surgery, risk of PTOA over time after ACL surgery, and the effect of age at ACL surgery. The effects of these factors on PTOA development were elucidated in the present study: increased PTOA occurs with increasing time from surgery, increased age at the time of surgery, and a greater interval between injury and surgery. These findings also have the ability to change practice for all clinicians and lower disease burden in a young population through early treatment and preventative programs.

As the number of participants in youth sports increases, the implications of the rising numbers of ACL tears on the individual and population-wide lifetime development of PTOA are concerning given that the rate of ACL tear per sports exposure for women and men is 0.081 and 0.05 per 1000, respectively.[18] This risk, coupled with the findings of the present study, highlights the need for an emphasis on ACL injury prevention programs, meniscal repairs over meniscectomies, and early injury detection. Several studies have reported a successful decrease in the number of ACL tears after implementing a preseason neuromuscular training program.[3,11,36] In general, these programs have been difficult to initiate in the United States. However, because of the increased burden on patients and society from an ACLR over time attributed to the development of PTOA in a large number of these relatively young patients, incorporation of the successful portions of these prevention programs in practice and pregame sessions should be reemphasized.

Limitations

We acknowledge some limitations to the present study. First, it is worth noting that the studies reporting on PTOA are highly heterogeneous. Because of this heterogeneity, a cause-and-effect relationship between each factor and PTOA cannot be established. However, our findings suggest that the individual factors of the chronicity of the ACL tear before surgery and the patient's age at the time of surgery can increase the proportion of patients in a given cohort who will develop PTOA after ACLR. Second, different classification systems of radiographic OA were used and grouped for the purposes of this study and may not be perfectly generalizable. The possibility of aggregation bias ("ecological fallacy"), which can occur when covariates are inferred from study means rather than individual-level data, was also a theoretical limitation of our metaregressions. Finally, this study analyzed only the patients who were treated with surgical reconstruction.

CONCLUSION

The prevalence of OA after an ACLR significantly increased with time. The chronicity of ACL tear and an older age at the time of surgery were significantly positively correlated with the development of OA. Timely referral and treatment of symptomatic patients are vital to diminish the occurrence of PTOA. These findings can profoundly affect all health care providers by allowing them to diagnose patients with ACL injuries early, through referral or imaging, and to better counsel patients on the best treatment for preventing the associated morbidity and costly cascade of OA.

An online CME course associated with this article is available for 1 *AMA PRA Category 1 Credit*™ at http://www.sportsmed.org/aossmimis/Members/Education/AJSM%20Current%20Concepts%20Store.aspx. In accordance with the standards of the Accreditation Council for Continuing Medical Education (ACCME), it is the policy of The American Orthopaedic Society for Sports Medicine that authors, editors, and planners disclose to the learners all financial relationships during the past 12 months with any commercial interest (A 'commercial interest' is any entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients). Any and all disclosures are provided in the online journal CME area which is provided to all participants before they actually take the CME activity. In accordance with AOSSM policy, authors, editors, and planners' participation in this educational activity will be predicated upon timely submission and review of AOSSM disclosure. Noncompliance will result in an author/editor or planner to be stricken from participating in this CME activity.

REFERENCES

1. Abrams GD, Frank RM, Gupta AK, Harris JD, McCormick FM, Cole BJ. Trends in meniscus repair and meniscectomy in the United States, 2005-2011. *Am J Sports Med*. 2013;41(10):2333-2339.
2. Ahlden M, Kartus J, Ejerhed L, Karlsson J, Sernert N. Knee laxity measurements after anterior cruciate ligament reconstruction, using either bone-patellar-tendon-bone or hamstring tendon autografts, with special emphasis on comparison over time. *Knee Surg Sports Traumatol Arthrosc*. 2009;17(9):1117-1124.
3. Alentorn-Geli E, Myer GD, Silvers HJ, et al. Prevention of non-contact anterior cruciate ligament injuries in soccer players. Part 2: a review of prevention programs aimed to modify risk factors and to reduce injury rates. *Knee Surg Sports Traumatol Arthrosc*. 2009;17(8):859-879.
4. Andriacchi TP, Mundermann A, Smith RL, Alexander EJ, Dyrby CO, Koo S. A framework for the in vivo pathomechanics of osteoarthritis at the knee. *Ann Biomed Eng*. 2004;32(3):447-457.
5. Barenius B, Ponzer S, Shalabi A, Bujak R, Norlen L, Eriksson K. Increased risk of osteoarthritis after anterior cruciate ligament reconstruction: a 14-year follow-up study of a randomized controlled trial. *Am J Sports Med*. 2014;42(5):1049-1057.
6. Bjorkman P, Sandelin J, Harilainen A. A randomized prospective controlled study with 5-year follow-up of cross-pin femoral fixation versus metal interference screw fixation in anterior cruciate ligament reconstruction. *Knee Surg Sports Traumatol Arthrosc*. 2015;23(8):2353-2359.
7. Björnsson H, Samuelsson K, Sundemo D, et al. A randomized controlled trial with mean 16-year follow-up comparing hamstring and patellar tendon autografts in anterior cruciate ligament reconstruction. *Am J Sports Med*. 2016;44(9):2304-2313.
8. Bulgheroni E, Grassi A, Bulgheroni P, Marcheggiani Muccioli GM, Zaffagnini S, Marcacci M. Long-term outcomes of medial CMI implant versus partial medial meniscectomy in patients with concomitant ACL reconstruction. *Knee Surg Sports Traumatol Arthrosc*. 2015;23(11):3221-3227.
9. Claes S, Hermie L, Verdonk R, Bellemans J, Verdonk P. Is osteoarthritis an inevitable consequence of anterior cruciate ligament reconstruction? A meta-analysis. *Knee Surg Sports Traumatol Arthrosc*. 2013;21(9):1967-1976.
10. de Campos GC, Nery W Jr, Teixeira PE, Araujo PH, Alves WM Jr. Association between meniscal and chondral lesions and timing of anterior cruciate ligament reconstruction. *Orthop J Sports Med*. 2016;4(10):2325967116669309.

11. DiStefano LJ, Marshall SW, Padua DA, et al. The effects of an injury prevention program on landing biomechanics over time. *Am J Sports Med*. 2016;44(3):767-776.
12. Drogset JO, Grontvedt T. Anterior cruciate ligament reconstruction with and without a ligament augmentation device: results at 8-year follow-up. *Am J Sports Med*. 2002;30(6):851-856.
13. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56(2):455-463.
14. Ferretti A, Monaco E, Giannetti S, Caperna L, Luzon D, Conteduca F. A medium to long-term follow-up of ACL reconstruction using double gracilis and semitendinosus grafts. *Knee Surg Sports Traumatol Arthrosc*. 2011;19(3):473-478.
15. Fithian DC, Paxton EW, Stone ML, et al. Prospective trial of a treatment algorithm for the management of the anterior cruciate ligament-injured knee. *Am J Sports Med*. 2005;33(3):335-346.
16. Frobell RB, Roos EM, Roos HP, Ranstam J, Lohmander LS. A randomized trial of treatment for acute anterior cruciate ligament tears. *N Engl J Med*. 2010;363(4):331-342.
17. Frobell RB, Roos HP, Roos EM, Roemer FW, Ranstam J, Lohmander LS. Treatment for acute anterior cruciate ligament tear: five year outcome of randomised trial. *BMJ*. 2013;346:f232.
18. Gornitzky AL, Lott A, Yellin JL, Fabricant PD, Lawrence JT, Ganley TJ. Sport-specific yearly risk and incidence of anterior cruciate ligament tears in high school athletes. *Am J Sports Med*. 2016;44(10):2716-2723.
19. Healthcare Cost and Utilization Project. *NIS 2011 and NEDS 2010*. Rockville, MD: Agency for Healthcare Research and Quality; 2011.
20. Hedges LV, Vevea JL. Fixed- and random-effects models in meta-analysis. *Psychol Meth*. 1998;3(4):486.
21. Holm I, Øiestad BE, Risberg MA, Aune AK. No difference in knee function or prevalence of osteoarthritis after reconstruction of the anterior cruciate ligament with 4-strand hamstring autograft versus patellar tendon-bone autograft: a randomized study with 10-year follow-up. *Am J Sports Med*. 2010;38(3):448-454.
22. Ichiba A, Nakajima M, Fujita A, Abe M. The effect of medial collateral ligament insufficiency on the reconstructed anterior cruciate ligament: a study in the rabbit. *Acta Orthop Scand*. 2003;74(2):196-200.
23. Janssen RP, du Mee AW, van Valkenburg J, Sala HA, Tseng CM. Anterior cruciate ligament reconstruction with 4-strand hamstring autograft and accelerated rehabilitation: a 10-year prospective study on clinical results, knee osteoarthritis and its predictors. *Knee Surg Sports Traumatol Arthrosc*. 2013;21(9):1977-1988.
24. Karikis I, Desai N, Sernert N, Rostgard-Christensen L, Kartus J. Comparison of anatomic double- and single-bundle techniques for anterior cruciate ligament reconstruction using hamstring tendon autografts: a prospective randomized study with 5-year clinical and radiographic follow-up. *Am J Sports Med*. 2016;44(5):1225-1236.
25. Keays SL, Bullock-Saxton JE, Keays AC, Newcombe PA, Bullock MI. A 6-year follow-up of the effect of graft site on strength, stability, range of motion, function, and joint degeneration after anterior cruciate ligament reconstruction: patellar tendon versus semitendinosus and gracilis tendon graft. *Am J Sports Med*. 2007;35(5):729-739.
26. Kessler MA, Behrend H, Henz S, Stutz G, Rukavina A, Kuster MS. Function, osteoarthritis and activity after ACL-rupture: 11 years follow-up results of conservative versus reconstructive treatment. *Knee Surg Sports Traumatol Arthrosc*. 2008;16(5):442-448.
27. Kullmer K, Letsch R, Turowski B. Which factors influence the progression of degenerative osteoarthritis after ACL surgery? *Knee Surg Sports Traumatol Arthrosc*. 1994;2(2):80-84.
28. Leys T, Salmon L, Waller A, Linklater J, Pinczewski L. Clinical results and risk factors for reinjury 15 years after anterior cruciate ligament reconstruction: a prospective study of hamstring and patellar tendon grafts. *Am J Sports Med*. 2012;40(3):595-605.
29. Liden M, Sernert N, Rostgard-Christensen L, Kartus C, Ejerhed L. Osteoarthritic changes after anterior cruciate ligament reconstruction using bone-patellar tendon-bone or hamstring tendon autografts: a retrospective, 7-year radiographic and clinical follow-up study. *Arthroscopy*. 2008;24(8):899-908.
30. Lohmander LS, Englund PM, Dahl LL, Roos EM. The long-term consequence of anterior cruciate ligament and meniscus injuries: osteoarthritis. *Am J Sports Med*. 2007;35(10):1756-1769.
31. Louboutin H, Debarge R, Richou J, et al. Osteoarthritis in patients with anterior cruciate ligament rupture: a review of risk factors. *Knee*. 2009;16(4):239-244.
32. Matsumoto A, Yoshiya S, Muratsu H, et al. A comparison of bone-patellar tendon-bone and bone-hamstring tendon-bone autografts for anterior cruciate ligament reconstruction. *Am J Sports Med*. 2006;34(2):213-219.
33. Meuffels DE, Favejee MM, Vissers MM, Heijboer MP, Reijman M, Verhaar JA. Ten year follow-up study comparing conservative versus operative treatment of anterior cruciate ligament ruptures: a matched-pair analysis of high level athletes. *Br J Sports Med*. 2009;43(5):347-351.
34. Mihelic R, Jurdana H, Jotanovic Z, Madjarevic T, Tudor A. Long-term results of anterior cruciate ligament reconstruction: a comparison with non-operative treatment with a follow-up of 17-20 years. *Int Orthop*. 2011;35(7):1093-1097.
35. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151(4):264-269, w264.
36. Myklebust G, Engebretsen L, Braekken IH, Skjolberg A, Olsen OE, Bahr R. Prevention of anterior cruciate ligament injuries in female team handball players: a prospective intervention study over three seasons. *Clin J Sport Med*. 2003;13(2):71-78.
37. National Center for Health Statistics. *National Health Interview Survey: Adult Sample*. Atlanta, GA: Centers for Disease Control and Prevention; 2012.
38. Neuman P, Englund M, Kostogiannis I, Friden T, Roos H, Dahlberg LE. Prevalence of tibiofemoral osteoarthritis 15 years after nonoperative treatment of anterior cruciate ligament injury: a prospective cohort study. *Am J Sports Med*. 2008;36(9):1717-1725.
39. O'Neill DB. Arthroscopically assisted reconstruction of the anterior cruciate ligament: a follow-up report. *J Bone Joint Surg Am*. 2001;83(9):1329-1332.
40. Øiestad BE, Holm I, Aune AK, et al. Knee function and prevalence of knee osteoarthritis after anterior cruciate ligament reconstruction: a prospective study with 10 to 15 years of follow-up. *Am J Sports Med*. 2010;38(11):2201-2210.
41. Øiestad BE, Holm I, Engebretsen L, Risberg MA. The association between radiographic knee osteoarthritis and knee symptoms, function and quality of life 10-15 years after anterior cruciate ligament reconstruction. *Br J Sports Med*. 2011;45(7):583-588.
42. Øiestad BE, Holm I, Gunderson R, Myklebust G, Risberg MA. Quadriceps muscle weakness after anterior cruciate ligament reconstruction: a risk factor for knee osteoarthritis? *Arthritis Care Res (Hoboken)*. 2010;62(12):1706-1714.
43. Pinczewski LA, Deehan DJ, Salmon LJ, Russell VJ, Clingeleffer A. A five-year comparison of patellar tendon versus four-strand hamstring tendon autograft for arthroscopic reconstruction of the anterior cruciate ligament. *Am J Sports Med*. 2002;30(4):523-536.
44. Pinczewski LA, Lyman J, Salmon LJ, Russell VJ, Roe J, Linklater J. A 10-year comparison of anterior cruciate ligament reconstructions with hamstring tendon and patellar tendon autograft: a controlled, prospective trial. *Am J Sports Med*. 2007;35(4):564-574.
45. Risberg MA, Øiestad BE, Gunderson R, et al. Changes in knee osteoarthritis, symptoms, and function after anterior cruciate ligament reconstruction: a 20-year prospective follow-up study. *Am J Sports Med*. 2016;44(5):1215-1224.
46. Roe J, Pinczewski LA, Russell VJ, Salmon LJ, Kawamata T, Chew M. A 7-year follow-up of patellar tendon and hamstring tendon grafts for arthroscopic anterior cruciate ligament reconstruction: differences and similarities. *Am J Sports Med*. 2005;33(9):1337-1345.
47. Ruffilli A, Buda R, Pagliazzi G, et al. Over-the-top anterior cruciate ligament reconstruction using single- or double-strand hamstrings autograft. *Orthopedics*. 2015;38(7):e635-e643.
48. Sajovic M, Strahovnik A, Dernovsek MZ, Skaza K. Quality of life and clinical outcome comparison of semitendinosus and gracilis tendon

versus patellar tendon autografts for anterior cruciate ligament reconstruction: an 11-year follow-up of a randomized controlled trial. *Am J Sports Med*. 2011;39(10):2161-2169.
49. Sajovic M, Vengust V, Komadina R, Tavcar R, Skaza K. A prospective, randomized comparison of semitendinosus and gracilis tendon versus patellar tendon autografts for anterior cruciate ligament reconstruction: five-year follow-up. *Am J Sports Med*. 2006;34(12):1933-1940.
50. Schwarzer G. Meta: an R package for meta-analysis. *R News*. 2007;36:40-45.
51. Seon JK, Song EK, Park SJ. Osteoarthritis after anterior cruciate ligament reconstruction using a patellar tendon autograft. *Int Orthop*. 2006;30(2):94-98.
52. Shelbourne KD, Gray T. Minimum 10-year results after anterior cruciate ligament reconstruction: how the loss of normal knee motion compounds other factors related to the development of osteoarthritis after surgery. *Am J Sports Med*. 2009;37(3):471-480.
53. Song EK, Seon JK, Yim JH, Woo SH, Seo HY, Lee KB. Progression of osteoarthritis after double- and single-bundle anterior cruciate ligament reconstruction. *Am J Sports Med*. 2013;41(10):2340-2346.
54. Suomalainen P, Jarvela T, Paakkala A, Kannus P, Jarvinen M. Double-bundle versus single-bundle anterior cruciate ligament reconstruction: a prospective randomized study with 5-year results. *Am J Sports Med*. 2012;40(7):1511-1518.
55. Svoboda SJ. ACL injury and posttraumatic osteoarthritis. *Clin Sports Med*. 2014;33(4):633-640.
56. Thompson SM, Salmon LJ, Waller A, Linklater J, Roe JP, Pinczewski LA. Twenty-year outcome of a longitudinal prospective evaluation of isolated endoscopic anterior cruciate ligament reconstruction with patellar tendon or hamstring autograft. *Am J Sports Med*. 2016;44(12):3083-3094.
57. Tran G, Smith TO, Grice A, Kingsbury SR, McCrory P, Conaghan PG. Does sports participation (including level of performance and previous injury) increase risk of osteoarthritis? A systematic review and meta-analysis [published online September 28, 2016]. *Br J Sports Med*.
58. US Consumer Product Safety Commission. *National Electron Injury Surveillance System*. Bethesda, MD: US Consumer Product Safety Commission; 2013.
59. van Meer BL, Meuffels DE, van Eijsden WA, Verhaar JA, Bierma-Zeinstra SM, Reijman M. Which determinants predict tibiofemoral and patellofemoral osteoarthritis after anterior cruciate ligament injury? A systematic review. *Br J Sports Med*. 2015;49(15):975-983.
60. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *Journal of Statistical Software*. 2010;36(3):48.
61. Webster KE, Feller JA, Hartnett N, Leigh WB, Richmond AK. Comparison of patellar tendon and hamstring tendon anterior cruciate ligament reconstruction: a 15-year follow-up of a randomized controlled trial. *Am J Sports Med*. 2016;44(1):83-90.
62. Wellsandt E, Gardinier ES, Manal K, Axe MJ, Buchanan TS, Snyder-Mackler L. Decreased knee joint loading associated with early knee osteoarthritis after anterior cruciate ligament injury. *Am J Sports Med*. 2016;44(1):143-151.
63. Wickham H. *GGplot2: Elegant Graphics for Data Analysis*. New York, NY: Springer-Verlag; 2009.
64. Wright JG, Swiontkowski MF, Heckman JD. Introducing levels of evidence to the journal. *J Bone Joint Surg Am*. 2003;85(1):1-3.
65. Zaffagnini S, Marcacci M, Lo Presti M, Giordano G, Iacono F, Neri MP. Prospective and randomized evaluation of ACL reconstruction with three techniques: a clinical and radiographic evaluation at 5 years follow-up. *Knee Surg Sports Traumatol Arthrosc*. 2006;14(11): 1060-1069.