Posttraumatic Arthritis After Anterior Cruciate Ligament Injury

Machine Learning Comparison Between Surgery and Nonoperative Management

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Background: Nonoperative and operative management techniques after anterior cruciate ligament (ACL) injury are both appropriate treatment options for selected patients. However, the subsequent development of posttraumatic knee osteoarthritis (PTOA) remains an area of active study.

Purpose: To compare the risk of PTOA between patients treated without surgery and with ACL reconstruction (ACLR) after primary ACL disruption using a machine learning causal inference model.

Study Design: Cohort study; Level of evidence, 3.

Methods: A geographic database identified patients undergoing ACLR between 1990 and 2016 with minimum 7.5-year follow-up. Variables collected include age, sex, body mass index, activity level, occupation, relevant comorbid diagnoses, radiographic findings, injury characteristics, and clinical course. Treatment effects of ACLR on the development of PTOA and progression to total knee arthroplasty (TKA) were analyzed with machine learning models (MLMs) in a causal inference estimator (targeted maximum likelihood estimation, TMLE), while controlling for confounders.

Results: The study included 1194 patients with a minimum follow-up of 7.5 years, among whom 974 underwent primary reconstruction and 220 underwent nonoperative treatment. A total of 215 (22%) patients developed symptomatic PTOA in the ACLR group compared with 140 (64%) in the nonoperative treatment group ($P < .001$), whereas 25 (3%) patients underwent TKA in the ACLR group compared with 50 (23%) in the nonoperative treatment group ($P < .001$). Patients in the ACLR group had delayed TKA compared with patients in the nonoperative treatment group (193.4 vs 166.0 months, respectively; $P = .02$). TMLE evaluation revealed that reconstruction decreased the risk of PTOA by 11% (95% CI, 8%-13%; $P < .001$) compared with nonoperative treatment but did not demonstrate a significant effect on the rate of progression to TKA. Survival analysis with random forest algorithm demonstrated significant delay to the onset of PTOA as well as time to progression of TKA in patients undergoing ACLR. Additional risk factors for the development of PTOA, irrespective of treatment, included older age at injury, greater body mass index, total number of arthroscopic knee surgeries, and residual laxity at follow-up.

Conclusion: MLMs in a causal inference estimator found ACLR to exert a significant treatment effect in reducing the rate of development of PTOA by 11% compared with nonoperative treatment. ACLR also delayed the onset of PTOA and progression to TKA.

Keywords: artificial intelligence; posttraumatic osteoarthritis; anterior cruciate ligament reconstruction; machine learning; nonoperative treatment; targeted maximum likelihood estimation

Injuries to the anterior cruciate ligament (ACL) occur frequently in young athletes who participate in pivoting and jumping sports such as football, basketball, and soccer. These injuries sideline patients from activities and sports and may also contribute to the development of arthritis. Prospective data from the MOON cohort revealed a 37% incidence of posttraumatic knee osteoarthritis (PTOA) 10 years after ACL reconstruction (ACLR).[4] Despite the negative long-term effect that PTOA has on joint health, the risks and mechanisms of PTOA after ACL injury remain

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incompletely understood. Cited contributors to PTOA include (1) initial structural damage; (2) mechanical sequelae from recurrent instability; (3) biologic factors, including inflammatory cytokines; and (4) neurological factors such as altered mechanoreceptor function.[6,37] ACLR seeks to restore knee stability and prevent further damage of the menisci and cartilage. However, evidence on the comparative effectiveness of reconstruction versus nonoperative approaches in mitigating PTOA is lacking, secondary to the lack of either high-quality data or effective methods to eliminate confounding. More robust data on this subject matter would provide significant benefit in counseling young patients on the long-term outlook of their knees after this injury and has potential for altering the natural history with existing treatments. The purpose of this study was to compare the risk of PTOA between patients treated with ACLR and those treated without surgery after primary ACL disruption using machine learning models (MLMs) in a causal inference estimator, an alternative statistical strategy to simulate level I evidence from observational cohorts.[35,36] We hypothesized that patients undergoing ACLR would have decreased and delayed rates of PTOA compared with the nonoperative cohort.

METHODS

Guidelines

We used the Guidelines for Developing and Reporting Machine Learning Models in Biomedical Research and the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines in directing the data analysis and reporting of results in this study.[3,20]

Data Source

This study was performed with approval from our local institutional review board (IRB No. 14-005089). To generate the study cohort, a National Institutes of Health–sponsored, established longitudinal geographic database for residents of Olmstead County, Minnesota, otherwise known as the Rochester Epidemiology Project (REP), was queried for patients who experienced an ACL injury between January 1, 1990, and July 31, 2016. The REP contains >500,000 individual medical records collected from residents of Olmstead County as well as neighboring counties in southeast Minnesota and western Wisconsin.[19] Patients were identified using the appropriate diagnosis codes for ACL rupture from the International Classification of Diseases, 9th and 10th Revisions. After initial cohort generation, individual patient charts were reviewed by a team of research personnel in a stepwise, systematic approach. This included, first, confirmation of ACL injury diagnosis, via either arthroscopy or magnetic resonance imaging. Second, inclusion and exclusion criteria were applied to the screened patients. The study included (1) patients with a primary ACL partial or complete rupture who underwent subsequent ACLR, (2) patients with a minimum of 90 months (7.5 years) of follow-up, and (3) patients who gave consent for research. Patients were excluded if they (1) underwent multiligament reconstructions or revision ACLR or (2) were followed <90 months. Specifically, nonoperative management was defined to include aspiration or injection, bracing, formalized physical therapy, or some combination thereof. Third, patient medical records were reviewed for data extraction, which included the following variables: age, sex, body mass index (BMI), activity level, occupation, relevant comorbid diagnoses, number of arthroscopic surgeries on the index knee, treatment methods, concomitant radiographic findings, intraoperative findings in patients undergoing reconstruction, and clinical course after treatment. Additionally, outcomes of interest were reviewed, which included (1) the diagnosis of symptomatic PTOA, defined as documented radiographic osteoarthritis with accompanying symptoms in the index knee at final follow-up by the treating surgeon, and (2) progression to total knee arthroplasty (TKA) at final follow-up. More than 60 covariates were obtained from the REP for feature selection and modeling (Table 1). Given the nature of the database, radiographs were unavailable for direct examination; thus, radiology reports were reviewed for documentation of osteoarthritis or moderate to severe degenerative changes as criteria for radiographic PTOA.

Missing Data

Given the predilection for complete case analysis to produce biased model predictions and discriminatory

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TABLE 1
Baseline Characteristics of Study Population (N = 1194)[a]

Variable	ACLR (n = 974)	Nonoperative (n = 220)	*P*
Age at injury, y	26 (19-35)	38.5 (32-45)	**<.001**
Male sex	565 (58.0)	121 (55.0)	.46
Body mass index, kg/m^2	26.9 (24.1-30.1)	28.4 (26.5-32.1)	**<.001**
Race			.86
American Indian	1 (0.1)	0 (0)	
Asian	17 (1.7)	3 (1.4)	
Asian Indian	1 (0.1)	0 (0)	
Black	59 (4.3)	11 (3.1)	
White	923 (94.8)	211 (95.9)	
Pacific Islander	1 (0.1)	0 (0)	
Hispanic ethnicity	9 (0.9)	1 (0.5)	.779
Smoker			**.008**
Former	52 (5.3)	21 (9.5)	
Current	160 (16.4)	47 (21.4)	
Never	762 (78.2)	152 (69.1)	
Diabetes mellitus	10 (1.0)	7 (3.2)	**.034**
Systemic inflammatory disease	14 (1.4)	8 (3.6)	.056
Hypermobility	4 (0.4)	2 (0.9)	.677
Right knee	493 (50.6)	117 (53.2)	.54
Activity level			**<.001**
Competitive	214 (22.0)	10 (4.5)	
Recreational	664 (68.2)	119 (54.1)	
Sedentary	96 (9.9)	91 (41.4)	
Occupation			**<.001**
Laborer	317 (32.5)	80 (36.4)	
Sedentary	346 (35.5)	126 (57.3)	
Student	311 (31.9)	14 (6.4)	
Malalignment	10 (1.0)	3 (1.4)	.94
Type of sport			
High-impact rotational landing	12 (0.9)	0 (0)	.218
Noncontact	136 (9.9)	31 (10.5)	.835
Limited contact	112 (8.2)	17 (5.8)	.202
Contact	525 (38.3)	27 (9.2)	**<.001**
Collision	125 (9.1)	11 (3.7)	**.003**
Workers' compensation	25 (2.6)	16 (5.4)	**.002**
Tear type			**<.001**
Partial	75 (5.5)	67 (22.8)	
Complete	1294 (94.5)	227 (77.2)	
Tear location			**.048**
Femoral avulsion	12 (1.2)	7 (3.2)	
Proximal	48 (4.9)	12 (5.5)	
Midsubstance	558 (57.3)	116 (52.7)	
Distal	356 (36.6)	84 (38.2)	
Tibial avulsion	0 (0.0)	1 (0.5)	
Injury mechanism			**<.001**
Noncontact	842 (86.4)	138 (62.7)	
Contact	115 (15.6)	59 (26.8)	
Concomitant meniscal injury			**.001**
Both	157 (16.1)	28 (12.7)	
Lateral	227 (23.3)	29 (13.2)	
Medial	270 (27.7)	70 (31.8)	
None	320 (32.9)	93 (42.3)	
Concomitant PCL injury	11 (1.1)	4 (1.8)	.622
Concomitant MCL injury	161 (16.5)	28 (12.7)	.196
Concomitant LCL injury	36 (3.7)	11 (5.0)	.48
Concomitant PLC injury	27 (2.8)	3 (1.4)	.333
Concomitant patellar instability	17 (1.7)	2 (0.9)	.55
Articular cartilage	236 (24.2)	36 (16.4)	**.015**

(continued)

TABLE 1
(continued)

Variable	ACLR (n = 974)	Nonoperative (n = 220)	P
VAS score on initial presentation	5.9 (3.0-6.5)	3.0 (2.1-6.0)	<.001
Received aspiration or injection	67 (6.9)	45 (20.5)	**<.001**
Brace	585 (60.1)	184 (83.6)	**<.001**
Physical therapy	782 (80.3)	203 (92.3)	**<.001**
Days to return to unrestricted activity	401 (230.6-790.5)	414 (304-741.5)	.38
Months of follow-up	161 (119.9-210.7)	199.8 (150.9-250.8)	**<.001**
PTOA	215 (22.1)	140 (63.6)	**<.001**
Months to PTOA	147 (84-213)	122 (49-198)	.2
TKA	25 (2.6)	50 (22.6)	**<.001**
Months to TKA	193.4 (140.9-252.7)	166.0 (120.9-228.2)	**.02**

[a]Data are presented as n (%) or median (interquartile range). LCL, lateral collateral ligament; MCL, medial collateral ligament; PCL, posterior cruciate ligament; PLC, posterolateral corner; PTOA, posttraumatic knee osteoarthritis; TKA, total knee arthroplasty; VAS, visual analog scale.

algorithmic decision-making,[5] missing data were imputed.[12,34] In brief, variables were assumed to be missing-at-random based on epidemiological convention,[24] and the missForest multiple imputation method was used to impute variables with <35% missing data,[13,31] with variable-wise level of missingness provided in Table 1. The success of imputation was assessed using the out-of-bag prediction error. After imputation of missing data, highly collinear variables (defined as Spearman correlation coefficients >0.75 or those considered clinically confounding) were identified and excluded.

Targeted Maximum Likelihood Estimation

The treatment effect of ACLR on the development of PTOA as well as progression to TKA was then evaluated using TMLE, a method to obtain valid statistical inference using MLMs.[35,36] As previously described, TMLE is a double-robust estimator that can simulate the conditions of a randomized controlled study in noncontrolled observational data via independent estimations about (1) the treatment assignment in each population distribution and (2) the outcome of a given treatment. This is different from traditional models for outcome regression and treatment assignment (eg, propensity scoring), which remain unbiased only given correct assumptions about the underlying distribution of data. Additionally, the accuracy and flexibility of TMLE can be augmented through data-adaptive MLMs, which can accommodate high-dimensional data and nonlinear relationships better than classic statistical models.[9,26,33,36] We performed TMLE using a Super Learner library that compiles the output from a diverse ensemble of algorithms (random forest, Xtreme gradient boosting, elastic net linear regression, and support vector machines) to generate an estimation of the treatment effect of ACLR on development of symptomatic PTOA.

Time-to-Event Analysis With Interpretable Machine Learning

An additional analysis was performed to compare the time-dependent risk of developing PTOA and progressing to TKA between ACLR and nonoperatively treated patients. For this analysis, random survival forests were created for nonparametric comparisons of time-to-event data in group-based fashion,[2,27] where the study cohort is dichotomized based on treatment received (reconstruction vs nonoperative management) and survival curves are drawn for each group. Models were trained and validated via 0.632 bootstrapping with 1000 resampled datasets, as previously described,[27,32] which ensures that the model is trained and tested on all data points available. Performance evaluation metrics are summarized with standard distributions of each iteration.[27,32] The optimal model hyperparameters are chosen based on the out-of-bag c-statistic, otherwise known as the area under the receiver operating characteristic curve (AUROC), with a c-statistic of 0.70 to 0.80 considered acceptable and 0.80 to 0.90 considered excellent.[11]

Global variable importance and partial dependence curves were generated to assist in model prediction interpretability. A global model variable importance plot provides a visualization of the ranked variable importance normalized against the covariate considered most contributory to the fidelity of model predictions; that is, the variable considered most important contributed the most to the discriminative performance of the model. Partial dependence plots were also generated to illustrate the risk of outcomes-free survivorship (y-axis) as a function of the range of values of each feature while other covariate values are held constant (x-axis), stratified by patients who encountered the outcome compared with those without the outcome.[8] All data analysis was performed with R 4.1.3 using RStudio Version 1.2.5001.

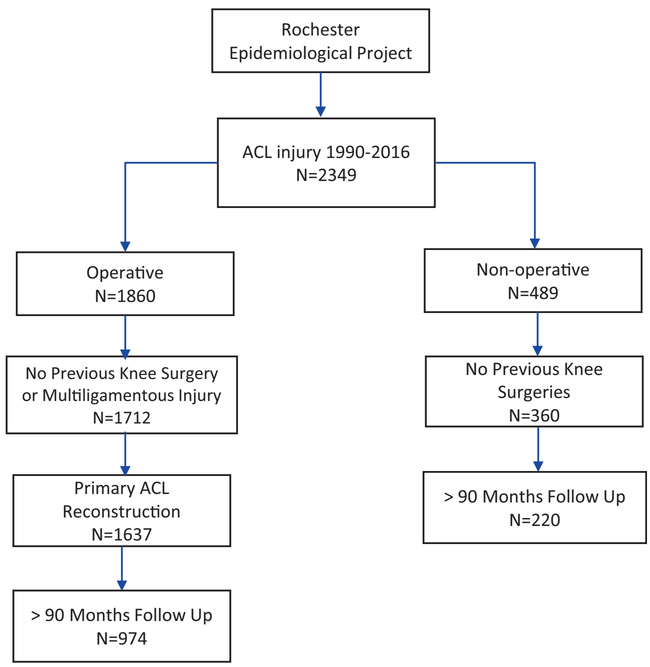

Figure 1. Flow chart of patient selection process.

RESULTS

Variable Breakdown

During the study period of 1990 to 2016, a total of 2349 patients had documented ACL injury in the medical record; of these, 1860 (79.2%) patients underwent ACLR and 489 (20.8%) were treated nonoperatively. Chart review identified 974 ACLR-treated and 220 nonoperatively treated patients with >90 months of follow-up. These patients comprised the final study cohort (Figure 1). The median age at injury was 26 years (IQR, 19-35 years) among patients who were treated with ACLR, significantly younger than those treated nonoperatively (median age, 38 years; IQR, 32-45 years). Additionally, patients who underwent ACLR had significantly lower BMI (26.9 vs 28.4; $P <$ .001), carried fewer comorbidities such as diabetes mellitus (10 [1%] vs 7 [3.2%]; P = .034) or smoking (160 [16.4%] vs 47 [21.4%]), had a higher rate of engagement in recreational activity (664 [68.2%] vs 119 [54.1%]), and had a lower rate of receiving workers' compensation (25 [1.8%] vs 16 [5.4%]; P = .002) when compared, respectively, with patients who were treated nonoperatively. With regard to treatment breakdown, 92.3% of patients in the nonoperatively managed cohort underwent physical therapy, 83.6% were treated with bracing, and 20.5% received aspiration or injection; these rates were significantly increased compared with those in the ACLR cohort (Table 1).

Bivariate comparison of outcomes between the 2 groups showed that nonoperatively treated patients had a significantly increased rate of both the development of symptomatic PTOA (63.6% vs 22.1%; $P <$ .001) and progression to TKA (22.6% vs 2.6%; $P <$ .001) when compared, respectively, with patients who underwent ACLR. Additionally, nonoperatively treated patients underwent TKA at significantly accelerated timing compared with patients who were treated with ACLR (166.0 vs 193.4 months, respectively; P = .02).

Targeted Maximum Likelihood Estimation Analysis

On TMLE analysis, ACLR was found to exert a treatment effect of −0.11 (95% CI, –0.13 to −0.08; $P <$ .001) compared with nonoperative treatment on the development of symptomatic PTOA; that is, patients who underwent ACLR as an intervention had a reduction of 11% (95% CI, 8% to 13%) in the risk of developing symptomatic PTOA compared with matched controls who were treated nonoperatively. However, when the risk of progression to TKA in those undergoing ACLR as an intervention was examined, no treatment effect was identified compared with nonoperatively treated controls (0; 95% CI, –0.002 to 0.002; P = .99).

Time-to-Event Analysis

On time-to-event analysis, ACLR significantly delayed the onset of symptomatic PTOA and progression to TKA compared with nonoperative treatment (Figures 2 and 3). Based on variable importance (Figure 4) and partial dependence plot analysis (Figures 5 and 6), the features contributing most significantly to the development of symptomatic PTOA, irrespective of treatment, included older age at injury, total number of arthroscopic procedures on the index knee before the diagnosis of arthritis, greater pain at presentation, shorter time to return to sport, residual laxity at follow-up, concomitant cartilage or meniscal injury, and greater BMI. With respect to progression to TKA, the most significant contributors to model performance included older age at injury, total number of arthroscopic procedures on the index knee before the diagnosis of arthritis, sedentary activity level, residual laxity at follow-up, hypermobility, greater pain at presentation, systemic inflammatory disease, and greater BMI.

DISCUSSION

The principal findings of this study are as follows: (1) The rate of symptomatic PTOA at 7.5 years of follow-up was 22.1% in the ACLR cohort and 63.6% in the nonoperative cohort; (2) when we controlled for differences in demographic and injury characteristics in our cohort, ACLR reduced the overall risk of PTOA by 11% (95% CI, 8%-13%) compared with nonoperative treatment and delayed the onset and reduced the severity of PTOA; (3) risk factors for the development of PTOA included older age, secondary surgeries, concomitant meniscal or chondral injuries, and residual laxity.

The significant uncertainty regarding the rate of PTOA after ACL injury is evident from a cursory review of the existing literature, with reported values as widely

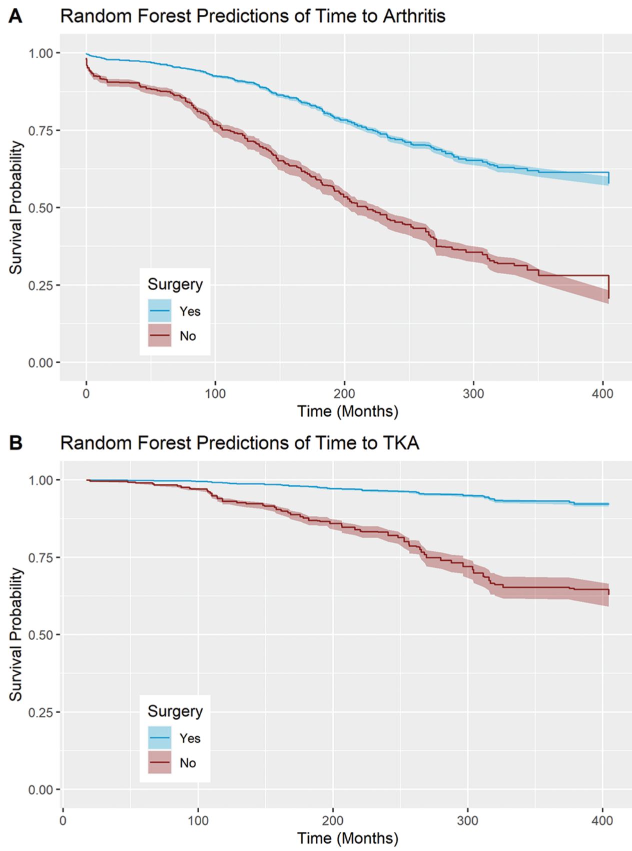

Figure 2. (A) Composite survival curve predictions for development of symptomatic osteoarthritis after anterior cruciate ligament reconstruction (ACLR) compared with nonoperative treatment. (B) Composite survival curve predictions for progression to total knee arthroplasty (TKA) after ACLR compared with nonoperative treatment.

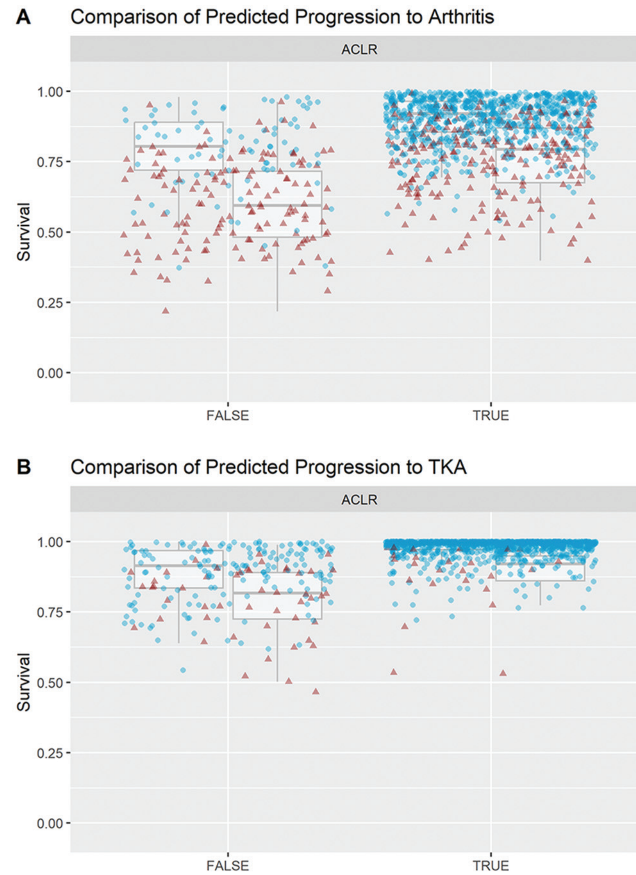

Figure 3. (A) Partial dependence curves illustrating the effect of anterior cruciate ligament reconstruction (ACLR) on the development of posttraumatic knee osteoarthritis (PTOA). Red triangles denote patients who developed PTOA, whose overall risk is illustrated by the box-and-whisker plot to the right of midline, and blue circles denote patients who did not, whose overall risk is illustrated by the box-and-whisker plot to the left of midline. Compared with patients who did not undergo reconstruction (False column), more patients who underwent ACLR (True column) were PTOA-free at final follow-up. (B) Partial dependence curves illustrating progression to total knee arthroplasty (TKA), where patients who underwent reconstruction are at significantly reduced risk of TKA compared with those treated nonoperatively.

disparate as 0% to 100%. The challenge with elucidating this question remains the scarcity of either rigorously constructed methods or sufficiently powered cohorts with adequate follow-up. Indeed, in the most up-to-date systematic review of the evidence, Lie et al[16] identified 41 studies, of which less than half (n = 19) were considered of high methodological quality. A more recent, prospective study from the MOON cohort assessed radiographic PTOA at 10 years after ACLR in young athletes using both osteophyte- and joint space–based definitions and identified rates of 37% and 23%, respectively.[4] Nonoperative management of ACL injuries is frequently transferred to therapists and primary care sports medicine physicians, which can decrease the availability of long-term follow-up. This, combined with lack of standardization among treatment methods, poses significant challenges to the collection and maintenance of long-term radiographic outcomes. We identified a single Swedish series on outcomes after nonoperative management, which reported a 75% rate of radiographic tibiofemoral/patellofemoral PTOA at >30-year follow-up.[10] Notably, a large percentage of these cases remained asymptomatic.

Consequently, comparisons of the epidemiological patterns after operative and nonoperative management are even sparser. A Cochrane database systematic review in 2016 yielded only a single randomized controlled study of nonoperative treatment compared with ACLR.[7,23] Although that study reported a higher incidence of radiographically detected PTOA in the ACLR group, the reviewers found this observation to be of "very low-quality evidence."[23] Subsequent 5-year follow-up data from the same cohort revealed no differences in radiographic

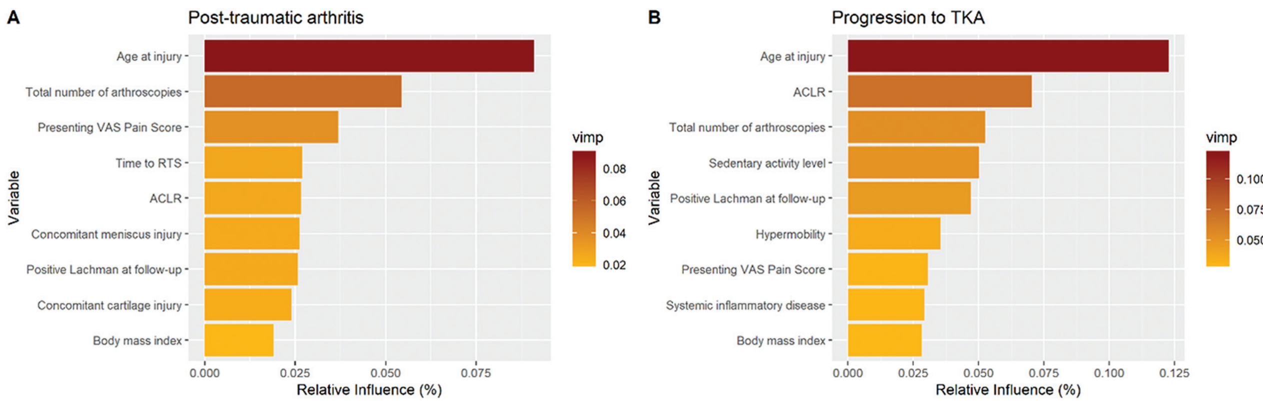

Figure 4. Variable importance plots illustrating rankings of input variables' contributions to the accuracy of model predictions for (A) posttraumatic knee osteoarthritis (PTOA) and (B) progression to total knee arthroplasty (TKA) for the entire cohort of patients, irrespective of treatment. For example, age at injury was the most important variable for prediction accuracy for both the model for prediction of PTOA as well as progression to TKA. Vimp, variable importance.

PTOA but reported 51% crossover of patients in the nonoperatively treated group to receiving delayed ACLR.[7] A 5-year follow-up from the Delaware-Oslo ACL cohort study is among the few examples of prospectively collected mid-term outcomes data in this regard[25]; initial comparisons between nonoperative treatment and delayed or early reconstruction found no significant differences in the rate of radiographic PTOA. The differences observed between our study, where ACLR reduced the risk of PTOA by 11% (95% CI, 8%-13%) at 7.5-year follow-up, and those by previous authors are likely due to differences in patient selection criteria (eg, preinjury sports participation) between the studies as well as inherent demographic and lifestyle differences between Scandinavian patient populations and those in the US Midwest (eg, BMI). Nevertheless, long-term follow-up data remain elusive and are crucial to compare the effectiveness of treatment strategies in curtailing PTOA.

Despite the significant difference in the rate of PTOA and progression to TKA between our operative and nonoperative cohorts, risk factors in progression to these endpoints remain consistent between the 2 groups. The largest predictor for progression to PTOA and TKA was older age at the time of injury. Age-related chondrocyte degeneration is a well-understood pathway, with recent studies suggesting similar catabolic signaling in trauma as seen with aging.[28] Compression and shear forces on the cartilage during an ACL injury lead to escalation of catabolic changes within the knee, which is additive in a knee with age-associated degeneration.[1,28] The findings in our study corroborate previous observations, such as those from the MOON cohort,[15] which suggest that any further insults on the knee such as additional arthroscopic surgeries and ongoing laxity are highly associated with PTOA and progression to TKA. Although many injury-associated factors are nonmodifiable, a higher BMI, shorter time to return to sport, and sedentary activity level were modifiable factors associated with symptomatic PTOA and progression to TKA within our cohort. As noted in other studies, this finding emphasizes the critical importance of thorough rehabilitation as well as active and healthy behavior not only for the acute return to activity but also for the longevity of an injured joint.[38,39] Our findings add to the abundance of evidence highlighting the detrimental effect of concomitant meniscal injury on long-term knee joint preservation.[14,15,17] Based on variable importance analysis, the inclusion of a variable accounting for concomitant meniscal injury was a significant contributor to correct model predictions regarding the presence of PTOA irrespective of ACL management. Furthermore, partial dependence curves illustrated that meniscal injury similarly imparted a greater risk of PTOA in both cohorts. The cited study by the MOON investigators highlights that concomitant meniscal injury requiring either meniscectomy or repair at the time of ACLR significantly contributes to short-term PTOA, with meniscectomy unsurprisingly portending a higher risk of PTOA.[14] These findings again emphasize the need for technically satisfactory meniscal repair at the time of reconstruction in appropriately selected patients in order to optimize long-term joint health.

Although the use of MLMs in the sports medicine literature has seen significant growth, the applications remain limited to outcome prediction (eg, regression or classification problems) rather than causal inference.[18,19,21,22] This is partly due to the absence of asymptotic properties in the output of models that are required for inference (eg, standard errors). However, TMLE is a semiparametric estimation framework that can leverage flexible MLMs to provide a target estimand (eg, average treatment effect). This approach is also doubly robust, meaning we need to correctly model either the treatment assignment or the treatment response, but not both.[30] Specifically, in head-to-head comparisons, TMLE has proven to be more reliable and accurate than combined parametric models with propensity scores.[26,29]

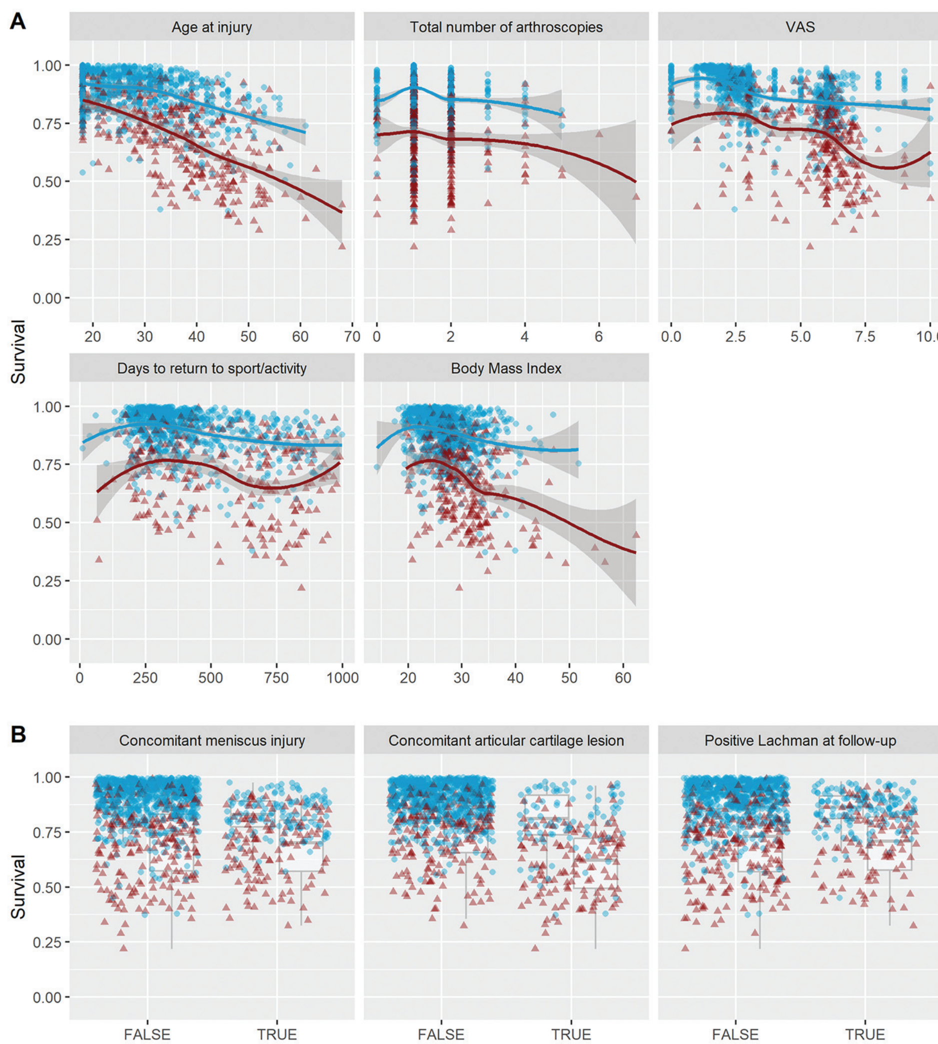

Figure 5. Partial dependence curves demonstrating the (A) continuous and (B) categorical variable contributions to knee survivorship without symptomatic posttraumatic knee osteoarthritis (PTOA), regardless of treatment. Survival is plotted on the y-axis whereas the range of values of each covariate is plotted on the x-axis; blue circles represent patients without PTOA at final follow-up and red triangles represent patients who developed PTOA. For categorical variables, boxplots demonstrating the mean overall survival probability of each group are provided. For each value of the categorical variable (True or False), boxplots for patients who did not develop PTOA are left of midline whereas those for patients who developed PTOA are right of midline.

Although the current study is strengthened by longitudinal follow-up, a large sample size, and the use of a double-robust statistical estimator, it is not without several potential limitations. First, as a retrospective study, correlations can be drawn between treatment options and risk factors associated with symptomatic PTOA and progression to TKA, but conclusions cannot be drawn regarding causation. This inherent limitation can be mitigated using machine learning with targeted estimators such as TMLE; however, baseline differences between the reconstruction and nonoperatively managed cohorts, the inability to directly examine radiographs, and the possible presence of unmeasured confounders still have the potential to dilute these findings. Second, age was noted to be the largest risk factor for PTOA and TKA. The median age of the ACLR cohort was 12 years less than that of the nonoperative group, and it is possible that late onset rates of PTOA may be similar between the 2 groups. Third, our population was from a single geographic database. As such, it may be less generalizable compared with sampling on a national level, as there are significant population-level differences even at the regional level in North America. Fourth, the longevity of this study is a significant strength, but despite our best attempts at documentation and controlling for variations in treatment protocols, it is certainly possible that unaccounted, nuanced differences in operative techniques, bracing, and rehabilitation persisted within the study duration. Fifth, TMLE itself can

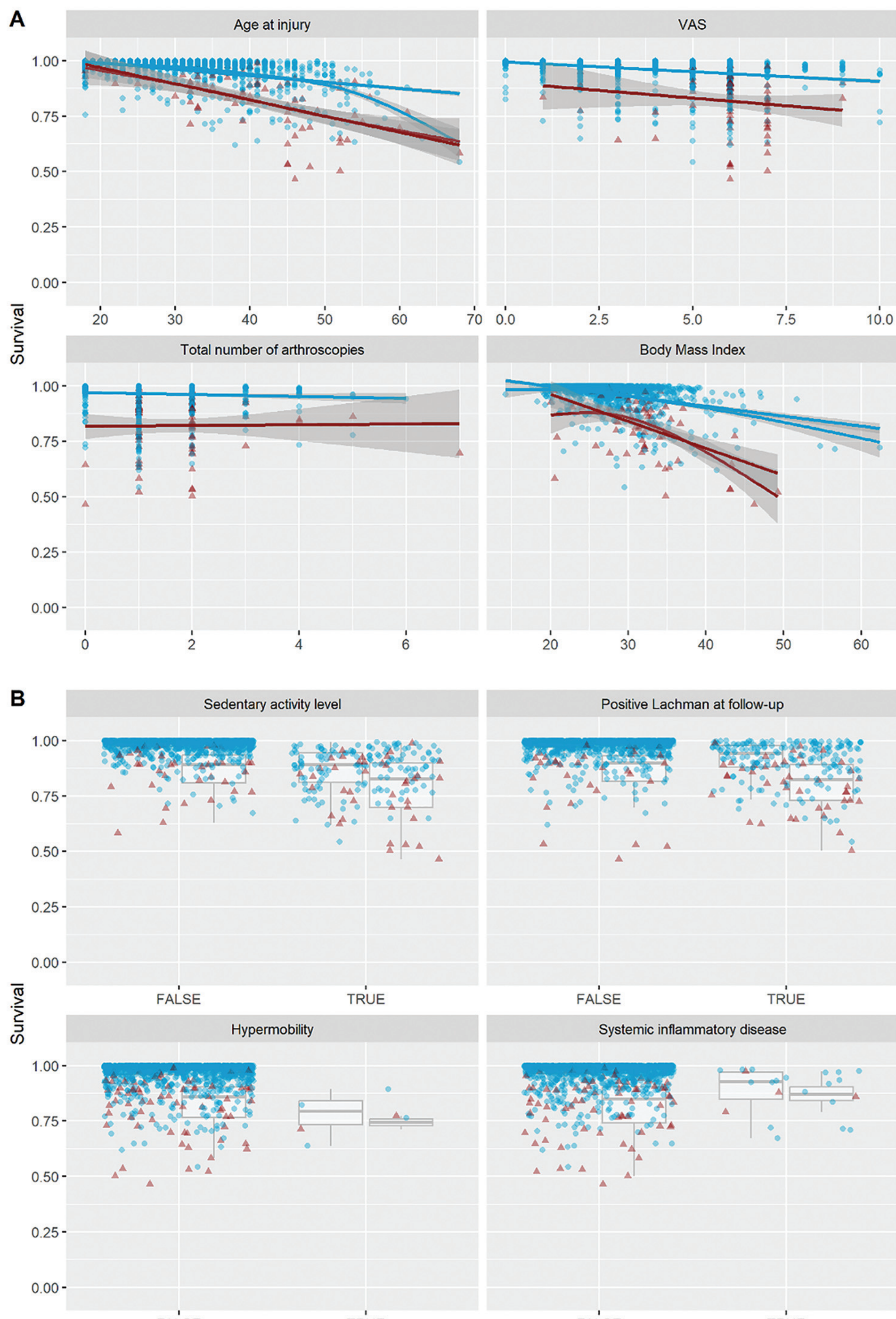

Figure 6. Partial dependence curves demonstrating the (A) continuous and (B) categorical variable contributions to knee survivorship without progression to total knee arthroplasty (TKA), regardless of treatment. Survival is plotted on the y-axis whereas the range of values of each covariate is plotted on the x-axis; blue circles represent patients who did not undergo TKA at final follow-up, and red triangles represent patients who underwent TKA. For categorical variables, boxplots demonstrating the mean overall survival probability of each group are provided. For each value of the categorical variable (True or False), boxplots for patients who did not undergo TKA are left of midline whereas those for patients who underwent TKA are right of midline.

be subject to the effects of outliers as well as positivity violations (eg, when the likelihood of receiving an intervention is <0), especially with small to moderate samples sizes.

CONCLUSION

A machine learning causal inference model found ACLR to exert a significant treatment effect in reducing the rate of development of PTOA by 11% compared with nonoperative treatment. ACLR also delayed the onset of PTOA and progression to TKA.

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