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Original Research

Evidence-based machine learning algorithm to predict failure following cartilage procedures in the knee

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ABSTRACT

Introduction: Clinical decision-making is highly based on expert opinion. Machine learning is increasingly used to develop patient-specific risk prediction analysis to improve patient selection prior to surgery.
Objectives: To develop machine learning algorithms to predict failure of surgical procedures that address cartilage defects of the knee and detect variables associated with failure.
Methods: An institutional database was queried for cartilage procedures performed between 2000 and 2018. Failure was defined as revision cartilage surgery or knee arthroplasty. One hundred and one preoperative and intraoperative features were evaluated as potential predictors. Four machine learning algorithms were trained and internally validated.
Results: One thousand and ninety-one patients with a minimum follow-up of 2 years were included and underwent chondroplasty (n = 560; 51%), osteochondral allograft transplantation (n = 306; 28%), microfracture (n = 150; 14%), autologous chondrocyte implantation (n = 39; 4%), or osteochondral autograft transplantation (n = 36; 3%). The Random Forest algorithm was the best-performing algorithm, with an area under the curve of 0.765 and a Brier score of 0.135. The most important features for predicting failure were symptom duration, age, body mass index, lesion grade, and total lesion area. Local Interpretable Model-agnostic Explanations analysis provided patient-specific comparisons for the risk of failure of an individual patient being assigned various types of cartilage procedures.
Conclusions: Machine learning algorithms were accurate in predicting the risk of failure following cartilage procedures of the knee, with the most important features in descending order being symptom duration, age, body mass index, lesion grade, and total lesion area. Machine learning algorithms may be used to compare the risk of failure of specific patient-procedure combinations in the treatment of cartilage defects of the knee.

The study was approved by the institutional audit and review board.

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Introduction

Two million patients underwent a surgical procedure addressing a cartilage defect between 2004 and 2011 in the United States, with an annual incidence growth of 5% and current estimations of 200,000 to 300,000 procedures performed annually.[1,2] Management of symptomatic patients who failed conservative treatment for focal chondral and osteochondral defects in the knee is complex and multifactorial.[3] Although studies have reported the outcomes of different procedures in thousands of patients, there is a lack of evidence-based methods for the treatment of cartilage defects of the knee.[4] Common surgical treatment options include debridement, microfractures, osteochondral autologous transplantation (OAT), osteochondral allografts (OCA), and autologous chondrocyte implantation (ACI).[5]

Current literature supports the use of debridement, microfracture, and OAT for smaller lesions (2-3 cm^2 or less), while OCA and ACI are used for larger lesions (3-4 cm^2 or more).[3,6] However, numerous factors have been shown to influence the outcomes in these patients, including patient demographics (demand, age, and gender),[7–12] etiology of the lesion (traumatic, degenerative, or osteochondral defect),[12–16] location of the lesion,[17–21] the formation pattern of lesions (isolated, multifocal, and bipolar),[7,10,15,22,23] associated pathology (ligament tear, meniscus pathology, and malalignment), and concomitant procedures (ligament reconstruction, meniscectomy, meniscus repair or transplant, and corrective osteotomy).[7,8,10,15,24–27]

The selection process of a surgical treatment modality for a specific patient is complex. Several treatment decision trees have been described for the management of cartilage defects based on several clinical outcome studies.[3,28,29] These decision trees generally consider the location and size of the defect, as well as the “demand” of the patient. Many of these guidelines have been developed based on surgeons' experience and expert opinion (level V evidence), but the algorithms themselves have not yet been shown by clinical studies to provide clinical benefit.

Thus, clinical decision-making today is highly based on expert opinion during the patient-physician encounter. In some cases, physician recommendations may not be in line with the most recent literature or appropriate treatment guidelines. Even when treatment guidelines and algorithms are adhered to, patients are not assured optimal quality of care based on their individual attributes, as many treatment guidelines and algorithms used today are based on individualized expert opinion rather than high-level evidence studies.

In recent years, machine learning tools have been increasingly utilized to improve the repeatability and accuracy of outcome predictions.[30] The application of artificial intelligence and machine learning provides the ability to further improve feature selection and outcome classification, resulting in an optimized ability to evaluate the risk of adverse outcomes.[31] Studies in orthopedic literature are increasingly utilizing machine learning tools and validating machine learning algorithms.[31–36] These efforts will hopefully allow for patient-specific risk prediction analysis and provide tools that improve patient selection and expectation management prior to surgery.[31]

The objectives of this investigation were to develop machine learning algorithms to predict the failure of surgical procedures that address cartilage defects of the knee and detect the most valuable variables associated with failure. This will hopefully set the basis for the development of an evidence-based algorithm for surgical management of cartilage defects of the knee. The hypothesis is that machine learning algorithms will demonstrate high discriminatory performance for predicting failure following surgical procedures to address cartilage defects of the knee.

Methods

Data collection

Institutional review board approval was obtained prior to study initiation. A single institution's prospectively collected database of cartilage procedures was queried for procedures performed between 2000 and 2018. Procedures were identified using CPT codes for the following procedures: cartilage debridement (chondroplasty), microfracture, OCA, OAT, and ACI/matrix-induced chondrocyte implantation.

A chart review was performed for all patients to assess their qualification for inclusion and exclusion criteria. Inclusion criteria were defined as (1) patients between 15 and 60 years of age at the time of surgery, (2) at least 1 cartilage defect present in the knee, (3) underwent a surgical procedure for the treatment of a cartilage defect, and (4) a minimum of 2-year follow-up. Exclusion criteria were defined as (1) the presence of inflammatory arthropathy, (2) the presence of septic arthritis, and (3) less than 2-year follow-up.

Features and outcomes

Eligible patients were chart reviewed for patient demographics, clinical and radiographic characteristics, and patient outcomes.

Patient demographics: Gender, age, body mass index (BMI), self-reported athletic status (nonathlete, recreational, professional), number and type of previous surgeries, etiology (degenerative, traumatic, osteochondritis dissecans), worker's compensation, and systemic comorbidities (diabetes mellitus, hypertension, osteoporosis, thyroid disease, etc).

Physical examination: Effusion, tenderness, range of motion, and coronal alignment (varus/neutral/valgus as per the physical exam).

Intraoperative details: Lesion details as viewed by arthroscopy, including lesion location (medial femoral condyle [MFC], lateral femoral condyle, medial tibial plateau, lateral tibial plateau, patella, and trochlea), lesion size (width, length, area), lesion depth, International Cartilage Regeneration & Joint Preservation Society grade, cartilage procedure performed, concomitant pathologies, and associated procedures (osteotomies, ligament reconstruction, and treatments for meniscal pathology).

Primary outcome definition

Failure of the procedure was defined as subsequent revision cartilage procedure or arthroplasty.

Statistical analysis

Methodology

Analysis was performed in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) guidelines and the Guidelines for Developing and Reporting Machine Learning Models in Biomedical Research.[37]

Covariate prediction features and handling of missing data

Patient demographics, preoperative physical examination, and intraoperative features as mentioned above were analyzed as predictors. Missing data points were random following database exploration. All covariates did not exceed 30% for missing data and were therefore included as potential factors predicting failure following cartilage procedures.[38,39] Missing data were accounted for via iterative imputation in ascending order.[40]

Development and assessment of algorithm performance

We used a stepwise feature selection algorithm on our prediction sample to specify the best prediction model for the success of surgery. The Random Forest algorithm was used to perform recursive feature elimination and determine the most important feature covariates (those demonstrating the highest predictive values).[41]

We divided our sample into 2 subsamples randomly: the training set "prediction sample" (70%) and the independent testing set "out of sample/hold-out" (30%), using a computerized randomization tool. Four machine learning algorithms were utilized: Random Forest, elastic-net penalized logistic regression (ENPLR), gradient boosting trees (XGBoost),[42] and neural network (multilayer perceptron (MLP)). We performed hyperparameter tuning to each of the models using 10-fold cross-validation.

Subsequently, the performance of each algorithm was assessed using the independent test set of patients to allow for internal validation. Optimal algorithm performance was assessed using the area under the curve (AUC), calibration intercept and slope, and the Brier score.[31,43] Higher AUC values demonstrate the greater performance of an algorithm, with > 0.700 denoting acceptable discriminative performance. A calibration slope and intercept of 1 and 0, respectively, demonstrate the perfect prediction of an algorithm.[31] Lower Brier scores indicate improved predictive capabilities of an algorithm, with a score of 0 representing perfect calibration.

Local Interpretable Model-agnostic Explanations (LIMEs) were utilized to provide patient-specific explanations for given classifiers of the best-performing machine learning algorithm. This allows insight into the complex "black-box" decision process and enables sanity checking of the optimized algorithm.[44] In the present study, LIME demonstrates the relative contribution of specific variables, such as age and BMI, toward increasing or decreasing the probability of a surgical treatment's success.

Results

Study population

A total of 1091 patients who underwent surgical procedures addressing cartilage defects in the knee with a minimum 2-year follow-up were included. The mean follow-up was 3.5 ± 2.8 years and the mean age at the time of surgery was 40.5 ± 15 years. There were 205 (18.8%) patients who failed at the final follow-up. The demographic and clinical characteristics are detailed in Table 1.

Five hundred and eighty patients (53.2%) had at least 1 prior procedure on the index knee, with a mean number of prior surgeries of 1.1 ± 1.5. Details regarding prior surgical procedures are presented in Table 2.

Surgical details, including cartilage lesion location, defect area, defect grade, and concomitant surgical procedures, are reported in Table 3.

Feature selection

Algorithm performance was optimized by the combination of 22 features. The 10 most important features for predicting failure following surgical procedures addressing cartilage defects of the knee were symptom duration, age, BMI, lesion grade, total lesions area (sum of all lesion areas), number of previous surgeries, number of lesions in the knee, gender, athletic level, and traumatic etiology (Fig. 1).

Estimated cutoffs for the association of a greater likelihood for failure were symptom duration ≥2 years, age ≥51.6 years old, BMI $> 28.3\ kg/m^2$, lesion grade ≥3, total lesion area ≥886, number of previous surgeries ≥2, and number of lesions in the knee ≥3.

Table 1
Demographic and clinical characteristics.

	Overall ($N = 1091$)
Age at time of surgery (years)	40.5 ± 15
Gender	
Male	550 (50.4%)
Female	541 (49.6%)
Body mass index	28.2 ± 6
Laterality	
Right	569 (52.2%)
Left	522 (47.8%)
Smoking	
Never	937 (86%)
Yes	46 (4.2%)
Former	108 (9.8%)
Diabetes mellitus	24 (2.2%)
Hypertension	142 (13%)
Thyroid disease	61 (5.6%)
Athlete	293 (26.9%)
Worker's compensation	119 (10.9%)
Traumatic event	439 (40.2%)
Symptom duration (years)	2.7 ± 4.7
Osteochondritis dissecans	85 (7.8%)
Recurrent effusion	468 (42.9%)
Preoperative flexion (degrees)	127 ± 15.9
Preoperative extension (degrees)	0.9 ± 6.3
Preoperative alignment	
Neutral	977 (89.6%)
Varus	58 (5.3%)
Valgus	56 (5.1%)
Follow-up (years)	3.5 ± 2.8
Mean time to follow-up per intervention	
Chondroplasty	2.2 ± 0.6*
Microfracture	3.6 ± 3.5
OCA	5.5 ± 3.4
OATS	4.6 ± 3.9
MACI	4.6 ± 3.2

Abbreviations: MACI, matrix-induced chondrocyte implantation; OATS, osteochondral autologous transplantation system; OCA, osteochondral allografts.
Continuous variables are presented as means ± standard deviation.
Binomial variables are presented as frequencies (proportions).
* Time to follow-up was significantly different (shorter) for the chondroplasty group ($P < .001$). Therefore, relevant predictions were controlled for time to follow-up.

Table 2
Prior surgical procedures.

	Overall
Number of patients with at least 1 prior procedure of the index knee	**580 (53.2%)**
Number of prior surgeries, mean	1.1 ± 1.5
Number of patients with prior cartilage surgery	**386 (35.4%)**
Chondroplasty	335 (35.7%)
Microfractures	132 (12.1%)
Osteochondral autograft transplantation	15 (1.4%)
Fixation of OCD	24 (2.2%)
DeNovo (particulated juvenile allograft)	4 (0.4%)
BioCartilage (cartilage extracellular matrix)	4 (0.4%)
Autologous chondrocyte implantation	23 (2.1%)
Osteochondral allograft transplantation	5 (0.5%)
Number of patients with prior meniscal surgery	**253 (23.2%)**
Meniscal repair	32 (2.9%)
Lateral meniscectomy	120 (11%)
Medial meniscectomy	127 (11.6%)

Abbreviation: OCD, osteochondritis dissecans.
Continuous variables are presented as means ± standard deviation.
Binomial variables are presented as frequencies (proportions).

Table 3
Surgical details and concomitant procedures.

Cartilage lesion location	
MFC	554 (50.8%)
MTP	144 (13.2%)
LFC	285 (26.1%)
LTP	145 (13.3%)
Trochlea	293 (26.9%)
Patella	329 (30.2%)
Defect area (mm^2, mean ± SD)	
MFC	17.8 ± 14
MTP	10.2 ± 9.4
LFC	18.7 ± 13.9
LTP	11.7 ± 10.1
Trochlea	16.4 ± 13.8
Patella	16 ± 13.5
Cartilage lesion grade	N = 783
I	34 (4.3%)
II	118 (15.1%)
III	135 (17.2%)
IV	496 (63.4%)
Cartilage procedure	
Chondroplasty	560
Microfracture	150
Osteochondral allograft transplantation	306
Osteochondral autograft transplantation	36
Articular chondrocyte implantation	39
Concomitant procedure	
Medial meniscectomy	481 (44.1%)
Lateral meniscectomy	289 (26.5%)
Medial meniscus repair	13 (1.2%)
Lateral meniscus repair	7 (0.6%)
Medial MAT	53 (4.8%)
Lateral MAT	77 (7.1%)
High tibial osteotomy	32 (2.9%)
Distal femoral osteotomy	25 (2.3%)
Tibial tuberosity osteotomy	51 (4.7%)
ACL reconstruction	157 (14.4%)
Platelet-rich plasma injection	14 (1.3%)
Bone marrow aspirate concentrate	11 (1%)

Abbreviations: ACL, anterior cruciate ligament; LFC, lateral femoral condyle; LTP, lateral tibial plateau; MAT, meniscal allograft transplantation; MFC, medial femoral condyle; MTP, medial tibial plateau.
Continuous variables are presented as means ± standard deviation.
Binomial variables are presented as frequencies (proportions).

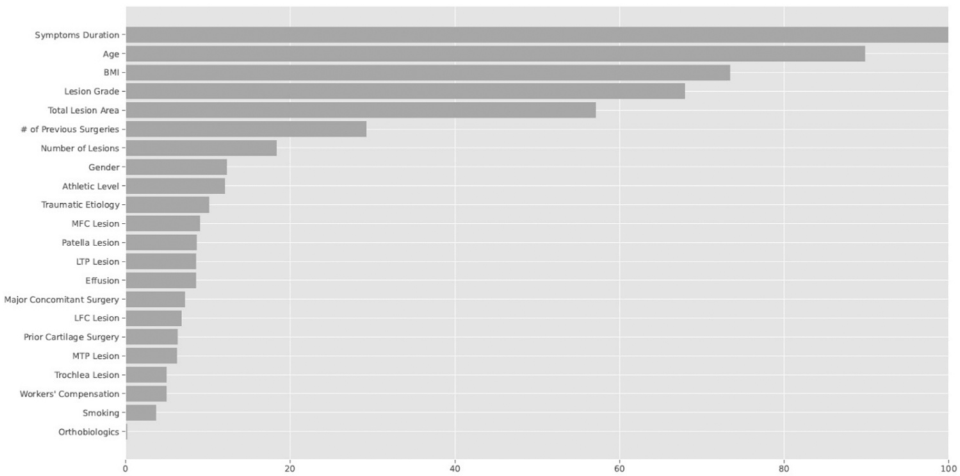

Fig. 1. Global feature importance plot displaying (in descending order) the most important predictors of failure following surgical procedures addressing cartilage defects of the knee. BMI, body mass index; LFC, lateral femoral condyle; LTP, lateral tibial plateau; MFC, medial femoral condyle; MTP, medial tibial plateau.

Table 4
Performance characteristics of the 4 algorithms.

	ENPLR	Random Forest	Neural network	XGBoost
C-statistic (AUC)	0.725	0.765	0.742	0.757
Brier score	0.136	0.135	0.136	0.138

Abbreviations: AUC, area under the curve; ENPLR, elastic-net penalized linear regression.

Algorithm performance assessment

The Random Forest algorithm was found to be the best-performing algorithm, with an AUC of 0.765, calibration slope of 1.4, calibration intercept of −0.11, and a Brier score of 0.135. The c-statistic (AUC) and the Brier score of each algorithm are detailed in Table 4.

The corresponding receiver operating characteristic curve analysis is presented in Figure 2.

Algorithm fidelity, individual predictions, and treatment modality comparison

The LIME technique was used to provide insight into the complex "black-box" machine learning models.[31] This technique was used to provide predictions and visual representations of individual patients receiving different types of cartilage treatments. A

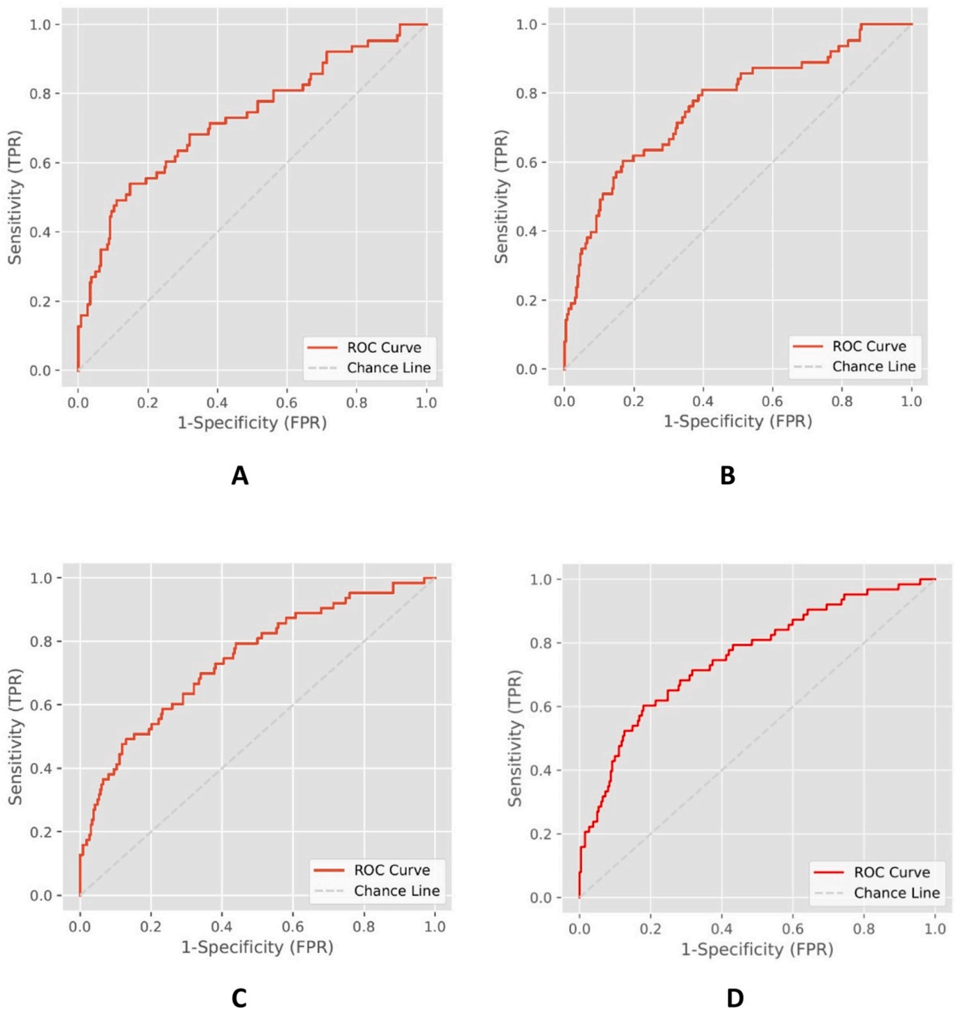

Fig. 2. **A-D**, The corresponding receiver operating characteristic (ROC) curve analysis of the 4 algorithms. **A**, Elastic-net penalized linear regression (ENPLR, AUC = 0.725); **B**, Random Forest (AUC = 0.765); **C**, Neural network (AUC = 0.742); **D**, XGBoost (AUC = 0.757). AUC, area under curve.

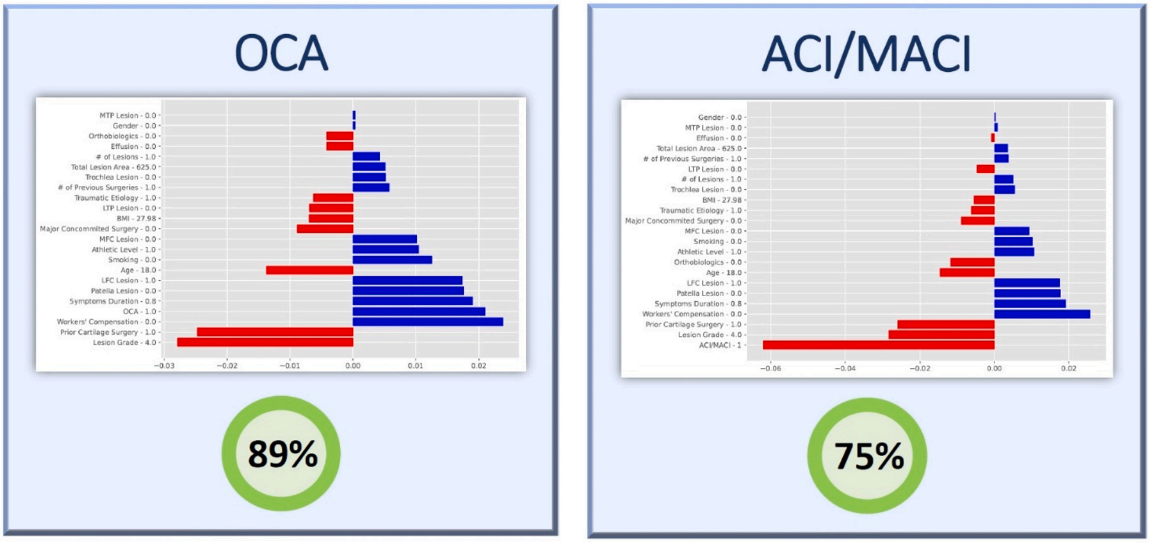

Fig. 3. An individual's treatment success prediction for an 18 year-old male, BMI = 28 kg/m^2, nonsmoker, recreational athlete, 1 prior cartilage procedure, no worker's compensation, 8 months duration of knee pain without effusion following a traumatic injury, and a grade 4, 25 mm × 25 mm lateral femoral condyle lesion. Patient-specific analysis and propensity probability of survival free from failure for this individual patient if treated with **A**, osteochondral allograft (OCA) transplantation; or **B**, autologous chondrocyte implantation (ACI)/matrix-induced chondrocyte implantation (MACI). BMI, body mass index, LFC, lateral femoral condyle; LTP, lateral tibial plateau; MFC, medial femoral condyle; MTP, medial tibial plateau.

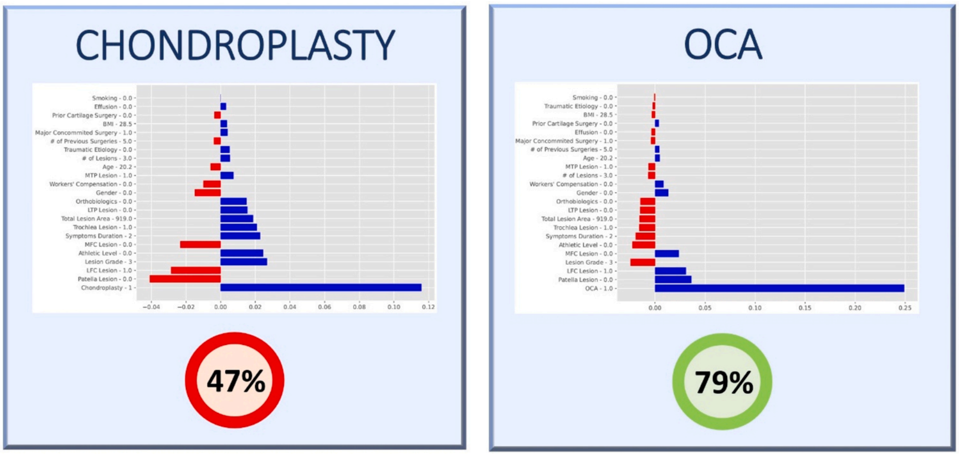

Fig. 4. An individual's treatment success prediction for a 40-year-old male, BMI = 28.7 kg/m^2, nonsmoker, nonathlete, 6 prior procedures, no worker's compensation, 2 years duration of knee pain without a known traumatic event, without knee effusion, with both a grade 3, 18 mm × 18 mm medial femoral condyle lesion and a grade 3, 16 mm × 16 mm trochlea lesion. Patient-specific analysis and propensity probability of survival free from failure for this individual patient if treated with **A**, chondroplasty; or **B**, osteochondral allograft (OCA) transplantation. BMI, body mass index, LFC, lateral femoral condyle; LTP, lateral tibial plateau; MFC, medial femoral condyle; MTP, medial tibial plateau.

demonstration of the clinical usefulness of the machine learning algorithm as a decision-making support tool for the surgeon and patient is shown in Figures 3–6.

Discussion

The main finding of this study was the creation of an evidence-based machine learning algorithm for predicting failure following cartilage preservation procedures in the knee. The Random Forest algorithm was found to be the best-performing algorithm. The machine-learning algorithm was used to demonstrate an estimation of the patient-specific risk of failure following various types of

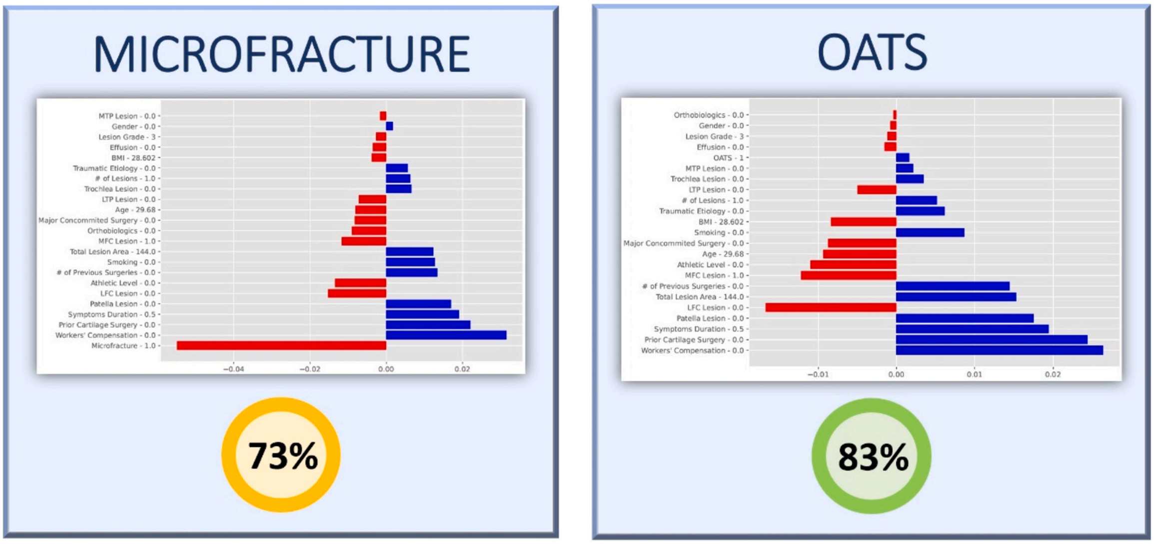

Fig. 5. An individual's treatment success prediction for a 29-year-old female, BMI = 28 kg/m^2, nonsmoker, nonathlete, no relevant past surgical history, no worker's compensation claim, with 6 months duration of knee pain without effusion, and a grade 3, 12 mm × 12 mm medial femoral condyle lesion. Patient-specific analysis and propensity probability of survival free from failure for this individual patient if treated with **A**, microfracture; or **B**, osteochondral autologous transplantation system (OATS). BMI, body mass index; LFC, lateral femoral condyle; LTP, lateral tibial plateau; MFC, medial femoral condyle; MTP, medial tibial plateau.

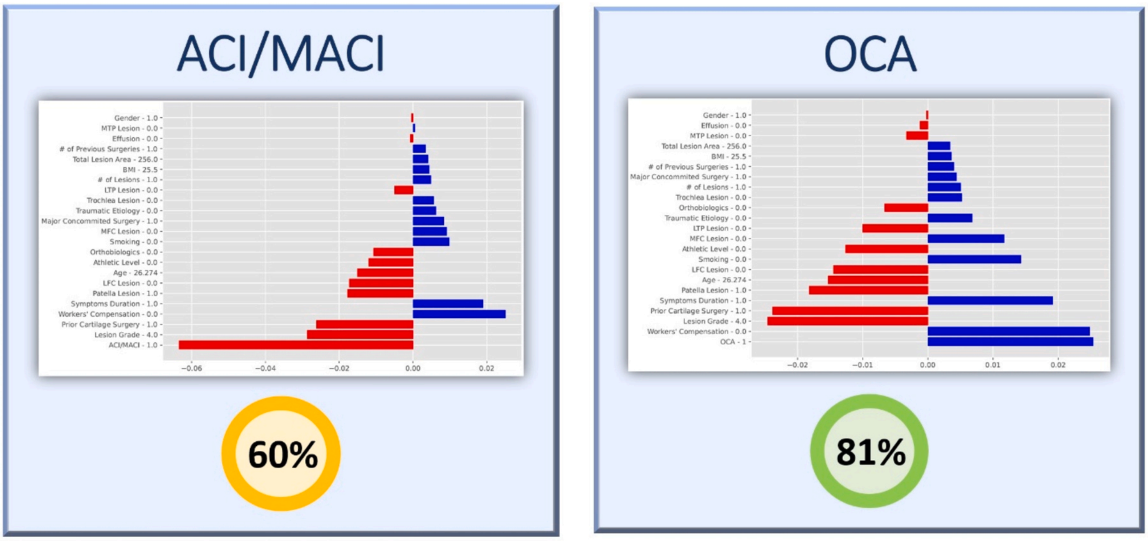

Fig. 6. An individual's treatment success prediction for a 26-year-old female, BMI = 25.5 kg/m^2, nonsmoker, nonathlete, 1 previous knee surgery, no worker's compensation claim, with 1 year duration of knee pain without effusion, and a grade 4, 16 mm × 16 mm patellar lesion. Patient-specific analysis and propensity probability of survival free from failure for this individual patient if treated with **A**, autologous chondrocyte implantation (ACI)/matrix-induced chondrocyte implantation (MACI); or **B**, osteochondral allograft (OCA) transplantation. BMI, body mass index; LFC, lateral femoral condyle; LTP, lateral tibial plateau; MFC, medial femoral condyle; MTP, medial tibial plateau.

cartilage preservation procedures. This novel algorithm may be used to provide machine-learning-supported clinical decision-making for patients and surgeons contemplating surgical procedures to manage cartilage defects of the knee.

Previous literature has described treatment algorithms for the management of cartilage lesions, primarily based on patient demand and lesion size and location.[29,45] In this study, the 10 most important features for predicting failure were found to be symptom duration, age, BMI, lesion grade, total lesion area (sum of all lesions' areas), number of previous surgeries, number of lesions in the knee, gender, athletic level, and traumatic etiology. Previously published studies have reported on the variables associated with outcomes of the aforementioned cartilage preservation procedures and attempted to develop a suitable treatment algorithm. Behery et al[46] performed a systematic review to determine the factors that should be used in determining the course of surgical treatment for symptomatic cartilage lesions of the knee. They concluded that defect size, location, knee alignment, and patient demand should be included in such an algorithm and that patient sex and BMI may also be considered. In contrast to this study, they found that patient age was not significantly associated with clinical outcomes. Bekkers et al[47] also performed a systematic review to identify evidence-based parameters for treatment selection in articular cartilage lesions of the knee. They found lesion size, activity level, and patient age were parameters that influenced the outcomes of articular cartilage repair surgery, which is consistent with factors that were also found to be significant in this study. Most of the significant factors from our algorithm have been reported as predictors of failure following various cartilage preservation procedures.[48–53]

An additional interesting factor is whether or not the subchondral bone is involved and to what extent. Hinckel et al[54] published a review of the literature discussing classic and new treatment modalities to manage grade 3 to 4 focal cartilage defects of the knee. Their algorithm tree included lesion size and the presence or absence of a subchondral lesion. Ramkumar et al[55] reported that the absence of preoperative osseous edema on MRI was associated with failure to achieve clinically significant outcomes following OCA transplantation. However, other studies have not found subchondral bone involvement and bone marrow lesions to affect failure following cartilage preservation procedures.[56] The current study was unable to assess the extent of bone marrow lesions and subchondral bone involvement that will dictate a specific cartilage intervention or render another inappropriate. However, the authors recognize that the integrity of the subchondral bone bed may be a significant factor affecting certain cartilage preservation procedures' outcomes and should be taken into consideration by the surgeon.[57]

Several studies have utilized machine learning algorithms in orthopedics and sports medicine assessing outcomes of various procedures, such as anterior cruciate ligament reconstruction, hip arthroscopy, total shoulder arthroplasty, and more.[31,33–35,58–61] Ramkumar et al[55] assessed the effects of preoperative imaging and patient factors on clinically meaningful outcomes following OCA transplantation in 153 patients. Using machine learning tools, they found that BMI, knee malalignment, absence of preoperative bone edema, concomitant anterior cruciate ligament or meniscal injury, larger defect size, and the implantation of > 1 OCA graft were associated with failure to achieve the MCID or SCB at 2 years postoperatively. Pareek et al[62] performed a retrospective analysis of 249 patients using Lasso regression and found that lateral meniscus extrusion, Kellgren-Lawrence grade 4 osteoarthritis, subchondral insufficiency fracture of medial femoral condyle, lateral meniscus root tear, and medial meniscus extrusion were the most important factors in predicting progression to knee arthroplasty (in that order). Liu et al[63] performed a meta-analysis on mesenchymal stem cell therapies for cartilage repair using machine learning tools. They identified defect area percentage, defect depth percentage, implantation cell number, body weight, tissue source, and the type of cartilage damage as critical properties that may significantly impact cartilage repair. Although these studies were not focused on assessing failure following cartilage preservation procedures, the important features highlighted in the machine learning algorithms of these studies are similar to those presented in this study, strengthening the findings of the current study.

While machine-learning algorithms may provide support to clinical decision-making, the current available technology is far from being capable of replacing human clinical acumen. Without the insight of an experienced physician, even well-developed machine-learning algorithms may produce serious errors and provide meaningless and illogical results. Therefore, at this time, it appears that the optimal way to administer high-end clinical care relies on an experienced physician supported by machine-learning tools consulting an informed patient.

This study is not without limitations. The main limitation is its retrospective nature. Given the nature of this medium-term large cohort study, we could not ascertain exact compliance rates, but we assume these were relatively low. Also, several different surgical interventions to address the cartilage defects of the knee, such as chondroplasty, microfracture, OATS, ACI, and OCA, were included. While this may have increased the heterogeneity of the cohort, there is no consensus regarding the superiority of any of these treatment modalities, allowing us to obtain a relatively large cohort to strengthen the study results. We controlled for this variable, as well as other significant variables, such as lesion location and duration of follow-up, which may cause heterogeneity. Additional variables such as subchondral bone status, socioeconomic factors, and adherence to postoperative physical therapy regimens were not analyzed in the present study and could have exerted an influence on the observed outcomes.

Additionally, this is a single institution-based cohort spanning 18 years of practice, which may have been affected by changes in data collection methods, evolving surgical techniques, and other related factors. Lastly, the cohort is based on treatments that may have been selected based on the surgeon's expertise, predilections, and mindset and therefore biases may have been introduced and causal inference hindered. Therefore, the applicability of these findings needs to be further validated externally by other surgeons and institutions.

Conclusions

Machine learning algorithms were accurate in predicting the risk of failure following cartilage procedures of the knee, with the most important features in descending order being symptom duration, age, BMI, lesion grade, and total lesion area. Machine learning algorithms may be used to compare the risk of failure of specific patient-procedure combinations in the treatment of cartilage defects of the knee.

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Ethics approval

The study was approved by the institutional audit and review board.

Authorship Contributions

All authors contributed substantially to the conception, data acquisition, or data analysis of this manuscript. All authors helped in drafting and approving the final manuscript.

Declaration of Competing Interest

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