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Machine-learning model successfully predicts patients at risk for prolonged postoperative opioid use following elective knee arthroscopy

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Abstract

Purpose Recovery following elective knee arthroscopy can be compromised by prolonged postoperative opioid utilization, yet an effective and validated risk calculator for this outcome remains elusive. The purpose of this study is to develop and validate a machine-learning algorithm that can reliably and effectively predict prolonged opioid consumption in patients following elective knee arthroscopy.

Methods A retrospective review of an institutional outcome database was performed at a tertiary academic medical centre to identify adult patients who underwent knee arthroscopy between 2016 and 2018. Extended postoperative opioid consumption was defined as opioid consumption at least 150 days following surgery. Five machine-learning algorithms were assessed for the ability to predict this outcome. Performances of the algorithms were assessed through discrimination, calibration, and decision curve analysis.

Results Overall, of the 381 patients included, 60 (20.3%) demonstrated sustained postoperative opioid consumption. The factors determined for prediction of prolonged postoperative opioid prescriptions were reduced preoperative scores on the following patient-reported outcomes: the IKDC, KOOS ADL, VR12 MCS, KOOS pain, and KOOS Sport and Activities. The ensemble model achieved the best performance based on discrimination (AUC = 0.74), calibration, and decision curve analysis. This model was integrated into a web-based open-access application able to provide both predictions and explanations.

Conclusion Following appropriate external validation, the algorithm developed presently could augment timely identification of patients who are at risk of extended opioid use. Reduced scores on preoperative patient-reported outcomes, symptom duration and perioperative oral morphine equivalents were identified as novel predictors of prolonged postoperative opioid use. The predictive model can be easily deployed in the clinical setting to identify at risk patients thus allowing providers to optimize modifiable risk factors and appropriately counsel patients preoperatively.

Level of evidence III.

Keywords Machine learning · Ensemble · Knee arthroscopy · Opioids · Knee surgery · Postoperative opioids

Introduction

The widespread use and availability of opioids in the United States has resulted in a public health epidemic [1, 2]. In the last 15 years, opioid-related drug overdoses have tripled, with over half of overdose deaths being related to prescription opioids [3, 4]. The pervasive use of opioids began as an effort to treat pain as the fifth vital sign [5]. However, opioid use has since been associated with serious complications including dependency and abuse, which in turn have resulted in significant morbidity and mortality [6]. Despite the fact that exposure to opioids following surgery is a major

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risk factor for chronic use and abuse, prescription opioid medications continue to serve key roles in the management of postoperative pain following elective orthopaedic surgery [6, 7]. For many patients, surgery may be the first time they are prescribed opioids. This is particularly concerning for patients undergoing arthroscopic knee surgery, as a large proportion of these patients are relatively young and otherwise healthy [8, 9].

A critical step in mitigating the morbidity related to opioid use in orthopaedic surgery is to identify and understand patient-specific risk factors for prolonged opioid use. Several studies have sought to identify risk factors for this outcome for various orthopaedic procedures, including arthroscopic meniscectomy [8, 10–12]. However, these authors employed linear and logistic regression models to determine independent risk factors for prolonged opioid use, which recent evidence suggest may underperform when compared to supervised machine-learning classifiers[13–15]. Machine learning (ML) refers to the science of utilizing computerized neural networks to create and optimize regression algorithms for complicated data [13]. This allows researchers to incorporate patient-specific variables into predictive models which can provide individualized risk assessments to patients and clinicians [13, 16, 17].

The purpose of this study was (1) to develop a predictive model using ML algorithms to predict postoperative opioid use following knee arthroscopy and (2) incorporate the best performing ML algorithm into an open-access web application to allow providers to assess patient-specific risk factors in real time for predicting postoperative opioid use after knee arthroscopy. Consequently, providers would be able to address modifiable risk factors preoperatively and counsel patients appropriately regarding opioid use and risk of prolonged use. The hypothesis was that the ML model would be able to reliably identify novel risk factors for prolonged postoperative opioid consumption following knee arthroscopy and outperform conventional regression in predictive capabilities.

Materials and methods

The present study utilized previously collected patient data and, as such, was granted IRB exemption by the IRB at Rush University. The analysis was performed adherent to 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 [18, 19].

Data source

Following approval by our university's institutional review board (IRB), an institutionally maintained, prospectively collected, digital patient-reported outcomes collections platform (Outcome Based Electronic Research Database [OBERD]; Universal Research Solutions, Columbia, MO) was queried for patients undergoing elective knee arthroscopy from January 1st, 2017 and October 1st, 2018. Inclusion criteria for the study were (1) adult patients 18 years of age or older receiving knee arthroscopy for the indications of meniscal tears, cartilage pathology, loose body, and arthrofibrosis and (2) completion of baseline PROM questionnaires. Demographic characteristics, medical comorbidities, and preoperative medications were compiled from the outcome data collection platform.

A comprehensive search of electronic patient charts in conjunction with the state prescription monitoring databases was undertaken to determine patient's opioid consumption history. Information regarding opioid medications filled was documented for two separate time periods: the preoperative period, defined as within 1-year to 30 days prior to surgery and the 6-month follow-up period, defined as any dates within 30 days of the 6-month follow-up period. Based on preoperative consumption, patients were categorized as either opioid-naïve (N-OU), defined as no opioid prescriptions filled within 12 months of surgery, or opioid-users (OU), defined as those with a filled prescription 12 months before surgery and those who endorsed opioid use at the time of surgery. The period of time from 30 days prior to the index surgery date to 14 days following surgery was designated the perioperative period, and a total oral morphine equivalent (OME) consumed during this period was calculated based on the prescriptions filled, the dosage, and the duration of consumption.

Patients were excluded if they did not complete baseline PROM questionnaires, were consuming opioid medications due to a surgical procedure within 1 year of the index surgery date, or underwent a concomitant ligamentous procedure, a cartilage restoration procedure, or biological augmentation.

Variables

Variables documented by the outcomes collection platform were used for feature selection. These include demographic characteristics, nonoperative treatments attempted, procedures, comorbidities, preoperative medications. Neighborhood characteristics of the patients were abstracted from the United States Censuses Bureau

Table 1 Baseline characteristics of the study population, $n = 381$

Variable	*n* (%) ǀ median (IQR)	*n* (%) missing
Age	50.5 (37.3–60.7)	1 (0.3)
Female gender	182 (47.8)	–
BMI	29.1 (25.1–34.3)	12 (3.2)
Preoperative pain	6.3 (4.6–7.6)	14 (3.7)
Days of exercise	3 (0–4)	–
Smoker		65 (17.1)
Current smoker	14 (3.7)	
Former smoker	56 (14.7)	
Never smoker	246 (64.6)	
Duration of symptoms (months)	7.8 (3.1–23)	53 (13.9)
Nonoperative treatments		
Physical therapy	178 (46.7)	–
Injections or nerve blocks	121 (31.8)	–
Medications	197 (51.7)	–
Supplements	197 (51.7)	–
Alternative	197 (51.7)	–
None	110 (28.9)	–
Medications		
Depression medication	22 (5.8)	–
NSAID	32 (8.4)	–
Comorbidities		
Arthritis	49 (12.9)	–
Depression	60 (15.7)	–
High blood pressure	73 (19.2)	–
Thyroid problem	46 (12.1)	–
Preoperative PROM scores		
IKDC	39.1 (28.7–51.2)	–
KOOS sport and activities	30.0 (5.0–10.0)	–
KOOS quality of Life	25.0 (12.5–37.5)	–
KOOS physical symptoms	40.3 (32.3–48.5)	–
KOOS symptoms	57.1 (42.9–67.9)	–
KOOS pain	52.8 (44.4–66.7)	–
KOOS JR	57.1 (47.5–63.8)	–
KOOS activities of daily living	64.7 (47.1–77.9)	–
VR12 PCS	36.5 (28.5–45.5)	–
VR12 MCS	58.7 (51.5–62.8)	–
Procedure		1 (0.3)
Chondroplasty	85 (22.3)	
Meniscectomy	256 (67.2)	
Preoperative opioid consumption	26 (6.8)	
Perioperative OME consumed	280 (100–300)	–
Extended postoperative opioid consumption	60 (20.3)	–

IQR interquartile range

American Community Survey zip code data. The complete list of variables considered for modelling input are provided in Table 1, and a complete list of medication categories are provided in Additional File 1.

Missing data

Features with missing data were imputed to reduce bias and improve statistical power [20]. The missForest multiple imputation method was used to impute remaining variables with less than 30% missing data [21]. Cases with more than 30% missing data were excluded to minimize the risk of imputation bias based on the study by Stekhoven et al. which demonstrated that the missForest algorithm imputation error did not differ among an identical dataset with randomly introduced missing values of 10%, 20%, or 30% [21]. Proportion of missing cases for each feature is also provided in Table 1.

Statistical analysis

Outcomes

The primary outcome of interest was extended postoperative opioid consumption, defined as opioid consumption within 30 days of 6-month follow-up. Before features selection, highly collinear variables (defined as spearman's correlation coefficients > 0.75) were identified and removed. Feature selection using recursive feature elimination with random forest algorithms was utilized to select preoperative variables that significantly impacted extended postoperative opioid consumption. Modelling was performed using the selected features with each of the following candidate machine-learning algorithms: support vector machine (SVM), random forest (RF), extreme gradient boost (XGBoost), adaptive boosting (AdaBoost), and a linear ensemble of all four models. Ensemble methods are a type of meta-algorithm combining learning techniques of each individual model into one predictive model. Advantages of ensemble modelling include decreasing variance and bias as well as improving predictive performance [22].

Modeling

Models were trained and validated via 0.632 bootstrapping with 1000 resampled datasets. Patients who were used to test the model were never included in the training set for each repetition to prevent overfitting and artificial inflation of model accuracy. Bootstrapping has been found to optimize both model bias and variance compared to internal validation through splitting the data into training and holdout sets [23]. Models were compared by discrimination, calibration, and Brier score values. The current investigation was adherent to sample size recommendations in machine-learning algorithms made by Raudys and Jain [24].

Discriminative power was assessed via the c-statistic using receiver-operating curve (ROC) analysis. Calibration of the model's predicted probabilities as a function of observed frequencies within the test population are summarized in a calibration plot. The plot for an ideal model is a straight line with intercept 0 and slope of 1 (i.e. perfect concordance of model predictions to observed frequencies within the retrospective data). Finally, the mean squared difference between predicted probabilities of models and observed outcomes, known as the Brier score, was calculated for each candidate model. The Brier score of candidate algorithm are then assessed by comparison to the Brier score of the null model, which is a model that assigns a class probability equal to the sample prevalence of the outcome for every prediction.

Individual explanations for model behaviour were provided for transparency into the output. Decision curve analysis was used to determine the benefit of implementing the predictive algorithm in practice. The curve plots net benefit against the predicted probabilities of the outcome of interest, in this case extended opioid use, and provides the cost–benefit ratio for every value of the predicted probability. These ratios provide useful guidance for individualized decision making and accounts for variability in clinician and patients thresholds for what is considered high risk. In addition, decision curves for the default strategies of changing management for no patients or all patients are plotted for comparison purposes.

Digital application

The candidate algorithm with the best performance is integrated into an interactive, open-access, web-based application. Clinician input will be used to generate outcome predictions with accompanying explanations. All data analyses were performed using RStudio version 1.2.5001 (RStudio, Boston, MA).

Results

Variable breakdown

A total of 408 patients who underwent elective knee arthroscopy and completed baseline PROMs were available for eligibility screening, of these, a total of 381 (93.4%) patients were included in the analysis following application of the exclusion criteria. The full breakdown of variables available for feature selection is provided in Table 1. A total of 26 patients (6.8%) reported opioid consumption during the preoperative period (12 months prior to surgery to 1 month prior to surgery), whereas 60 patients (20.3%) reported extended opioid postoperative opioid consumption at 6-month follow-up. The median OME consumed during the perioperative period was 280 (IQR: 100–300).

Feature selection

Following recursive feature elimination with the random forest algorithm, the variables shown in Fig. 3 were included in the training and the candidate models. To better illustrate the effect of continuous features on model predictions, partial dependence plot for all continuous variables can be found in Additional File 2.

Model performance

Following model optimization, the candidate model discrimination, as measured by the AUROC, was assessed on both the training set (apparent) as well as the bootstrapped resamples (internal validation). Overall, the ensemble model demonstrated the best performance among the candidate models, with an AUROC of 0.74, a calibration intercept of 0.001, a calibration slope of 0.99, and a Brier score of 0.124 (Figs. 1, 2, Table 2). Details of individual models can be found in Table 2.

Decision curve analysis

Decision curve analysis were used to compare the net benefit derived from the trained ensemble algorithm against four alternatives: a logistic regression trained on the complete set of predictors, a simplified model using a single predictor (preoperative opioid use), as well as the two default practices of changing management for all patients or no patients. The complete ensemble algorithm demonstrated the greatest net

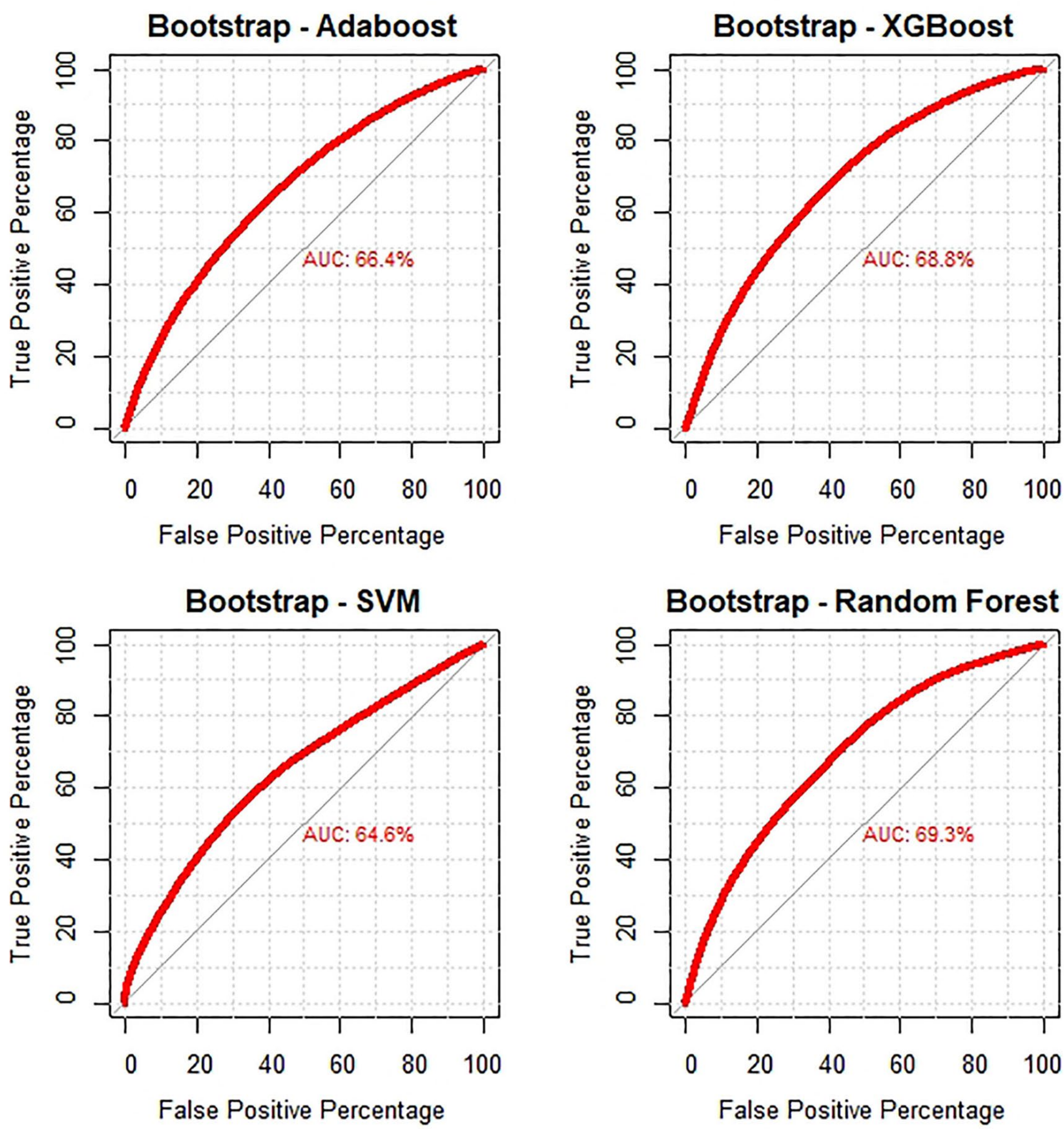

Fig. 1 Receiver-operating characteristics curves on internal validation by 0.632 bootstrap. Models demonstrate discrimination ranging from 0.648 for SVM to 0.693 for random forest

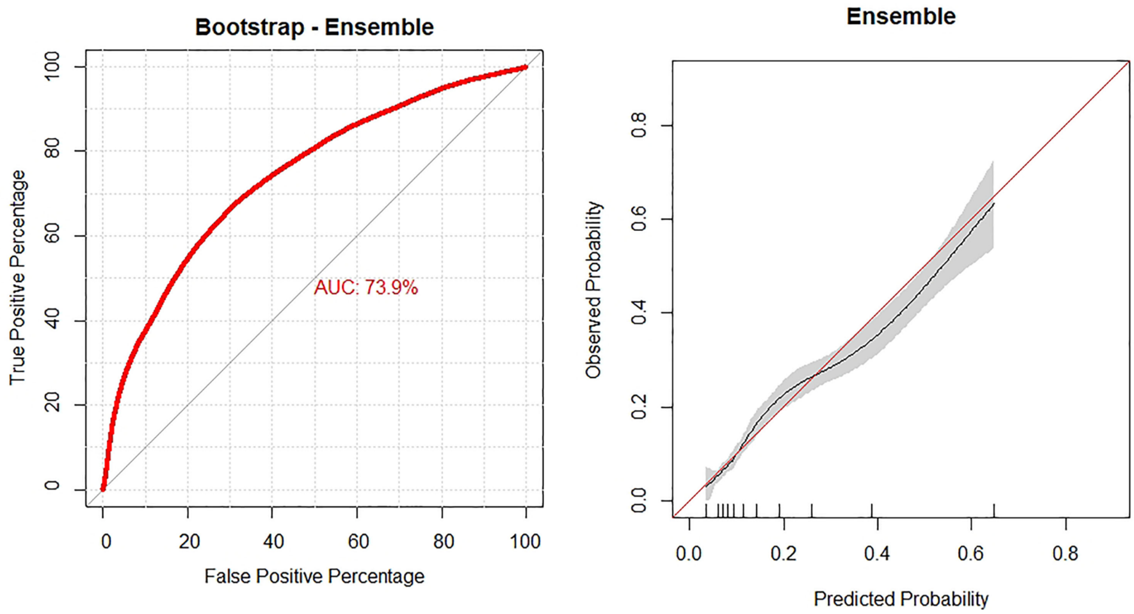

Fig. 2 The ensemble model demonstrated the best discrimination of all models with an AUC of 0.739. The calibration intercept of the ensemble was 0.001 and the calibration slope was 0.99; an ideal model is a straight line with an intercept of 0 and a slope of 1

Table 2 Model assessment on internal validation using 0.632 bootstrapping with 1000 resampled datasets, $n=381$

Metric	Area under the curve		Calibration slope	Calibration intercept	Brier score
	Apparent	Internal validation			
SVM	0.76 (0.74–0.78)	0.65 (0.64–0.65)	1.00 (0.98–1.02)	– 0.0004 (– 0.005–0.005)	0.12 (0.10–0.15)
Random forest	0.81 (0.79–0.84)	0.69 (0.69–0.70)	0.95 (0.93–0.97)	0.008 (0.005–0.012)	0.13 (0.11–0.16)
XGBoost	0.81 (0.78–0.83)	0.69 (0.68–0.69)	0.93 (0.91–0.95)	0.011 (0.008–0.016)	0.14 (0.11–0.16)
AdaBoost	0.79 (0.77–0.82)	0.66 (0.66–0.67)	0.95 (0.93–0.97)	0.008 (0.004–0.013)	0.14 (0.11–0.16)
Ensemble	0.75 (0.72–0.77)	0.74 (0.74–0.74)	0.99 (0.99–1.00)	0.001 (-0.0007–0.003)	0.12 (0.10–0.15)

Null model Brier score = 0.14

benefit at every value representing the high-risk threshold up to 0.6 and was at least of equal benefit to the other strategies beyond this threshold (Fig. 3b).

Explanations

An example of a patient-level explanation accompanying predicted probability of the outcome of interest generated by the final model is provided in Fig. 4. This patient, case #7, was assigned a probability of 0.31 for extended postoperative opioid consumption. Features that supported extended consumption may be found in Fig. 3.

The final model is incorporated into a web-based digital application accessible on desktops, tablets, and smartphones, and can be found at https://sportsmed.shinyapps.io/Opioid_Knee_Arthroscopy/. Default values are provided as placeholders in the interface and the model require complete cases to generate predictions and explanations.

Discussion

The principle findings of this study are as follows. First, after identification of demographic variables, comorbidities, and PROM scores that were important to the predictive performance, four candidate supervised learning algorithms were trained to predict prolonged opioid use in a cohort of patients following common knee arthroscopy procedures. Second, an ensemble model was constructed by aggregating the four machine-learning algorithms and demonstrated the best discrimination and calibration, and Brier score among candidate models. Finally, the model was incorporated into an open-access digital application deployable on mobile or desktop devices.

Feature selection established modifiable and non-modifiable factors that most strongly influenced model performance. Several of the identified features are corroborated

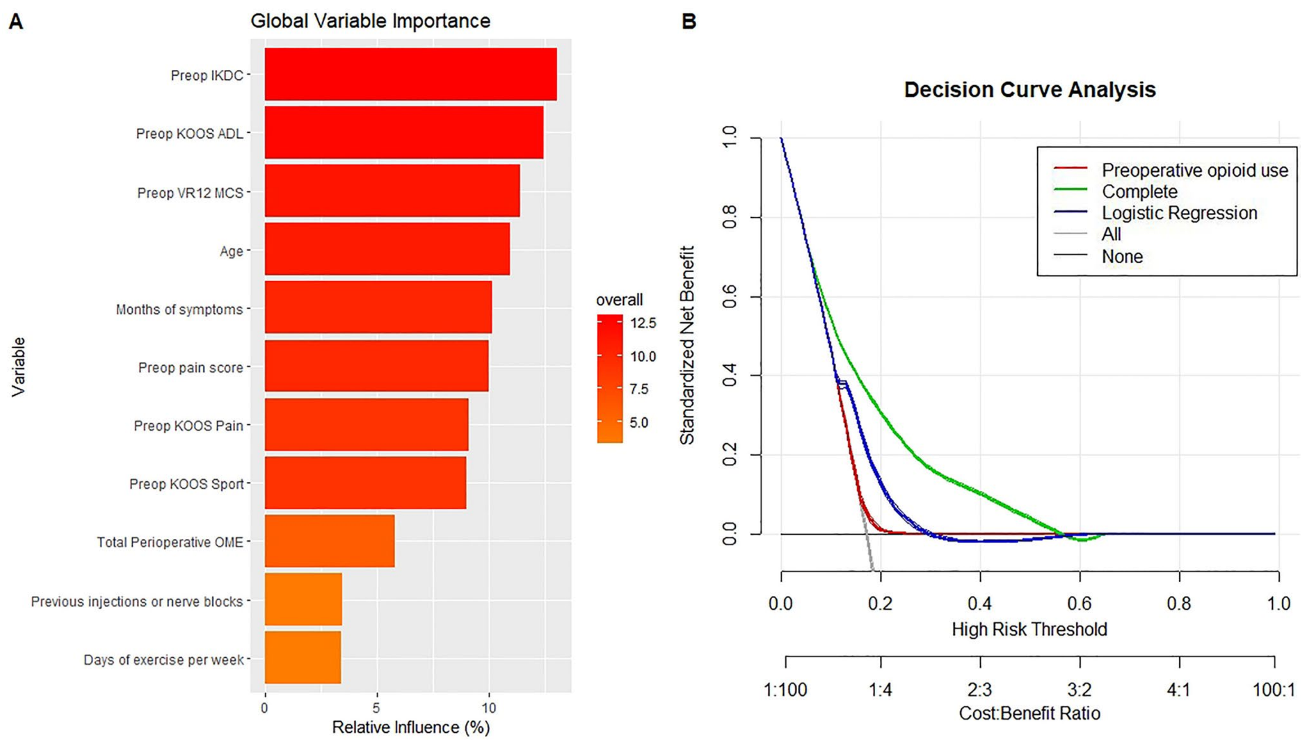

Fig. 3 **a** Variable importance plot of the ensemble model demonstrates the variables included in the model and the relative importance of the variables. **b** Decision curve analysis comparing the complete ensemble algorithm with conventional logistic regression and a simplified ensemble model using only preoperative opioid use as a predictor. The complete ensemble algorithm demonstrated the greatest net benefit at every value representing the high-risk threshold up to 0.6. The downsloping line marked by "All" plots the net benefit from the default strategy of changing management for all patients, while the horizontal line marked "None" represents the strategy of changing management for none of the patients (net benefit is zero at all thresholds). The "all" line slopes down because at a threshold of zero, false positives are given no weight relative to true positives; as the threshold increases, false-positive gain increased weight relative to true positives and the net benefit for the default strategy of changing management for all patients decreases

by the existing literature on postoperative opioid consumption, including total OME consumed during the perioperative period [25, 26], exercise frequency, for which the KOOS sports and recreational activities [27–29], duration of symptoms before presentation [26], mental health PROM scores [11, 26, 30],and preoperative diagnosis of chronic pain syndromes [31, 32]. Although these predictors have been previously reported as they relate to different procedures and patient populations, their identification as predictors for opioid consumption following knee arthroscopy is novel. This reflects the unique potential of the machine-learning methodology to be applied to a wide range of clinical questions.

Interestingly, the present study also identified utilization of steroid injection or nerve block as an important modelling variable. While intraarticular injections have been traditionally utilized for short-term relief of joint pain from a variety of inflammatory etiologies [33], a recent study by Wilson et al. observed a positive relationship between preoperative administration of > 2 intraarticular steroid injections and risks of increased chronic opioid use in patients following total knee arthroplasty [34]. The authors attributed this observation to either an increased time to surgery and subsequent deterioration of osteoarthritis or a decreased baseline pain threshold in patients requiring multiple injections. The present findings support the lag-time hypothesis, as duration of symptoms before presentation to the surgeon was similarly identified by the feature selection algorithm, and nonoperative treatment with nerve blocks or steroid injections may have contributed to an increase in the time to surgery.

Patient-reported outcome measures have become a mainstay utility among surgical subspecialties and are experiencing widespread implementation across orthopaedic clinics across the United States. Previous studies have highlighted the ability of scores on the IKDC and the KOOS component to predict achievement of clinically significant outcomes (CSO) such as the MCID, SCB, and PASS [35], as well as functional outcomes such as return to sport (RTS) [36, 37]. The present model also incorporated the IKDC, KOOS ADL, KOOS pain, and KOOS sports and recreational activities as predictive features. These findings are consistent with the other baseline modifiable variables produced by

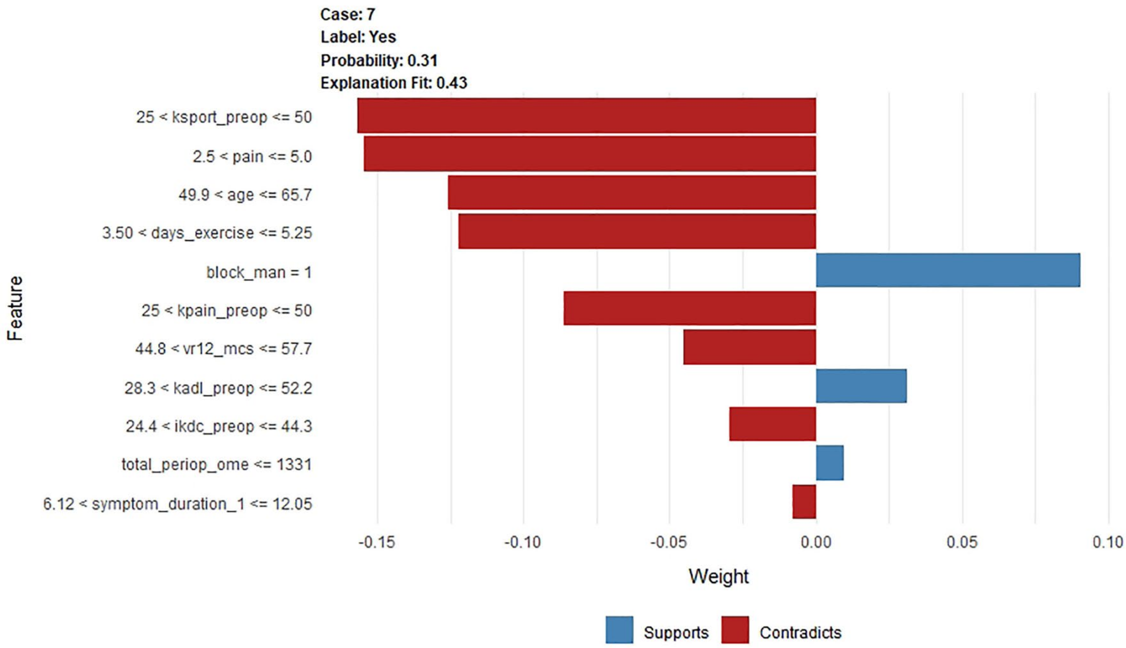

Fig. 4 Example of individual patient-level explanation for the ensemble algorithm. This patient was assigned a probability of 0.31 for extended postoperative opioid consumption. Features that supported the prediction were previous nerve block or injection, preoperative KOOS ADL score, and total OME consumed in the perioperative period. The most heavily weighted features that did not support the prediction were preoperative KOOS Sport score, VAS pain score, age, and days of exercises per week

feature elimination, including pain and exercise frequency, for which both the KOOS subscales [38] and the IKDC [39] have demonstrated high content and construct validity.

Multimodal pain management utilizing paracetamol or NSAIDs [40], regional nerve blocks [41], or local infiltration analgesia [42] has been shown to reduce short-term opioid consumption following a range of orthopaedic procedures. Similarly, team-based approaches have demonstrated efficacy in reducing postoperative opioid consumption. The high prevalence of knee arthroscopy among orthopaedic procedures places particular importance on the prompt identification of high-risk candidates, which can aid in the timely allocation of resources to plan perioperative pain management, mobilize team-based multidisciplinary preventative care, and manage expectations during patient-centred decision making. The validity and effectiveness of the present model has implications for clinical usefulness. First, a primary advantage of the current study design is the ability to easily utilize the present machine-learning model in a clinical setting. The web-based application herein was designed to be deployable during patient visits with minimal interruption of clinic workflow. Thus, the application can help providers accomplish the goal of identifying and appropriately managing high-risk candidates. Second, the performance of the algorithm suggests that the novel methodology of machine learning has broad potential application to orthopaedic sports medicine, including risk stratification, outcome prediction, postoperative analgesic planning, and even clinically significant outcomes.

The following limitations to the present study must be taken into consideration in the interpretation of findings: first, learning and validation of the candidate algorithms were dependent on the quality of the provided training data, and while sample size determinations for machine-learning performance has been largely heuristic in nature, it is possible that additional samples beyond the initial cohort can improve the performance of the final model. In addition, the model and the explanation algorithms perform optimally with inputs like the training set, and without external validation, it is possible to see decays in performance if given outlier inputs. Second, four different arthroscopic knee procedures were included in this study, thus the diversity of pre-, intra- and postoperative characteristics represented may affect the results. Third, preoperative opioid use was not identified to be a significant risk factor for postoperative use, contrary to overwhelming evidence in the literature, this is likely due to the small sample of positive cases in the training cohort, which may have exerted a negligible contribution to model performance, as such, further learning and validation using prospectively collected data may better capture the influence of preoperative opioid consumption. Furthermore, prolonged postoperative opioid consumption is a multifactorial phenomenon partly attributable to risk factors not recorded in the institutional database, such as social and cultural beliefs, surgeon-prescribing preferences, and psychological wellbeing.

The ensemble model presented here can be quickly and easily implemented in the clinical setting to assist in identifying patients at risk for prolonged postoperative opioid use. In addition, patient-specific risk factors can be optimized if modifiable, multi-modal analgesia may be employed for susceptible patients, and patients can be appropriately counseled regarding their risk for prolonged postoperative opioid consumption.

Conclusion

Following appropriate external validation, the algorithm developed presently could augment timely identification of patients who are at risk of extended opioid use. Patients with modifiable risk factors such as baseline exercise can attempt pre-habilitation to optimize their status and those with non-modifiable risk factors may be cautioned to monitor their OME intake. In addition, appropriately indicated patients should be counseled against delaying operative treatment to avoid undesirable outcomes.

Author contributions YL: study design, data acquisition, data analysis, data interpretation, manuscript drafting, and critical revision. EF: study design, data acquisition, data analysis, data interpretation, manuscript drafting, and critical revision. RRW: study design, data acquisition, data analysis, data interpretation, manuscript drafting, and critical revision. OLG: study design, data acquisition, data analysis, data interpretation, manuscript drafting, and critical revision. MCF: study design, data interpretation, manuscript drafting, and critical revision. ABY: study design, data interpretation, manuscript drafting, and critical revision. BJC: study design, data interpretation, manuscript drafting, and critical revision. NV: study design, data interpretation, manuscript drafting, and critical revision. BF: study design, data acquisition, data analysis, data interpretation, manuscript drafting, and critical revision.

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Compliance with ethical standards

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Ethical approval This study utilized previously collected data from an institutional database. The present study was granted IRB exemption by the IRB at Rush University and was adherent to all ethical standards put forth by IRB at Rush University.

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