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Clinical Study

Development of machine learning algorithms for prediction of prolonged opioid prescription after surgery for lumbar disc herniation

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Abstract

BACKGROUND CONTEXT: Spine surgery has been identified as a risk factor for prolonged postoperative opioid use. Preoperative prediction of opioid use could improve risk stratification, shared decision-making, and patient counseling before surgery.

PURPOSE: The primary purpose of this study was to develop algorithms for prediction of prolonged opioid prescription after surgery for lumbar disc herniation.

STUDY DESIGN/SETTING: Retrospective, case-control study at five medical centers.

PATIENT SAMPLE: Chart review was conducted for patients undergoing surgery for lumbar disc herniation between January 1, 2000 and March 1, 2018.

OUTCOME MEASURES: The primary outcome of interest was sustained opioid prescription after surgery to at least 90 to 180 days postoperatively.

METHODS: Five models (elastic-net penalized logistic regression, random forest, stochastic gradient boosting, neural network, and support vector machine) were developed to predict prolonged opioid prescription. Explanations of predictions were provided globally (averaged across all patients) and locally (for individual patients).

RESULTS: Overall, 5,413 patients were identified, with sustained postoperative opioid prescription of 416 (7.7%) at 90 to 180 days after surgery. The elastic-net penalized logistic regression model had the best discrimination (c-statistic 0.81) and good calibration and overall performance; the three most important predictors were: instrumentation, duration of preoperative opioid prescription, and comorbidity of depression. The final models were incorporated into an open access web application able to provide predictions as well as patient-specific

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Ethics Statement: This study was approved by our institutional review board.

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explanations of the results generated by the algorithms. The application can be found here: https://sorg-apps.shinyapps.io/lumbardiscopioid/

CONCLUSION: Preoperative prediction of prolonged postoperative opioid prescription can help identify candidates for increased surveillance after surgery. Patient-centered explanations of predictions can enhance both shared decision-making and quality of care.

Keywords: Disc herniation; Machine learning; Neurosurgery; Orthopaedics; Opioid dependence; Prediction; Spine surgery

Introduction

The rate of opioid overdoses in the United States has increased threefold since 2000. In 2015, over 33,000 Americans died from opioid overdose [1−3]. The prevalence of chronic opioid use has paralleled the rate of opioid prescriptions since the 1990s. However, there is currently nationwide recognition of opioid-related complications with resultant increased scrutiny of provider prescribing practices.[1,4,5] Previous studies have implicated surgery as a risk factor for chronic opioid use and highlighted spine surgery as a particularly high-risk care episode [3,6−9].

Preoperative prediction of opioid dependence after spine surgery could be used for risk stratification, shared decision-making, and patient counseling before surgery. Although, prior studies have identified risk factors for postoperative opioid dependence, there are few studies that have sought to develop preoperative predictive models for postoperative opioid use [3,6,9−11]. In addition, there are no studies in the lumbar spine literature that have sought to apply techniques such as machine learning for preoperative prediction of opioid use.

The primary purpose of this study was to develop algorithms for prediction of prolonged opioid prescription after surgery for lumbar disc herniation. Additional aims of this study were to provide explanations of the predictions generated by these models. Finally, web applications were developed for healthcare professionals to access the models developed here in order to enable patient-specific explanations for each prediction to improve counseling and shared decision-making.

Materials and methods

Guidelines

The following guidelines were followed: Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) and Guidelines for Developing and Reporting Machine Learning Models in Biomedical Research [12,13].

Data source

Our institutional review board approved retrospective medical records review; individual patient consent was waived because this study was confined to retrospective review alone. Patients from five medical centers were included in this study. The following inclusion criteria were applied: (1) age greater than or equal to 18 years, (2) inpatient or outpatient procedure between January 1, 2000 and March 1, 2018, and (3) lumbar spine surgery with operative diagnosis of disc herniation. The first surgery for lumbar disc herniation at our institutions within the time frame of the study was used as the index procedure. Surgeries with concurrent diagnosis of trauma, tumor, infection, inflammatory conditions, pseudarthrosis, and spinal deformity (scoliosis, spondylolisthesis) were excluded.

Outcomes

The definition of prolonged opioid prescription was based on prior research as sustained opioid prescriptions filled after surgery to at least 90 to 180 days after the index procedure for disc herniation [10,14]. The full list of medications included as opioids was also based on prior studies (Supplementary Table 1).

Variables

The following variables with less than 30% missing data were included as candidates based on previous research [3,6,9−11,14−16]: age (years), sex, marital status (defined as married if legally married or in a common law partnership), veteran, race (White, non-White), ethnicity (Hispanic, non-Hispanic), procedural factors (fusion, approach, multilevel surgery, instrumentation), history of previous spine surgery, laboratory values (white blood cell count [$\times 10^3$ per microliter {μL}]), hemoglobin (grams per deciliter [g/dL]), platelet count ($\times 10^3$ /μL), creatinine (mg/dL), prothrombin time (PT), insurance status (Medicaid, workers compensation, Medicare, uninsured), neighborhood characteristics based on the US Censuses Bureau American Community Survey data (median household income, median age, high school graduation or General Equivalency Diploma (GED) attainment, unemployment rate, population density (per square mile), preoperative medications (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, antidepressants, beta-2-agonists, beta-blockers, benzodiazepines, gabapentin, immunosuppressants, nonsteroidal anti-inflammatory drugs, opioids, typical antipsychotics, atypical antipsychotics), and preoperative comorbidities (tobacco use, drug abuse, diabetes, renal failure, malignancy, depression, psychoses, myocardial infarction, congestive heart failure, peripheral vascular disease, chronic obstructive pulmonary disease, arrhythmias, valvular disease, and liver disease) [17−21]. Medications included in each category (Supplementary Table 1) were identified in the year prior to the index procedure and based on prior research [11]. Preoperative opioid duration was categorized based on previous research as continuous prescriptions for greater than 180 days before surgery, opioid prescriptions for less than 180 days continuously, and no preoperative opioid prescription [22].

Missing data

Rates of missing data were: race 175 (3.2%), marital status 230 (4.2%), white blood cell count=1,303 (23.5%), hemoglobin=1,236 (22.3%), platelet=1,306 (23.6%), creatinine=1,593 (28.8%), median age of neighborhood 85 (1.5%), high school attainment 78 (1.4%), unemployment rate 81 (1.5%), population density 104 (1.9%). Multiple imputation with the missForest methodology was undertaken for variables with less than 30% missing data [23].

Model development

The available patient population was divided into a training set and an independent testing set in a stratified 80:20 split. Random forest algorithms and 10-fold cross validation were used for recursive feature selection [24]. The details of this methodology have been extensively described previously. The following algorithms were used on the subset of features identified by recursive feature selection: (1) random forest, (2) stochastic gradient boosting, (3) neural network, (4) support vector machine, and (5) elastic-net penalized logistic regression [25,26]. Ten-fold cross validation repeated three times was used to assess discrimination (c-statistic or area under the receiver operating curve—AUC), calibration (calibration slope, calibration intercept), and overall performance (Brier score) in the training and testing sets [27]. Decision curves were plotted for the algorithm with the best performance [27].

Model explanation

Explanations were provided for all patients in the testing and for selected cases as illustrative examples. Global variable importance plots provided a rank-ordered list of the most important variables for prediction across all patients in the testing set [28]. The relationship between continuous predictors and model predictions was explained with partial dependence plots. Individual patient-specific explanations were provided with Locally Interpretable Model Agnostic (LIME) explanations [29].

Web application

The final algorithm for prediction of postoperative opioid dependence was deployed as an open access web application. The Anaconda Distribution (Anaconda, Inc., Austin, TX), R version 3.5.0 (The R Foundation, Vienna, Austria), RStudio version 1.1.453 (RStudio, Boston, MA), and Python version 3.6 (Python Software Foundation, Wilmington, DE) were used for data analysis and application development.

Results

Overall, 5,413 patients underwent surgery for lumbar disc herniation with sustained postoperative opioid prescription of 416 (7.7%) at 90 to 180 days after surgery. Two thousand and twenty-four patients (44.8%) were female and the median age was 46 (interquartile range [IQR]=37−58; Table 1).

Variables identified for prediction of sustained postoperative opioid prescription by recursive feature selection were sex, surgical factors (instrumentation, previous spine surgery), comorbidity of depression, tobacco use, drug abuse, preoperative hemoglobin, white blood cell, and preoperative medications (opioids, gabapentin, benzodiazepines, beta-2 agonists).

On cross validation of the training set, n=4,331 (80%), the stochastic gradient boosting, neural network, and penalized logistic regression models performed similarly on discrimination (Table 2). In the independent sample, n=1,082 (20%), not used for algorithm development, the elastic-net penalized logistic regression had the best discrimination (AUC 0.81), calibration (slope=1.13, intercept=0.13), and overall performance (Brier=0.064) (Table 3). In comparison, the null model Brier score was 0.071. On global variable importance assessment, the three most important predictors were instrumentation, duration of preoperative opioid prescription, and comorbidity of depression (Fig. 1). Furthermore, on decision curve analysis, the elastic-net penalized logistic regression model showed greater standardized net benefit for management changes than the use of duration of preoperative opioid prescription alone as well as the default strategies of changing management for all patients or for no patients (Fig. 2).

Model explanations

Partial dependence plots were created to examine the relationship between the continuous predictors of preoperative hemoglobin and white blood cell and the models (stochastic gradient boosting, penalized logistic regression, and neural network) predicted probabilities (Fig. 3). Lower hemoglobin resulted in higher predicted probability of prolonged postoperative opioid prescription for all models. Higher white blood cell resulted in higher predicted probability of prolonged postoperative opioid prescription in all models. Patient-specific explanations for the neural network model are shown in Fig. 4. For example, consider a female patient with preoperative opioid prescription for greater than 180 days and comorbidity of depression. The model's prediction of prolonged postoperative opioid prescription for this patient was 0.16; in this case, preoperative opioid prescription for greater than 180 days and depression resulted in an adjustment that increased the likelihood of prolonged postoperative opioid prescription. However, the

Table 1
Baseline characteristics of study population, n=5,413

Variable	n (%) | median (IQR)
Age	46.0 (37.0−58.0)
Female sex	2,424 (44.8)
Race	
Non-White	581 (11.1)
White	4,657 (88.9)
Ethnicity	
Hispanic	199 (3.8)
Non-Hispanic	5,039 (96.2)
Marital status	
Married	3,188 (61.5)
Not married	1,998 (38.5)
Veteran	408 (8.0)
Disposition	
Inpatient	4,177 (77.2)
Outpatient	1,236 (22.8)
Surgical factors	
Fusion	488 (9.0)
Anterior approach	144 (2.7)
Instrumentation	446 (8.2)
Multilevel	747 (13.8)
Previous spine surgery	161 (3.0)
Preoperative lab values	
Hemoglobin (g/dL)	14.1 (13.2−15.1)
White blood cell (10^3/uL)	7.37 (6.01−8.90)
Platelet (10^3/uL)	264.0 (222.0−313.0)
Creatinine (mg/dL)	0.90 (0.78−1.01)
Insurance	
Medicaid	375 (6.9)
Medicare	761 (14.1)
Workers compensation	68 (1.3)
Uninsured	223 (4.1)
Neighborhood characteristics	
Median household income ($)	80,139 (61,527−99,924)
Median Age (y)	41.1 (36.3−44.5)
High school graduation rate (%)	24 (16−30)
Unemployment rate (%)	5.7 (4.6−7.2)
Population density (per square mile)	2,336 (862−7,069)
Preoperative medications	
ACE	251 (4.6)
ARB	97 (1.8)
Antidepressant	523 (9.7)
Beta-2 agonist	214 (4.0)
Beta-blocker	260 (4.8)
Benzodiazepines	787 (14.5)
Gabapentin	823 (15.2)
Immunosuppressant	824 (15.2)
NSAID	1,198 (22.1)
Opioid	1,874 (34.6)
Antipsychotic	129 (2.4)
Preoperative opioid duration	
Greater than 180 days	1,122 (20.7)
180 days or less	752 (11.7)
None	3,656 (67.5)
Comorbidities	
Tobacco use	595 (11.0)
Drug abuse	114 (2.1)
Diabetes	428 (7.9)
Renal failure	92 (1.7)
Depression	713 (13.2)
Psychoses	38 (0.7)
Myocardial infarction	114 (2.1)
Congestive heart failure	93 (1.7)
Peripheral vascular disease	107 (2.0)
Cerebrovascular accident	100 (1.8)
Chronic obstructive pulmonary disease	626 (11.6)
Arrhythmias	415 (7.7)
Valvular disease	142 (2.6)
Liver disease	139 (2.6)
Solid tumor	116 (2.1)

fact that the patient did not undergo instrumentation during surgery, did not use other preoperative medications (gabapentin, beta-2 agonists, benzodiazepines), had no history of drug abuse or tobacco use, was female, and had no previous spine surgeries resulted in an adjustment that reduced the estimation of prolonged postoperative opioid prescription.

The final model is available here: https://sorg-apps.shinyapps.io/lumbardiscopioid/

Discussion

Five models were developed for prediction of prolonged postoperative opioid prescription in patients undergoing surgery for lumbar disc herniation. The elastic-net penalized logistic regression algorithm achieved the best performance with c-statistic 0.81, good calibration, and overall performance. Explanations were provided for the model predictions globally (averaged across all patients) and locally (for individual patients).

Clarke et al. previously studied 39,140 opioid naïve Canadian patients 66 years or older undergoing major surgery (cardiac, pelvic) and found 3.1% had opioid use 90 days after surgery. Independent risk factors identified with increased risk of opioid dependence were younger age, lower household income, comorbidities (diabetes, heart failure, pulmonary disease), and preoperative medications (benzodiazepines, selective serotonin reuptake inhibitors, angiotensin converting enzyme inhibitors) [14]. Brummett et al. studied 36,177 patients with no recorded opioid prescriptions in the 12 months to 1-month time period prior to surgery from the Clinformatics Data Mart. The rate of postoperative opioid prescriptions in the surgery cohort at 90 and 180 days after the index operation ranged from 5.9% to 6.5%, in comparison to 0.4% in the nonoperative control cohort. Independent risk factors for opioid dependence were tobacco use, alcohol and substance abuse, anxiety, and preoperative pain disorders (back pain, neck pain, arthritis, centralized pain) [10].

Schoenfeld at al. studied 9,991 opioid naïve patients undergoing spine surgery from 2006 to 2014 in the TRICARE insurance claims database. At 3 months after surgery, 1% continued opioid use and independent risk factors for opioid dependence were arthrodesis relative to discectomy or decompression alone and depression [3]. Schoenfeld et al. also studied 27,031 patients from 2006 to 2014 in the TRICARE database undergoing lumbar interbody

Table 2
Discrimination and calibration of algorithms on repeated cross validation of training set, n=4,331, mean (95% confidence interval)

Metric	Stochastic gradient boosting	Random forest	Support vector machine	Neural network	Penalized logistic regression
AUC	0.79 (0.78, 0.81)	0.77 (0.75, 0.79)	0.56 (0.53, 0.59)	0.79 (0.77, 0.81)	0.80 (0.78, 0.82)
Intercept	0.05 (−0.13, 0.23)	−0.08 (−0.27, 0.11)	0.05 (−0.51, 0.62)	0.09 (−0.09, 0.28)	0.14 (−0.05, 0.32)
Slope	1.03 (0.94, 1.11)	0.53 (0.48, 0.59)	1.02 (0.80, 1.25)	1.08 (0.99, 1.16)	1.07 (0.98, 1.15)
Brier	0.062 (0.061, 0.064)	0.067 (0.066, 0.068)	0.069 (0.068, 0.070)	0.062 (0.061, 0.064)	0.062 (0.061, 0.063)

AUC, area under the receiver operating curve.
Null model Brier score=0.071.

Table 3
Discrimination and calibration of algorithms in holdout set, n=1,082

Metric	Stochastic gradient boosting	Random forest	Support vector machine	Neural network	Penalized logistic regression
AUC	0.79	0.73	0.57	0.79	0.81
Intercept	0.16	−0.02	1.19	0.15	0.13
Slope	1.03	0.52	1.46	1.06	1.02
Brier	0.065	0.068	0.069	0.065	0.064

AUC, area under the receiver operating curve.
Null model Brier score=0.071.

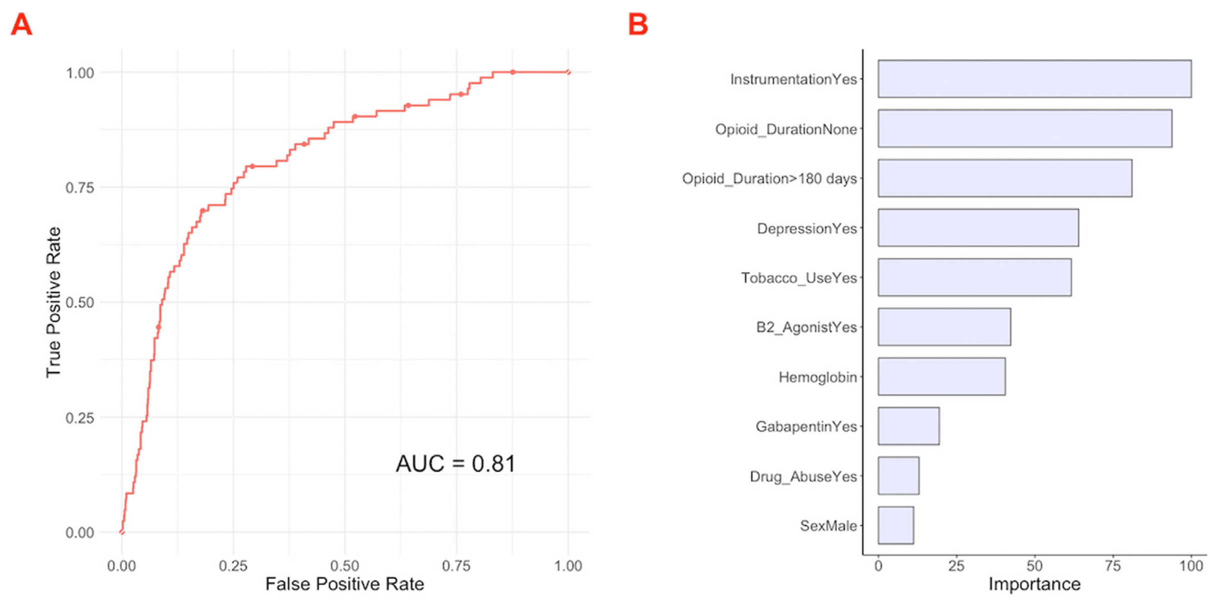

Fig. 1. (A) Area under the receiver operating curve (AUC) for elastic-net penalized logistic regression algorithm. (B) Global variable importance for prediction of prolonged opioid prescription. Abbreviations: AUC, area under receiver operating curve.

arthrodesis, lumbar discectomy, lumbar decompression, or lumbar posterolateral arthrodesis and found that 86.4% had stopped opioid use by 90 days and 8.8% continued use beyond 6 months. Independent risk factors for opioid dependence were duration of preoperative opioid use, fusion procedure, revision procedure, depression, generalized anxiety disorder, preoperative diagnosis of spinal fracture, junior officer rank, and length of hospital stay. Kalakoti et al. studied 26,553 patients undergoing lumbar spine surgery from 2007 to 2015 in the PearlDiver database and found preoperative opioid dependence to be the strongest risk factor for postoperative opioid dependence [30].

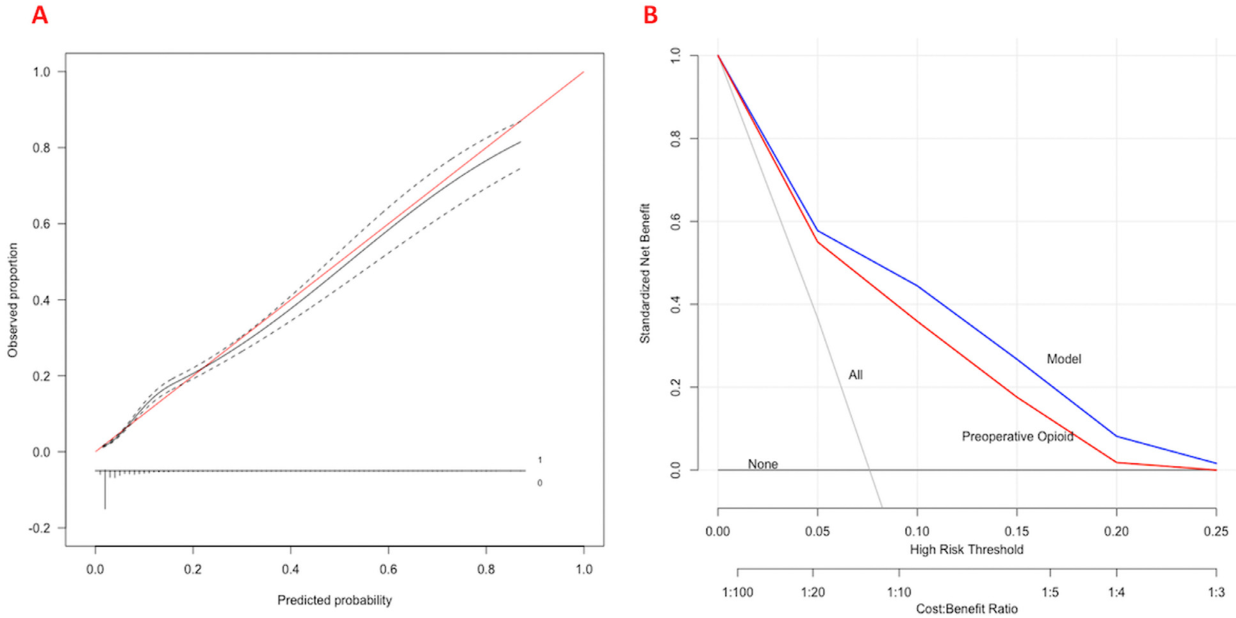

Fig. 2. (A) Calibration plot for elastic-net penalized logistic regression algorithm. (B) Decision curve analysis with standardized net benefit by threshold probability.

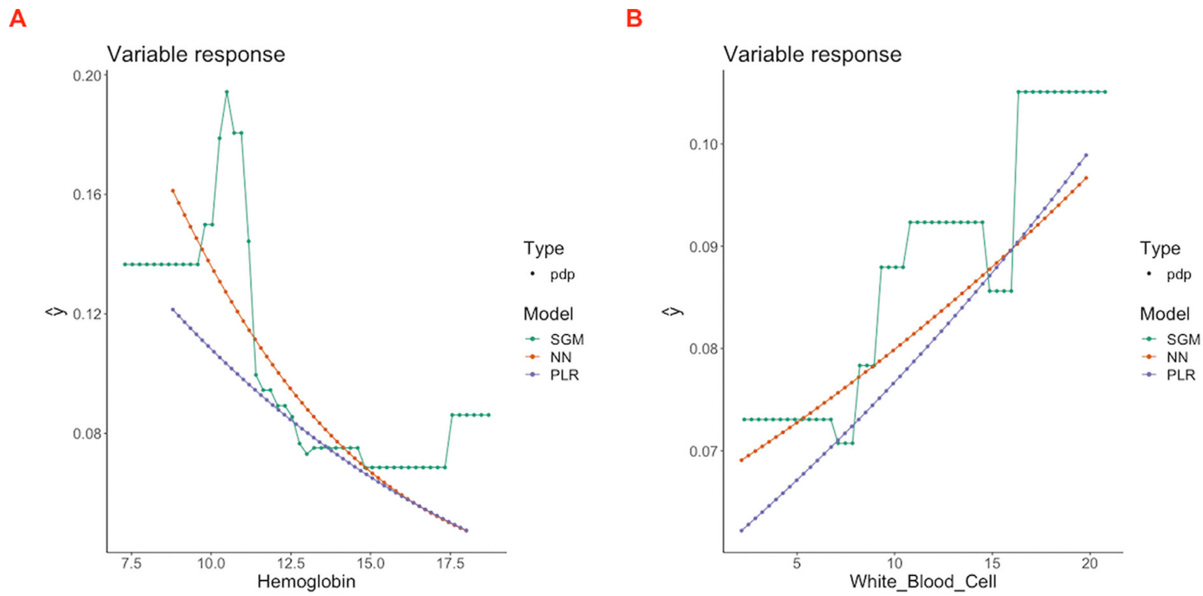

Fig. 3. Partial dependence plots for neural network (NN), stochastic gradient boosting (SGB), penalized logistic regression (PLR) (A) hemoglobin (B) white blood cell.

Connolly et al. used the Clinformatics Data Mart to study 8,377 adults between the ages of 21 and 63 undergoing lumbar fusion surgery and identified duration of preoperative opioid use, refusion surgery, and comorbidity of depression as risk factors for long-term opioid use (more than 365 days of opioids filled in the 2 years after the index surgery) [31]. The postoperative rates of prolonged opioid prescription found in this study and the variables identified in this study through recursive feature elimination concurred with these prior studies of opioid dependence in spine and nonspine surgery. Additional factors identified here (preoperative hemoglobin, preoperative white blood cell) concurred with other studies of increased healthcare utilization after spine surgery as derangements (anemia, leukocytosis) in these laboratory values are likely reflective of overall preoperative comorbidity burden [32,33].

There are a number of limitations to the work presented here. Opioid dose in oral morphine equivalents was not available from the pharmacy records of the previous electronic

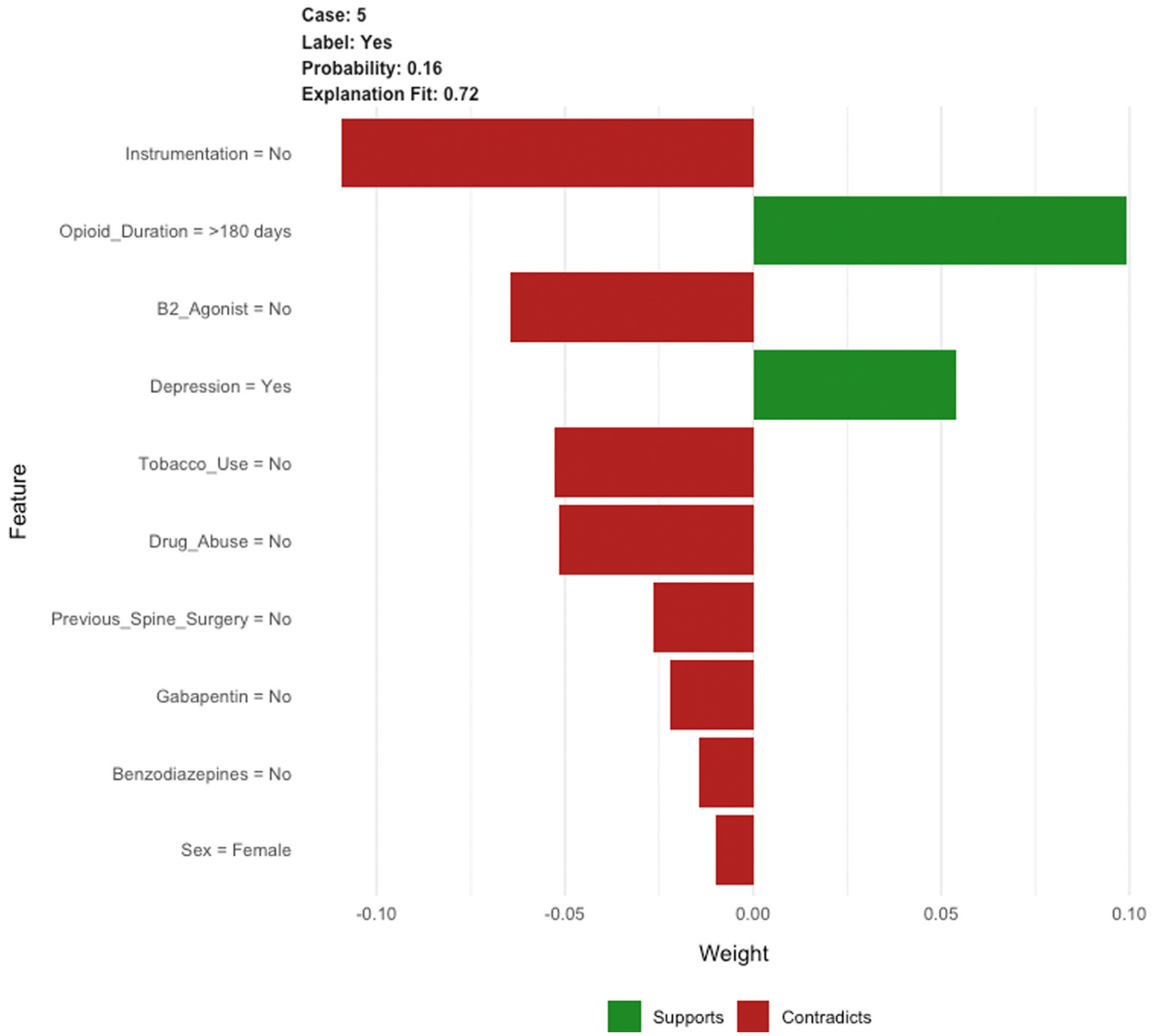

Fig. 4. Patient-specific explanation for prediction generated by the neural network model.

health record system at our institutions. Patients with illicit opioid prescriptions or opioid use from other means were not captured in this analysis and the study assumes that the medications were used as prescribed. In addition, the characterization of opioid use in either the pre- or postoperative periods is at best an approximation given the type of medical record data available to us. Patient-reported outcomes have been previously studied in relation to opioid dependence but were not routinely assessed or recorded for the majority of patients in this study. The focus of this study was lumbar disc herniations and the validity of these algorithms in other lumbar spinal conditions remains to be determined; future studies should be undertaken that validate or refute these algorithms for other spinal conditions. Additionally, the time frame (2000−2018) of this study was relatively long with changes to surgical techniques for lumbar disc herniation over this period; future multicenter studies may be able to obtain sufficient volumes of patients while incorporating a narrower time frame. Although five medical centers were included in this work, these institutions are part of a single healthcare corporation from one region with shared institutional practices and culture. The external validation of these findings in independent cohorts remains to be determined. The immediately available web application included in this study offers other investigators the opportunity to further evaluate the models presented here.

Despite the noted limitations, this study provides value to healthcare professionals caring for patients undergoing spine surgery for lumbar disc herniation. Preoperative prediction of increased risk of prolonged postoperative opioid prescription can result in management changes that provide more support and counseling to patients prior to surgery. The decision curve analysis presented in this study clearly demonstrated that our models offer greater value than management decisions based solely on duration of preoperative opioid prescription alone. The patient-specific explanations can further aid preoperative conversations around the need for increased surveillance following surgery as well as pooling multidisciplinary resources (pain medicine, mental health, case management) in changing the trajectory of prolonged postoperative opioid use.

The ultimate use of these models will be subject to external validation but the implications for practice include a patient-centered approach to postoperative management and increased leverage of techniques such as machine learning to mitigate adverse events associated with prolonged opioid use following surgery.

Conclusion

Preoperative prediction of prolonged postoperative opioid prescription can help identify candidates for increased surveillance after surgery. Patient-centered explanations of predictions can further enhance both shared decision-making and quality of care.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2019.06.002.

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