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Clinical Study

Predicting prolonged opioid prescriptions in opioid-naïve lumbar spine surgery patients

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Abstract

IMPORTANCE: Preoperative determination of the potential for postoperative opioid dependence in previously naïve patients undergoing elective spine surgery may facilitate targeted interventions.

OBJECTIVE: The purpose of this study was to develop supervised machine learning algorithms for preoperative prediction of prolonged opioid prescription use in opioid-naïve patients following lumbar spine surgery.

DESIGN: Retrospective review of clinical registry data. Variables considered for prediction included demographics, insurance status, preoperative medications, surgical factors, laboratory values, comorbidities, and neighborhood characteristics. Five supervised machine learning algorithms were developed and assessed by discrimination, calibration, Brier score, and decision curve analysis.

SETTING: One healthcare entity (two academic medical centers, three community hospitals), 2000 to 2018.

PARTICIPANTS: Opioid-naïve patients undergoing decompression and/or fusion for lumbar disk herniation, stenosis, and spondylolisthesis.

MAIN OUTCOME: Sustained prescription opioid use exceeding 90 days after surgery.

RESULTS: Overall, of 8,435 patients included, 359 (4.3%) were found to have prolonged postoperative opioid prescriptions. The elastic-net penalized logistic regression achieved the best performance in the independent testing set not used for algorithm development with c-statistic=0.70, calibration intercept=0.06, calibration slope=1.02, and Brier score=0.039. The five most important factors for prolonged opioid prescriptions were use of instrumented spinal fusion, preoperative benzodiazepine use, preoperative antidepressant use, preoperative gabapentin use, and uninsured status. Individual patient-level explanations were provided for the algorithm predictions and the algorithms were incorporated into an open access digital application available here: <https://sorg-apps.shinyapps.io/lumbaropioidnaive/>.

CONCLUSION AND RELEVANCE: The clinician decision aid developed in this study may be helpful to preoperatively risk-stratify opioid-naïve patients undergoing lumbar spine surgery.

FDA device/drug status: Not applicable.

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

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The tool demonstrates moderate discriminative capacity for identifying those at greatest risk of prolonged prescription opioid use. External validation is required to further support the potential utility of this tool in practice. © 2019 Elsevier Inc. All rights reserved.

Key words:

Disk herniation; Opioid; Prediction; Spine; Spondylolisthesis; Stenosis

Introduction

Mortality from unintentional drug overdoses is now the second-leading cause of accidental death in the United States [1]. In 2016, over 2 million individuals carried the diagnosis of an opioid use disorder and the majority of illicit heroin users started with prescription opioids [2,3]. The postoperative period after elective surgical procedures has been identified as a high-risk time for the development of opioid dependence, and orthopedic and neurosurgery patients have the highest rate of chronic opioid use [4–7].

Prior studies of lumbar spine surgery patients have identified risk factors for prolonged postoperative use, but few studies have specifically studied opioid-naïve patients [8–18]. Furthermore, to our knowledge, there are no preoperative clinical decision aids available for risk-stratifying opioid-naïve patients with respect to the predilection for sustained prescription opioid use following a lumbar spine operation.

The purpose of this study was to develop a clinical decision aid for opioid-naïve patients undergoing lumbar spine surgery for disk herniation, stenosis, or spondylolisthesis. The utility of supervised machine learning algorithms was investigated for this predictive analytic task and the best performing algorithm was then deployed to allow for both prediction and an in-depth explanation of the quantified risk at the individual patient level.

Materials and methods

Guidelines

The TRIPOD guidelines and the Guidelines for Developing and Reporting Machine Learning Models in Biomedical Research were followed for this analysis [19,20].

Data source

Institutional review board approval was granted for retrospective review of electronic health records at five medical centers affiliated with one healthcare entity. Criteria for inclusion were: (1) adult patients 18 years of age or older; (2) primary procedure of lumbar decompression with or without fusion between January 1, 2000 and May 1, 2018; (3) operative diagnosis of lumbar disk herniation, lumbar stenosis, or lumbar spondylolisthesis; and (4) no opioid prescriptions in the year before the index procedure. Patients were excluded if they underwent surgery for infection, trauma, tumor, pseudarthrosis, and scoliosis.

Outcomes

Prolonged opioid prescriptions were defined on the basis of prior studies as (1) first opioid prescription in the first 30 days after surgery, (2) second opioid prescription from days 31 to 90, and (3) third opioid prescription from days 91 to 180 after surgery [4,5]. Medications included as opioids are available for review in [Supplementary Table 1](#).

Variables

Candidate predictors for this analysis were demographics (age, sex, marital status, veteran status, race, ethnicity), disposition (inpatient, outpatient), operative diagnosis (disk herniation, spondylolisthesis, spinal stenosis), procedural factors (fusion, approach, instrumented fusion, multilevel intervention), history of any previous spine surgery in the year before the index procedure, laboratory values (white blood cell count [$\times 10^3$ per microliter { μL }], hemoglobin (grams per deciliter [g/dL]), platelet count ($\times 10^3/\mu\text{L}$), creatinine (mg/dL), insurance status (Medicaid, Medicare, workers compensation, uninsured, private), neighborhood (zip-code) characteristics (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 [ACE] inhibitor, angiotensin II receptor blocker [ARB], antidepressant, beta-2-agonists, beta-blockers, benzodiazepines, gabapentin, immunosuppressants, nonsteroidal anti-inflammatory drugs, antipsychotics), and preoperative comorbidities (tobacco use, alcohol abuse, drug abuse, diabetes, renal failure, depression, psychoses, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accident, chronic obstructive pulmonary disease, arrhythmias, valvular disease, liver disease, and malignancy). The 6 months before surgery were used to identify medications included in each category and the list is available for review in [Supplementary Table 1](#).

Missing data

Rates of missing data were: race 279 (3.3%), ethnicity 279 (3.3%), marital status 365 (4.3%), white blood cell count=1,741 (20.6%), hemoglobin=1,599 (19.0%), platelet=1,747 (20.7%), creatinine=1,992 (23.6%), median age of neighborhood 125 (1.5%), high school degree 118 (1.4%), unemployment rate 122 (1.4%), population density 172 (2.0%). Variables with less than 30% missing data underwent multiple imputation with the missForest methodology [21].

Model development

Detailed methodology used to develop the supervised machine learning algorithms has been described previously [22]. Briefly, a stratified 80:20 split was used to create the training (n=6,749) and testing (n=1,686) sets. Recursive feature selection with random forest algorithms was used to identify the subset of variables used for final model development in the training set. Ten-fold cross-validation repeated three times of the training set was used to develop the following algorithms: (1) random forest, (2) stochastic gradient boosting, (3) neural network, (4) support vector machine, and (5) elastic-net penalized logistic regression. Model performance was assessed in the independent testing set not used for algorithm development. Metrics used for algorithm performance assessment were discrimination (receiver operating curve, c-statistic or area under the receiver operating curve—AUC), calibration (calibration plot, calibration slope, calibration intercept), overall performance (Brier score), and decision curve analysis [23]. Model interpretation and explanations were provided at the global (averaged across all patients in the population) and local (individual-patient) levels. Finally, an open access web application was developed with the ability to provide both predictions and explanations based on the best performing model. 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. The application is available here: <https://sorg-apps.shinyapps.io/lumbaropioidnaive/>. The default values in the application are placeholders that can be adjusted by users to reflect the individual characteristics of the patient in question.

Results

Overall, 8,435 patients who were opioid-naïve before surgery were included in this investigation. Of these cases, the plurality underwent surgery for lumbar disk herniation (n=3,252, 38.6%), stenosis (n=3,052, 36.2%), or spondylolisthesis (n=1,840, 21.8%). Of these patients, 3,900 (46.2%) were female and the median age was 60 years (interquartile range=46–71; Table 1). The rate of sustained prescription opioid use (based on our operational definition) was 4.3% (n=359). Rates of prolonged postoperative opioid prescriptions among previously opioid-naïve patients by surgical condition were 2.5% (n=82) for disk herniation, 4.4% (n=135) for stenosis, and 6.5% (n=119) for spondylolisthesis.

Recursive feature selection with random forest algorithms identified the following variables for prediction of prolonged opioid prescriptions: demographics (age), procedural factors (instrumented spinal fusion, multilevel surgery, approach), uninsured insurance status, creatinine, comorbidities (tobacco use, alcohol abuse), medications

Table 1

Baseline demographics of study population, n=8,435

Variable	n (%) median (IQR)
Demographics	
Age (y)	60 (46–71)
Female sex	3,900 (46.2)
Race	
Non-White	677 (8.3)
White	7,479 (91.7)
Ethnicity	
Hispanic	156 (1.9)
Non-Hispanic	8,000 (98.1)
Marital status	
Married	5,151 (63.8)
Not married	2,919 (36.2)
Veteran	1,080 (13.4)
Disposition	
Inpatient	6,808 (80.7)
Outpatient	1,627 (19.3)
Operative diagnosis	
Disk herniation	3,252 (38.6)
Spondylolisthesis	1,840 (21.8)
Spinal stenosis	3,052 (36.2)
Operative factors	
Fusion	2,532 (30.0)
Anterior	399 (4.7)
Instrumentation	2,320 (27.5)
Multilevel	2,951 (35.0)
Previous spine surgery	385 (4.6)
Laboratory values	
Hemoglobin (g/dL)	13.9 (13.0–14.9)
White blood cell (10 ³ /uL)	7.17 (5.97–8.60)
Platelet (10 ³ /uL)	254 (214–302)
Creatinine (mg/dL)	0.90 (0.80–1.09)
Insurance	
Medicaid	447 (5.3)
Medicare	2,885 (34.2)
Workers compensation	86 (1.0)
Uninsured	255 (3.0)
Private insurance	4,880 (57.9)
Neighborhood characteristics	
Median household income (\$)	79,778 (62,114–99,441)
Median age (years)	42.1 (37.9–44.8)
High school graduation rate (%)	24 (16–31)
Unemployment rate (%)	5.6 (4.6–7.1)
Population density (per square mile)	1,962 (729–5,228)
Medications	
Angiotensin converting enzyme inhibitor	420 (5.0)
Angiotensin II receptor blocker	201 (2.4)
Antidepressant	492 (5.8)
Beta-2-agonist	183 (2.2)
Beta-blocker	466 (5.5)
Benzodiazepines	459 (5.4)
Gabapentin	614 (7.3)
Immunosuppressant	702 (8.3)
Nonsteroidal anti-inflammatory	827 (9.8)
Antipsychotic	82 (1.0)
Comorbidities	
Tobacco use	638 (7.6)
Alcohol abuse	97 (1.1)
Drug abuse	108 (1.3)
Diabetes	946 (11.2)
Renal failure	274 (3.2)
Depression	1,056 (12.5)
Psychoses	50 (0.6)

Table 1 (Continued)

Variable	n (%) median (IQR)
Myocardial infarction	320 (3.8)
Congestive heart failure	254 (3.0)
Peripheral vascular disease	411 (4.9)
Cerebrovascular accident	290 (3.4)
Chronic obstructive pulmonary disease	1,007 (11.9)
Arrhythmias	978 (11.6)
Valvular disease	380 (4.5)
Liver disease	182 (2.2)
Malignancy	229 (2.7)

(antidepressant, benzodiazepines, gabapentin). Observed rates of prolonged opioid prescriptions by these factors were: age less than 65: 4.6% (n=237), instrumented spinal fusion: 8.6% (n=187), multilevel surgery: 5.3% (n=156), anterior approach: 10.5% (n=42), uninsured insurance status: 9.4% (n=24), tobacco use: 8.0% (n=51), alcohol abuse: 12.4% (n=12), antidepressant use: 10.2% (n=50), benzodiazepine use: 10% (n=46), gabapentin use: 8.1% (n=50).

In the independent testing set, n=1,686 (20%), c-statistic of the models ranged from 0.46 to 0.70, calibration intercept ranged from −1.58 to 0.58, calibration slope ranged from 0.35 to 1.20, and Brier score ranged from 0.39 to 0.41 with a null model Brier score of 0.041 (Table 2). The elastic-net penalized logistic regression (PLR) model had superior performance across discrimination (AUC=0.70, Fig. 1, Left) and calibration (calibration intercept 0.06, calibration slope 1.02, Fig. 2, Left). Global variable importance plots for the PLR model showed that the five most important factors for prediction were instrumentation, benzodiazepine use, antidepressant use, gabapentin use, and uninsured status (Fig. 1, Right). On decision curve analysis, the PLR model resulted in greater net benefit for thresholds <0.20 than the default strategies of intervening for no patients or intervening for all patients.

An example of the individual patient-level explanations is shown in Fig. 3. The predicted probability of prolonged prescription opioid use was 0.24 for a patient who underwent instrumented fusion and used benzodiazepines and antidepressants before surgery. These factors increased the estimation for the likelihood of postoperative opioid prescriptions; however, having insurance, not undergoing an

anterior procedure, no history of alcohol abuse, and no gabapentin use decreased the likelihood of sustained prescription opioid use after surgery.

Discussion

Elective lumbar spine surgery in opioid-naïve patients may result in sustained prescription opioid use in nearly 1 in every 20 patients. Although this rate of sustained postoperative opioid use pales in comparison to that among preoperative opioid users [11–13,18], the opioid-naïve population may be the most responsive to any preoperative interventions intended to prevent this adverse outcome. Furthermore, the risk of opioid dependence may be considered for inclusion in preoperative counseling as the incidence approaches other common complications associated with elective lumbar spine surgery. In this study, the elastic-net penalized logistic regression algorithm was developed for this purpose and performed well on discrimination, calibration, Brier score, and decision curve analysis when evaluated on the independent testing set. Averaged across all patients (global explanations), the most important factors for prediction were use of instrumented spinal fusion, preprocedural benzodiazepine use, preprocedural antidepressant use, preprocedural gabapentin use, and uninsured status. The observed risk of sustained postoperative opioid prescription use based on these risk factors was instrumented spinal fusion (8.6%), uninsured insurance status (9.4%), antidepressant use (10.2%), benzodiazepine use (10%), and gabapentin use (8.1%).

The factors selected in this work by recursive feature selection with random forest algorithms to predict prolonged opioid use among previously naïve patients concurred with prior studies. Benzodiazepine use and antidepressant use were previously identified by Sun et al. for increased risk of chronic opioid use in the first year after surgery among opioid-naïve patients [6]. Similarly, tobacco use and alcohol abuse were identified by Brummett et al. as risk factors for new persistent opioid use among patients undergoing minor (eg, carpal tunnel) and major (eg, bariatric surgery) procedures [4]. Instrumented spinal fusion relative to discectomy or decompression alone was associated with higher rates of prolonged opioid prescriptions likely due to increased surgical invasiveness and increased postoperative morbidity [24]. Schoenfeld et al. studied opioid-naïve lumbar spine surgery patients and showed

Table 2

Machine learning model performance assessment in the testing set, n=1,617

Metric	Stochastic gradient boosting	Random forest	Support vector machine	Neural network	Elastic-net penalized logistic regression
AUC	0.70	0.63	0.46	0.69	0.70
Intercept	0.58	−1.26	−1.58	−0.17	0.06
Slope	1.20	0.35	0.50	0.96	1.02
Brier	0.039	0.041	0.040	0.039	0.039

AUC, area under the receiver operating curve.

Null model Brier score=0.041.

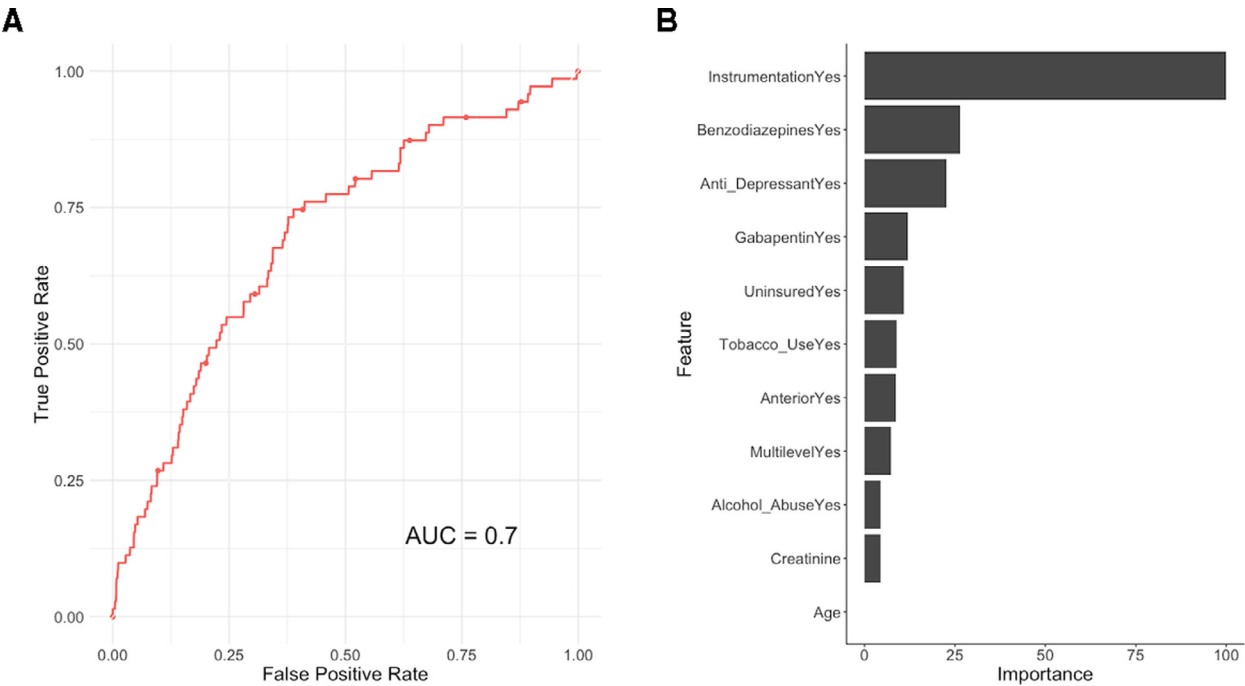


Fig. 1. (Left) Area under the receiver operating curve (AUC) for the elastic-net penalized logistic regression model. (Right) Global variable importance for prediction of prolonged postoperative opioid prescriptions. AUC, area under receiver operating curve.

that older patients, those with no history of depression and those who underwent discectomy or decompression alone relative to lumbar interbody arthrodesis had higher likelihood of discontinuing opioid use after surgery [17]. These authors found that only 1% of patients continued opioid use at 3 months. This was based on the definition of chronic opioid

use as opioid prescriptions in the first 30 days after surgery continued without an interruption of greater than 30 days between prescriptions. This difference in the definition of prolonged postoperative opioid prescriptions likely accounts for the lower rate of prolonged opioid users identified in that work compared to the current investigation.

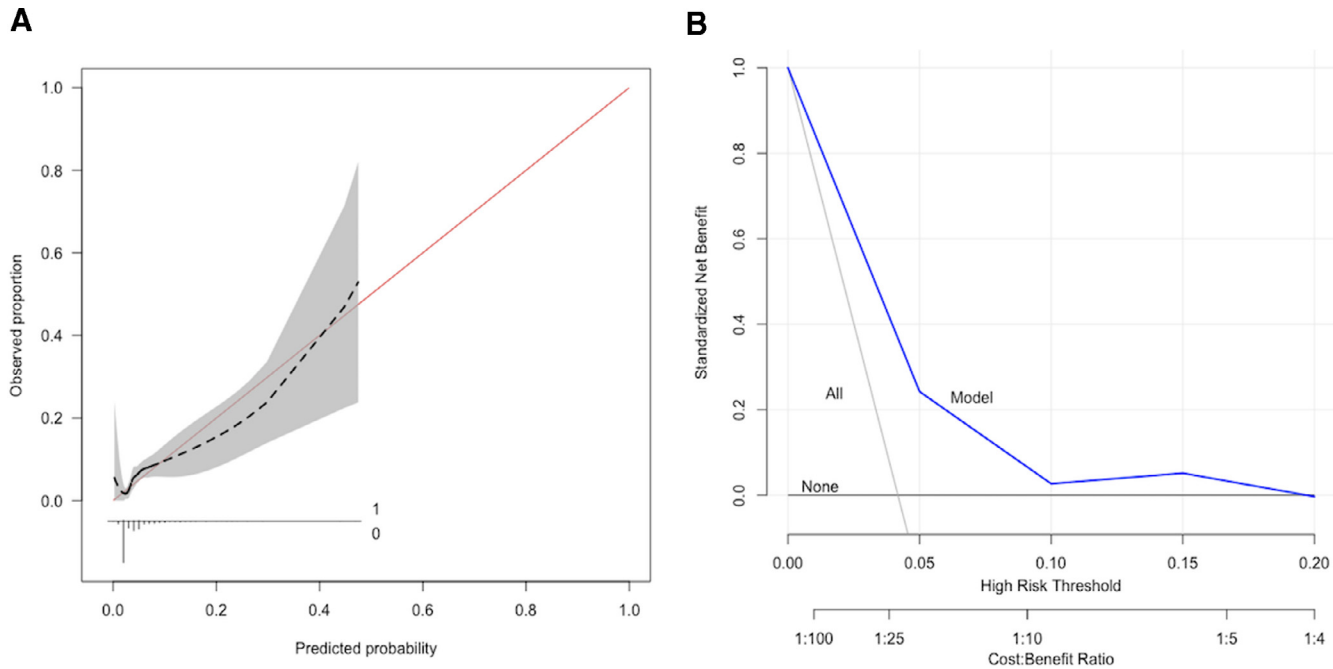


Fig. 2. (Left) Calibration plot for elastic-net penalized logistic regression model. (Right) Decision curve analysis with standardized net benefit by threshold probability.

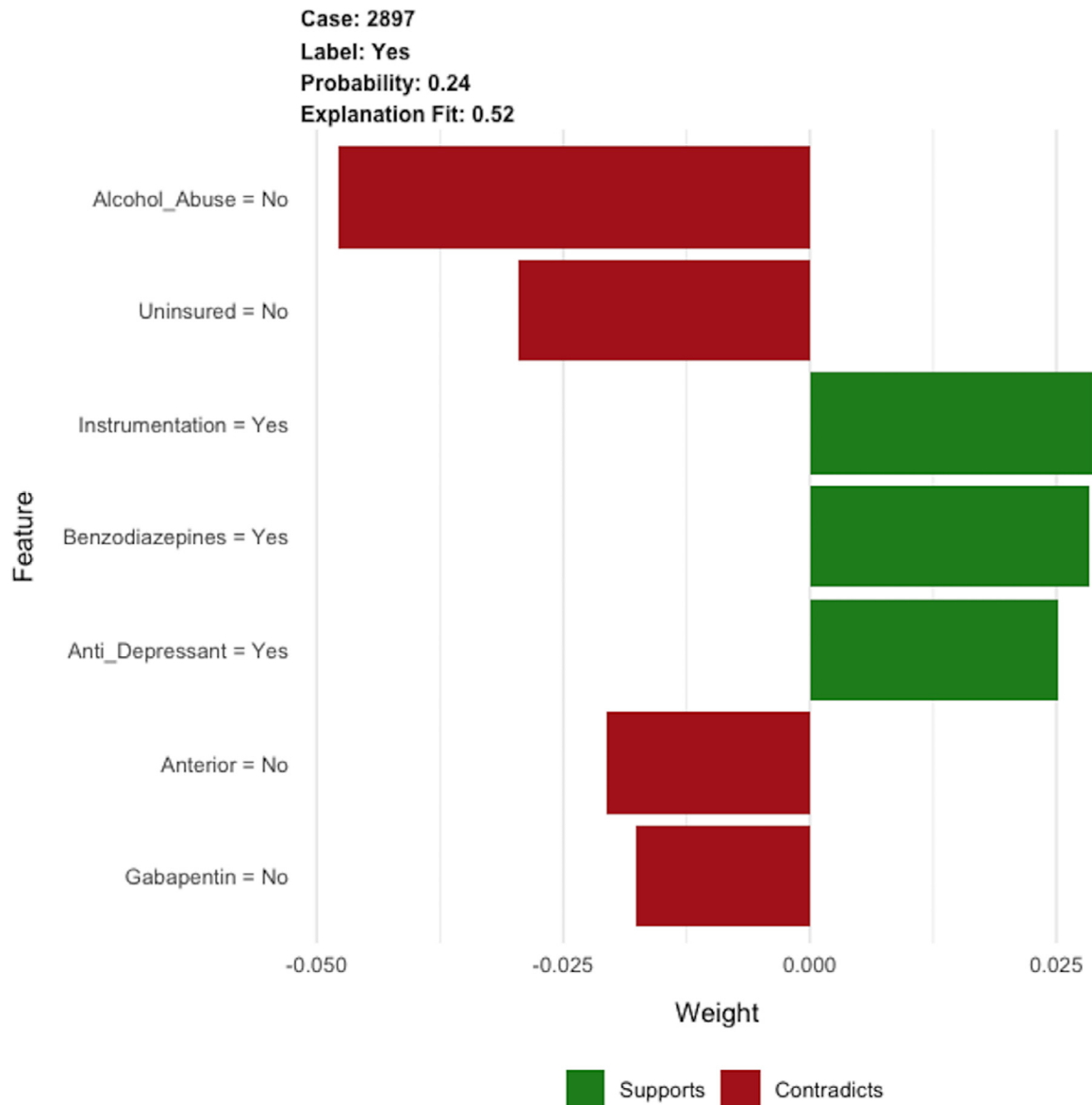


Fig. 3. Example of individual patient level explanation for prediction generated by the elastic-net penalized logistic regression model.

There are several limitations that must be acknowledged in order to appropriately interpret the results of this study. This was a retrospective study and determination of the generalizability of these algorithms to other populations requires external validation. The method of tracking postoperative opioid prescriptions was limited to the affiliated medical centers and did not account for patients who received opioids prescriptions from providers outside of this healthcare entity. Similarly, preoperative surveillance of opioid use may be limited and result in misclassification. Any illicit opioid use was also unable to be assessed in this study. Furthermore, patients who did not use the opioids as prescribed were unable to be identified. These limitations are likely to underestimate the true rate of opioid dependence, which serves to underscore the interpretation of these data. The criteria used to make preoperative diagnoses and the clinical rationale to use other

preoperative medications such as benzodiazepines or gabapentin could not be determined. Certain preoperative medications may have been prescribed for multiple indications such as neuropathic pain and depression, and these factors were not captured in this analysis. Preoperative medication dose and patient use of preoperative medications as prescribed was not assessed. The goal of this study was to develop a tool for preoperative prediction, and intraoperative and postoperative complications were unable to be assessed at this time point; further studies that might seek to develop algorithms for prehospital discharge might be able to include these factors. Only patients managed operatively were included in this analysis and opioid prescriptions in patients screened for surgery but managed nonoperatively were not studied. Surgeon-level factors such as years in practice and annual case volume were also not included in this analysis.

The efficacy of any interventions that may be directed by the clinical decision aid developed here remain to be determined. Finally, there may be a cluster effect from shared prescriber practices and preferences for postoperative opioid prescriptions that was not captured in this analysis.

Despite these limitations, this study offers a novel clinical decision tool for risk stratifying opioid-naïve patients in the setting of elective lumbar spine surgery. If found to be externally valid, providers might incorporate these algorithms into preoperative screening and counseling appointments for patients. Identification of high-risk patients may trigger preoperative conversations, shared decision-making, and multidisciplinary management. Inclusion of the visual algorithm explanations may allow patients to determine if any of the risk factors are modifiable before surgery. Targeted preoperative interventions based on the model predictions for the opioid-naïve patients at highest risk of sustained prescription opioid use may prevent or reduce the severity of this adverse outcome. Interventions such as opioid-free anesthesia, cognitive behavioral therapy, mindfulness-based stress reduction, distraction techniques, and increased reliance on opioid-sparing medications in the postoperative period may be indicated for such patients [25–28]. These algorithms may also become embedded into electronic health records and obviate the need for providers to manually enter in the values required for preoperative prediction. Providers may then be able to access these algorithms and predictions as part of the routine clinical workflow.

Conclusion

The clinician decision aid developed in this study may be helpful to preoperatively risk-stratify opioid-naïve patients undergoing lumbar spine surgery. The tool demonstrates moderate discriminative capacity for identifying those at greatest risk of prolonged prescription opioid use. External validation is required to further support the potential utility of this tool in practice.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.spinee.2019.12.019>.

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