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Clinical Study

Machine learning for prediction of sustained opioid prescription after anterior cervical discectomy and fusion

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Abstract

BACKGROUND CONTEXT: The severity of the opioid epidemic has increased scrutiny of opioid prescribing practices. Spine surgery is a high-risk episode for sustained postoperative opioid prescription.

PURPOSE: To develop machine learning algorithms for preoperative prediction of sustained opioid prescription after anterior cervical discectomy and fusion (ACDF).

STUDY DESIGN/SETTING: Retrospective, case-control study at two academic medical centers and three community hospitals.

PATIENT SAMPLE: Electronic health records were queried for adult patients undergoing ACDF for degenerative disorders between January 1, 2000 and March 1, 2018.

OUTCOME MEASURES: Sustained postoperative opioid prescription was defined as uninterrupted filing of prescription opioid extending to at least 90−180 days after surgery.

METHODS: Five machine learning models were developed to predict postoperative opioid prescription and assessed for overall performance.

RESULTS: Of 2,737 patients undergoing ACDF, 270 (9.9%) demonstrated sustained opioid prescription. Variables identified for prediction of sustained opioid prescription were male sex, multilevel surgery, myelopathy, tobacco use, insurance status (Medicaid, Medicare), duration of preoperative opioid use, and medications (antidepressants, benzodiazepines, beta-2-agonist, angiotensin-converting enzyme-inhibitors, gabapentin). The stochastic gradient boosting algorithm achieved the best performance with c-statistic=0.81 and good calibration. Global explanations of the model demonstrated that preoperative opioid duration, antidepressant use, tobacco use, and Medicaid insurance were the most important predictors of sustained postoperative opioid prescription.

FDA device/drug status: Not applicable.

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CONCLUSIONS: One-tenth of patients undergoing ACDF demonstrated sustained opioid prescription following surgery. Machine learning algorithms could be used to preoperatively stratify risk these patients, possibly enabling early intervention to reduce the potential for long-term opioid use in this population.

Keywords: Anterior cervical discectomy and fusion; Machine learning; Opioid use; Prediction; Spine surgery; Cervical spine; Predictive analytics

Introduction

Total US expenditures for prescription opioid abuse exceed $78 billion dollars [1]. In 2016, 11 million US citizens misused opioids whereas drug overdose deaths increased exponentially from 1979 to 2016 [1−5]. The severity of the opioid crisis has led to increased scrutiny of opioid prescribing practices after surgery. Spine surgery, in particular, has been implicated as a particularly high-risk episode for sustained postoperative opioid use [6,7].

Previous studies in spine surgery have examined large national administrative and insurance claims databases to identify trends in postoperative opioid use and risk factors for opioid use [8−12]. Although numerous socio-demographic and clinical characteristics have been identified as prognostic factors for sustained opioid use following spine surgery, no predictive algorithms presently exist for risk stratification of patients before an intervention.

The purpose of this analysis was to develop machine learning algorithms for preoperative prediction of sustained opioid prescription after anterior cervical discectomy and fusion (ACDF). Additional aims of this study were to provide explanations of model predictions at the individual patient level and finally to deploy these algorithms as open access applications for dissemination among the healthcare community.

Materials and methods

Guidelines

The Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis and JMIR guidelines for Developing and Reporting Machine Learning Models in Biomedical Research were followed for this analysis [13,14].

Data source

Institutional Review Board Approval was granted for retrospective review of electronic health records from two academic medical centers and three community hospitals. Individual patient consent was waived as the study was restricted to retrospective review of health records. Inclusion criteria for the study were (1) age 18 years or older, (2) primary index procedure of inpatient and outpatient ACDF, and (3) operative indication of cervical disc herniation, disc degeneration, stenosis, and/or other spondylotic condition. Procedures with concurrent operative diagnoses of cervical trauma, tumor, pathologic fracture, infection, pseudarthrosis, and scoliosis were excluded.

Outcome

Sustained postoperative opioid prescription was the primary outcome of interest as defined by continuous prescription opioid use following surgery and extending to at least 90−180 days following the procedure [7,15]. This was characterized through surveillance of the prescriptions issued through the integrated electronic health record and/or recorded in provider notes. The list of opioids is available for review in Supplementary Table 1.

Variables

A retrospective review was used to collect the following variables on the basis of previous research: [6,7,10−12,15−19] age, sex, race, Hispanic ethnicity, marital status, veteran status, preoperative neurologic deficit (myelopathy, radiculopathy), multilevel surgery, history of previous spine surgery, insurance status (Medicaid, Medicare, private insurance, uninsured, workers compensation), neighborhood characteristics based on the United States Censuses Bureau American Community Survey zip code data (median household income ($), high school graduation and General Equivalency Diploma rate (%), unemployment rate (%), population density [per square mile]), preoperative medications (angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, antidepressant, antipsychotics, beta-2-agonists, beta-blockers, benzodiazepines, gabapentin, immunosuppressants, nonsteroidal anti-inflammatory drugs). Duration of preoperative opioid use was categorized as continuous opioid use before and exceeding 180 days, less than 180 days, and none [20]. Medications were identified in the year before the index procedure and are available for review in Supplementary Table 1. Additional factors collected were preoperative comorbidities (tobacco use, drug abuse, diabetes, renal failure, malignancy, depression, psychoses, myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, hemiplegia/paraplegia, chronic obstructive pulmonary disease, arrhythmias, valvular disease, and liver disease) and preoperative laboratory values (hemoglobin [g/dL] white blood cell count [$\times 10^3/\mu$L], platelet count [$\times 10^3/\mu$L], creatinine level [mg/dL]) [21−25].

Table 1
Baseline characteristics of study population, n=2,737

Variable	n (%)/median (IQR)
Age (y)	51.0 (44.0−59.0)
Female sex	1,440 (52.6)
Race	
Non-White	280 (10.6)
White	2,369 (89.4)
Ethnicity	
Hispanic	55 (2.1)
Non-Hispanic	2,594 (97.9)
Marital status	
Married	1,668 (64.1)
Not-married	935 (35.9)
Veteran	175 (6.7)
Disposition	
Inpatient	2,293 (83.8)
Outpatient	444 (16.2)
Preoperative deficit	
Myelopathy	695 (25.4)
Radiculopathy	992 (36.2)
Surgical factors	
Multilevel	1,244 (45.5)
Previous spine surgery	130 (4.7)
Preoperative laboratory	
Hemoglobin (g/dL)	14.0 (13.2−15.0)
White blood cell ($10^3/\mu L$)	7.20 (5.95−8.64)
Platelet ($10^3/\mu L$)	258.0 (216.0−302.8)
Creatinine (mg/dL)	0.87 (0.74−1.00)
Insurance	
Medicaid	240 (8.8)
Medicare	424 (15.5)
Workers compensation	37 (1.4)
Uninsured	92 (3.4)
Private insurance	2,029 (74.1)
Neighborhood characteristics	
Median household income ($)	79,419 (62,027−95,665)
Median age (y)	41.5 (38.0−44.7)
High school graduation rate (%)	25.8 (18.1−31.3)
Unemployment rate (%)	5.8 (4.8−7.3)
Population density (per square mile)	1,886 (768−5,069)
Medications	
Angiotensin-converting enzyme	161 (5.9)
Angiotensin receptor blocker	59 (2.2)
Antidepressant	364 (13.3)
Beta-2-agonist	152 (5.6)
Beta-blocker	186 (6.8)
Benzodiazepines	398 (14.5)
Gabapentin	347 (12.7)
Immunosuppressant	398 (14.5)
Non-steroidal anti-inflammatory drug	501 (18.3)
Antipsychotic	71 (2.6)
Preoperative opioid duration	
None	2,028 (74.1)
<180 d	341 (12.5)
>180 d	368 (13.4)
Comorbidities	
Tobacco use	347 (12.7)
Alcohol abuse	66 (2.4)
Drug abuse	69 (2.5)
Diabetes	314 (11.5)
Renal failure	44 (1.6)
Depression	449 (16.4)
Psychoses	21 (0.8)
Myocardial infarction	60 (2.2)
Congestive heart failure	43 (1.6)
Peripheral vascular disease	64 (2.3)
Cerebrovascular accident	85 (3.1)
Hemiplegia/paraplegia	74 (2.7)
Chronic obstructive Pulmonary disease	440 (16.1)
Arrhythmias	224 (8.2)
Valvular disease	74 (2.7)
Liver disease	86 (3.1)
Malignancy	76 (2.8)

Missing data

Rates of missing data were race 93 (3.2%), marital status 140 (4.9%), veteran status 131 (4.6%), median household income 63 (2.2%), high school attainment 35 (1.2%), unemployment rate 35 (1.2%), population density 50 (1.7%), white blood cell count=561 (19.5%), hemoglobin=516 (18.0%), platelet=565 (19.7%), creatinine=618 (21.5%). Variables with less than 30% missing data were imputed with multiple imputations using the missForest methodology [26].

Model development

The patient population was divided into a training and testing set with a stratified 80:20 split. Multivariate variable selection with random forest algorithms was used to identify the subset of variables used for model development [27]. Five supervised machine learning algorithms (random forest, stochastic gradient boosting, neural network, support vector machine, elastic-net penalized logistic regression) were developed with this subset of variables in the training set [28,29]. The performance of the resultant models was assessed on the training set by 10-fold cross-validation repeated three times. The performance of the models was also assessed in the independent testing set not used for algorithm development. Metrics used for algorithm assessment were discrimination (c-statistic), calibration (calibration slope, calibration intercept), and overall performance (Brier score) [30]. In addition, we used decision curve analysis to examine the impact of true and false positives of the algorithm's predictions over the range of predicted probabilities [30]. The net benefit (sum of weighted true and false positives) of the algorithm was compared with the default strategies of changing management for no patients or for all patients. Finally, the net benefit of management changes based solely on preoperative opioid prescription was compared with the final machine learning model.

Model explanation

The final models were given explanations at the global and local levels. Models were explained at the global level by averaging the effect of individual variables across all patients to determine the most important variables for sustained postoperative opioid prescription [31]. Models were explained at the local level by showing how each patient-specific variable influenced the final prediction [32].

Web application

The best performing algorithm was deployed as an open access web application capable of providing predictions and individual patient-specific explanations. The Anaconda Distribution (Anaconda, Inc, Austin, TX, USA), R version 3.5.0 (The R Foundation, Vienna, Austria), RStudio version 1.1.453 (RStudio, Boston, MA, USA), and Python version 3.6 (Python Software Foundation, Wilmington, DE, USA) were used for data analysis.

Results

Of 2,737 patients undergoing ACDF, 270 (9.9%) patients were found to meet our criteria for sustained postoperative opioid prescription. Among the population as a whole, 1,440 (52.6%) patients were women and the median age was 51 (interquartile range=44−59) years (Table 1). Before surgery, 695 (25.4%) patients had myelopathy and 992 (36.2%) had radiculopathy. Overall, 2,028 (74.1%) patients had no opioid prescriptions in the year before surgery, 341 (12.5%) had opioid use for less than 180 days before surgery, and 368 (13.4%) had continuous opioid prescription for greater than 180 days before surgery. Among opioid naïve patients, the rate of postoperative opioid prescription was 87 (4.3%). Among patients with less than 180 days of preoperative opioid prescription, the rate of postoperative opioid prescription was 57 (16.7%) and among patients with greater than 180 days of continuous preoperative opioid prescription, the rate of postoperative opioid prescription was 126 (34.2%). Random forest algorithms identified the following subset of variables for machine learning model development: male sex, myelopathy, multilevel surgery, tobacco use, Medicaid insurance, Medicare insurance, preoperative opioid duration, and preoperative medications (antidepressants, benzodiazepines, beta-2-agonist, angiotensin-converting enzyme-inhibitors, gabapentin).

Machine learning model performance on cross-validation of the training set (n=2,190 [80%]) resulted in c-statistics ranging from 0.63 (support vector machine) to 0.80 (stochastic gradient boosting, elastic-net penalized logistic regression; Table 2). Model performance in the independent testing set (n=547 [20%]) resulted in c-statistics ranging from 0.58 (support vector machine) to 0.81 (stochastic gradient boosting and elastic-net penalized logistic regression; Table 3). Calibration plots of the final algorithms in the testing set showed that the stochastic gradient boosting algorithm was the best calibrated to the testing set with calibration intercept=−0.001 and calibration slope=1.05 (Supplementary Fig. 1). The Brier score for the stochastic gradient boosting model was 0.076 relative to the null model Brier score of 0.089. On global model explanation, preoperative opioid prescription duration, antidepressant use, tobacco use, and Medicaid insurance were the most important predictors of postoperative opioid use (Fig. 1). On decision curve analysis, the stochastic gradient boosting algorithm resulted in greater net benefit than the default strategies of changing management for no patients or for all

Table 2
Discrimination and calibration of algorithms on repeated cross-validation of training set, n=2,190, mean (95% confidence interval)

Metric	Stochastic gradient boosting	Random forest	Support vector machine	Neural network	Penalized logistic regression
AUC	0.80 (0.79, 0.82)	0.77 (0.76, 0.79)	0.63 (0.61, 0.66)	0.79 (0.77, 0.81)	0.80 (0.78, 0.82)
Intercept	0.03 (−0.13, 0.19)	−0.10 (−0.33, 0.12)	0.18 (−0.25, 0.60)	0.01 (−0.18, 0.18)	0.01 (−0.16, 0.18)
Slope	1.02 (0.94, 1.11)	0.44 (0.34, 0.53)	1.09 (0.89, 1.29)	1.04 (0.94, 1.14)	1.01 (0.92, 1.10)
Brier	0.075 (0.072, 0.078)	0.082 (0.080, 0.084)	0.083 (0.081, 0.085)	0.075 (0.072, 0.078)	0.075 (0.072, 0.078)

AUC, area under the receiver operating curve.
Null model Brier score=0.089.

Table 3
Discrimination and calibration of algorithms in holdout set, n=547

Metric	Stochastic gradient boosting	Random forest	Support vector machine	Neural network	Penalized logistic regression
AUC	0.81	0.73	0.58	0.80	0.81
Intercept	−0.001	0.17	0.23	0.10	−0.02
Slope	1.05	0.58	1.07	1.07	1.002
Brier	0.076	0.083	0.084	0.076	0.076

AUC, area under the receiver operating curve.
Null model Brier score=0.089.

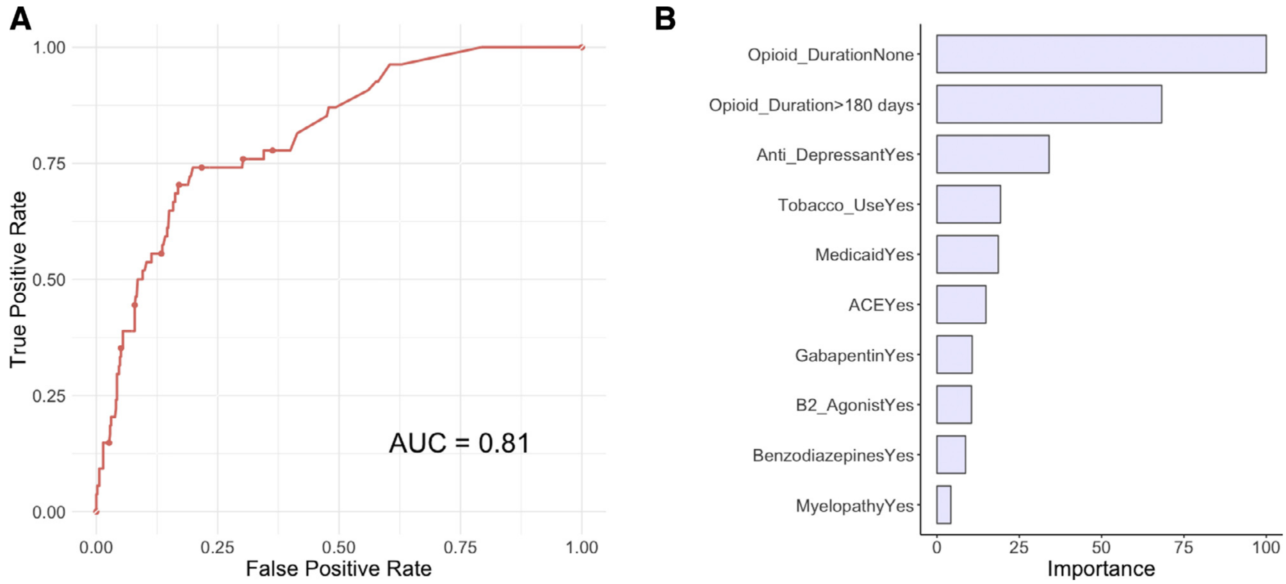

Fig. 1. (A) C-statistic (area under the receiver operating curve) for stochastic gradient boosting algorithm in the testing set. (B) Global variable importance for prediction of opioid dependence. AUC, area under receiver operating curve.

patients. In addition, the full algorithm showed greater net benefit than one based on preoperative opioid prescription alone (Fig. 2).

Model explanations

An example of explanation of the stochastic gradient boosting model at the individual patient level is shown in Figure 3. To illustrate, we consider the case of a female patient undergoing a single level ACDF with continuous preoperative opioid prescription for greater than 180 days before surgery and concurrent antidepressant use. The stochastic gradient boosting algorithm predicted a probability of 0.21 for sustained postoperative opioid prescription in this patient. For this patient, continuous preoperative opioid prescription and antidepressant use resulted in an adjustment that favored sustained postoperative opioid prescription. However, no tobacco use, non-Medicaid and non-Medicare insurance, female sex, single-level ACDF, and lack of other preoperative medication usage (gabapentin, beta-2-agonists, and angiotensin converting enzyme inhibitors) resulted in an adjustment that reduced the estimation

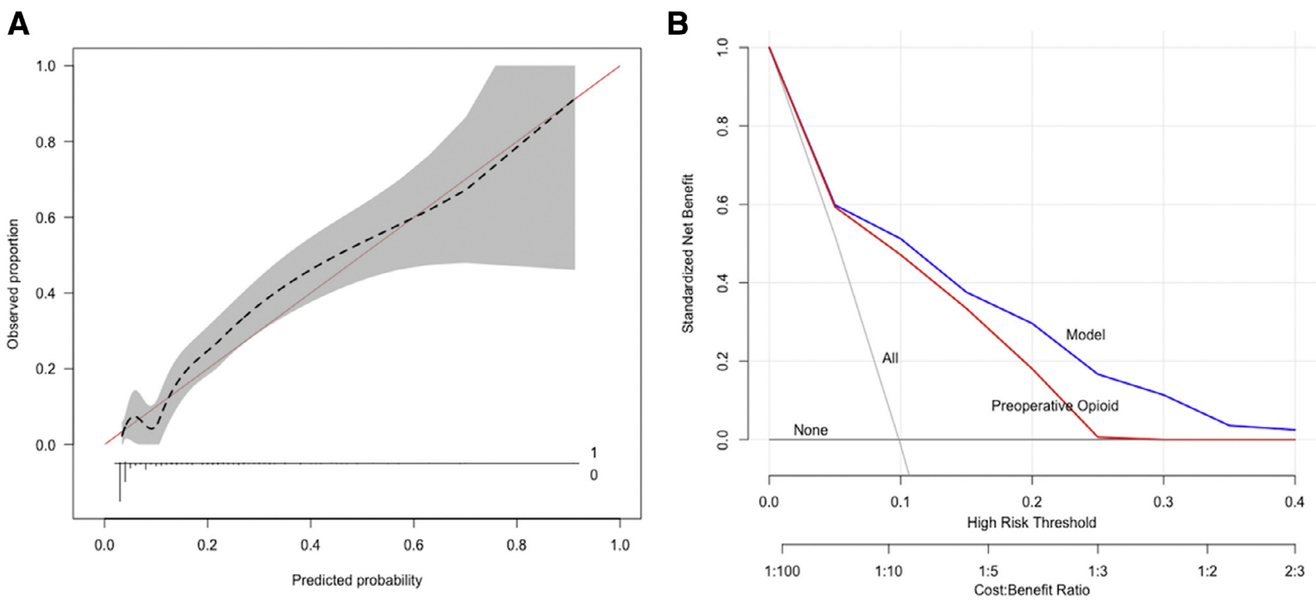

Fig. 2. (A) Calibration plot for stochastic gradient boosting algorithm. (B) Decision curve analysis with standardized net benefit of the stochastic gradient boosting algorithm relative to default strategies of changing management for no patients, for all patients, and for patients on the basis of preoperative opioid dependence alone.

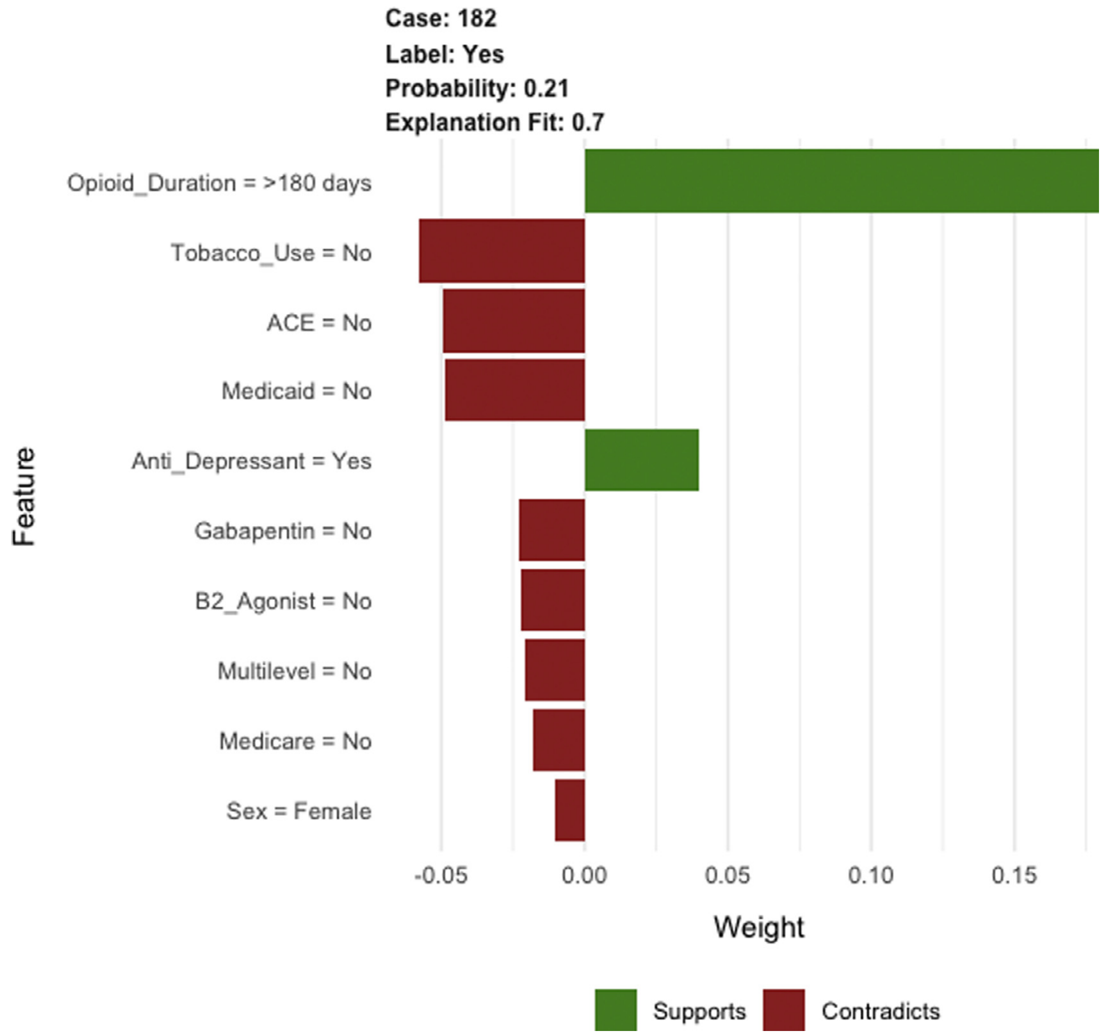

Fig. 3. Example of individual patient-specific explanation for prediction generated by the stochastic gradient boosting model

of the likelihood for postoperative opioid prescription. The final model is available here: https://sorg-apps.shinyapps.io/acdfopioid/

Discussion

In this study, one-tenth of patients undergoing ACDF demonstrated sustained opioid prescription after surgery. The prospect of sustained opioid prescription following surgery appeared to bedriven by a number of factors, including preoperative opioid prescription, antidepressant use, tobacco use, and Medicaid insurance status. Among the algorithms investigated in this analysis, the stochastic gradient boosting algorithm demonstrated the best discrimination, calibration, and overall performance in the independent testing set. Furthermore, predictions made by the algorithm were able to provide increased transparency of the relationships between the inputs and outputs of this machine learning model.

The factors identified in this analysis concur with prior studies of opioid use after spine surgery. Jain et al. studied patients undergoing cervical fusion and identified preoperative opioid exposure for greater than 6 months before surgery as the strongest risk factor for long-term postoperative use [11]. Other studies of the patients undergoing cervical and lumbar spine surgery for degenerative disease in the Humana database similarly linked preoperative opioid use to long-term dependence [12,33,34]. The duration of preoperative opioid use was previously validated as a risk factor for sustained postoperative use by Anderson et al. in a workers compensation population in Ohio and by Schoenfeld et al. using the TRICARE insurance claims [9,35]. Jain et al. also highlighted depression and tobacco use as characteristics associated with an increased risk of sustained postsurgical opioid use [11,12]. In a separate investigation, O'Connell et al. reported that preoperative depression increased cumulative opioid use and decreased the likelihood of postoperative opioid cessation following lumbar fusion procedures from the MarketScan database [36].

In contrast to prior work utilizing large administrative and insurance claims data, the present study relied on institutional records which allowed for a broader consideration of Medicare and uninsured patients. Of note, this allowed for the inclusion of Medicaid insurance status as a predictor of sustained postoperative opioid prescription, as supported by prior studies [19,37]. Review of institutional electronic pharmacy records also allowed for adjustment regarding other preoperative medications (benzodiazepines, serotonin-reuptake inhibitors, angiotensin-converting enzyme inhibitors, gabapentin) as mediators of sustained opioid prescription [15,18,38].

Nonetheless, this work is limited by the following considerations. This study relies on retrospective data from five medical centers affiliated with one health-care corporation. Clustering at the level of the providers and hospitals may be present as a result. Within the literature, there are heterogeneous criteria for the determination of sustained opioid use. Although the criteria used to define such use in this study is in line with prior work, the categorization remains subjective to some extent and findings may not be entirely translatable depending on how patients are designated as *sustained users*. For example, we do not possess sufficient clinical information to characterize chemical dependence or addiction. Urine drug tests to verify and distinguish opioid use from opioid prescription were not available in this analysis. The algorithms developed here remain to be validated in independent external samples, ideally in prospective study design. Preoperative opioid dose in oral morphine equivalents was not reliably available caused by changes in the electronic health record systems over the course of the time period under consideration. Furthermore, descriptive characterization of the changes in opioid dose and frequency before and after surgery as well as over time after surgery were not included in this analysis. This is an area for future work as in patients who are opioid dependent before surgery, the prediction of expected postoperative opioid dose in oral morphine milligram equivalents may be useful for preoperative planning. Though neighborhood socioeconomic characteristics were assessed by zip code of residence, more granular self-reported patient metrics such as income level and unemployment status could not be considered here. Similarly, patient reported outcomes measures as well as the rationale for the types of opioids and manner in which they were prescribed cannot be reliably determined given the data presently available. It is important to note that there is likely provider level variance in willingness to continue prescribing postoperative opioids. Furthermore, this study assumes patients were adhering to their prescriptions as directed by the surgeon, or other health-care provider, and cannot address illicit opioid use or opioid abuse.

Despite these limitations, this study offers the first predictive algorithm for opioid prescription in cervical spine surgery. The conventional drawbacks of machine learning models include lack of explanation and lack of accessibility in a manner similar to traditional risk scores or nomograms [39]. The openly available web application presented here, combined with the detailed explanations of the model predictions, mitigate these challenges, and potentiate daily application of these utilities in clinical practice. Clinicians could use these algorithms to screen patients preoperatively and identify high-risk candidates who might benefit from multidisciplinary interventions through social work, mental health, and pain medicine. Caution is warranted as these algorithms remain to be externally validated but the side-by-side explanations of the predictions generated by the machine learning algorithms allow clinicians to judge the predictions in the context of their own clinical expertise. Previous studies have shown that a combination of clinician experience and artificial intelligence algorithms results in improved performance [40].

Conclusions

In this investigation, one-tenth of patients undergoing ACDF demonstrated sustained prescription opioid prescription following surgery. Machine learning algorithms could be used to stratify patient risk and tailor preoperative management (eg, mental health/social work consultation and/or comanagement with pain medicine service) to reduce the potential for long-term opioid use in this population.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2019.01.009.

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