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A Risk Calculator for the Prediction of C5 Nerve Root Palsy After Instrumented Cervical Fusion

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Abstract

BACKGROUND: C5 palsy is a common postoperative complication after cervical fusion and is associated with increased health care costs and diminished quality of life. Accurate prediction of C5 palsy may allow for appropriate preoperative counseling and risk stratification. We primarily aim to develop an algorithm for the prediction of C5 palsy after instrumented cervical fusion and identify novel features for risk prediction. Additionally, we aim to build a risk calculator to provide the risk of C5 palsy.

METHODS: We identified adult patients who underwent instrumented cervical fusion at a tertiary care medical center between 2013 and 2020. The primary outcome was postoperative C5 palsy. We developed ensemble machine learning, standard machine learning, and logistic regression models predicting the risk of C5 palsy–assessing discrimination and calibration. Additionally, a web-based risk calculator was built with the best-performing model.

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CRediT AUTHORSHIP CONTRIBUTION STATEMENT

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RESULTS: A total of 1024 patients were included, with 52 cases of C5 palsy. The ensemble model was well-calibrated and demonstrated excellent discrimination with an area under the receiver-operating characteristic curve of 0.773. The following features were the most important for ensemble model performance: diabetes mellitus, bipolar disorder, C5 or C4 level, surgical approach, preoperative non-motor neurologic symptoms, degenerative disease, number of fused levels, and age.

CONCLUSIONS: We report a risk calculator that generates patient-specific C5 palsy risk after instrumented cervical fusion. Individualized risk prediction for patients may facilitate improved preoperative patient counseling and risk stratification as well as potential intraoperative mitigating measures. This tool may also aid in addressing potentially modifiable risk factors such as diabetes and obesity.

Keywords

C5 palsy; Cervical fusion; Instrumentation; Machine learning; Risk calculator

INTRODUCTION

Instrumented cervical fusion is often utilized for the treatment of degenerative disease of the cervical spine as well as trauma, infection, and deformity. The number of cervical fusions has been increasing in recent years.[1,2] Postoperative C5 palsy is a common complication after cervical spine surgery, occurring in 4%–24% of patients.[3–10] Presenting as unilateral or bilateral weakness of the deltoid and/or biceps brachii muscles, postoperative C5 palsy usually develops within the first 2 weeks after surgery.[4,5] While C5 palsy is typically a transient complication that resolves within 6 months, 15%–19% of patients may have residual deficits. A source of alarm and frustration for patients, postoperative C5 palsy is associated with a decreased quality of life.[11] Furthermore, the development of C5 palsy is associated with higher hospitalization-related and rehabilitation costs compared to patients who do not develop C5 palsy after cervical spine surgery.[11,12] Accurate prediction of C5 palsy risk may allow for preoperative patient counseling, mitigating measures, and optimization of potentially modifiable patient factors.

While there have been numerous studies identifying independent risk factors for C5 palsy, predictive models for the development of C5 palsy after cervical fusion remain scarce. Most reported studies employ multivariable logistic regression or meta-analyses.[4,5,13–20] Due to its ability to uncover complex factor-factor interactions, machine learning (ML) methodology has become increasingly popular and has been used to predict multiple clinical outcomes for a wide range of pathologies including degenerative disease, spinal infection, and spinal metastasis.[21–27] To our knowledge, there has been no ML algorithm reported for the prediction of C5 palsy after instrumented cervical fusion. With an institutional cohort, we aim to build an ML algorithm for the prediction of C5 palsy after instrumented cervical fusion. We aim to identify the features most important to the performance of this model. Finally, we aim to develop a web-based risk calculator that provides a patient-specific probability of postoperative C5 palsy risk.

METHODS

Study Design and Subjects

Our institutional review board approved a waiver of consent for this retrospective study. All patients ≥18 years of age who underwent instrumented cervical spinal fusion at our tertiary-care medical center between 2013 and 2020 were included. Patients who underwent revision of a prior instrumented fusion were excluded if new instrumentation was not placed. The cohort was identified by querying surgeon schedules and operative notes.

Outcome and Other Variables

The primary outcome measure was postoperative C5 palsy, defined as a postoperative decline in standard manual motor testing of the deltoid and/or biceps brachii muscles by at least one grade on the manual motor score without deteriorating myelopathic symptoms.[3,17,28,29] We extracted the following explanatory factors from the review of operative notes: performed surgical procedure, number of fused levels, and surgical indication. We extracted the following patient factors from the review of clinical notes: medical and psychiatric comorbidities, preoperative neurologic symptoms, medication history, body mass index (BMI), and smoking/drug history. We also extracted preoperative laboratory values, (e.g. white blood cell count, hemoglobin) if obtained within 30 days prior to index cervical fusion.

Continuous variables were included in this analysis if fewer than 30% of values were missing. Multiple imputations were performed with the missForest methodology.[30] The rates of missing data were 4.5% for white blood cell count, 5.0% for hemoglobin, and 28.4% for BMI.

Model Development and Evaluation

The cohort was divided into a training cohort (comprising 80% of the study population) and a hold-out testing cohort (comprising 20% of the study population). An ML-based ensemble prediction model for C5 palsy after instrumented cervical fusion was developed using AutoPrognosis. Utilizing the training cohort, Auto-Prognosis employs a Bayesian optimization algorithm to design a prognostic ensemble model comprised of a weighted combination of multiple ML pipelines.[31]

Using the training cohort, we built standard ML benchmark models spanning different classes of ML modeling approaches. Random forest is a tree-based classifier while AdaBoost, gradient boosting machines, and XGBoost are boosting classifiers.[32–35] We additionally built a model employing traditional multivariable logistic regression. We used the *scikit-learn* Python library to develop logistic regression, random forest, AdaBoost, and gradient boosting machines.[36] XGBoost models were developed using the *xgboost* Python library.[35] We used 20% of the training cohort for hyperparameter tuning. The hyperparameters of each benchmark model were selected via grid search. For random forest, AdaBoost, and gradient boosting models, the number and trees are chosen from the set {50, 100, 200, 300}. For XGBoost, the number of trees and the maximum depth of each tree were selected from sets {50, 100, 200, 300} and {2, 3, 4, 5}, respectively.

Performance Metrics

We employed five-fold stratified cross-validation–where the study population is split into a training cohort and a hold-out testing cohort–to evaluate discrimination and calibration for prognostic models.

In this study population, discrimination is a measure of how well a model distinguishes patients who develops C5 palsy from those who did not. We assessed discrimination with the area under the receiver operating characteristic curve (AUROC). AUROC represents the probability that a randomly selected patient who developed C5 palsy was assigned a higher risk by the model than a patient who did not. An AUROC of 0.5 indicates random prediction; a value between 0.7 and 0.9 indicates moderate-to-high accuracy.[37,38] Calibration is a measure of the agreement between the model's predictions and the observed outcomes in the study population. A calibration slope measures the spread of a model prediction; a slope of 1 indicates perfect spread. Calibration intercept is a measure of whether a model overestimates or underestimates the probability of an outcome. A perfect model has a calibration intercept of 0.[24,39]

The area under the precision-recall curve (AUPRC) is an additional measure of discrimination that is useful when assessing the performance of a model in a dataset in which negative cases outnumber positive cases. Constructed by plotting positive predictive value (precision) versus sensitivity (recall), the precision-recall curve depicts the ability of the model to correctly identify positive cases; it ignores true negatives, which is the dominant group in an imbalanced dataset.[40,41] The baseline AUPRC is the proportion of true positive cases; this is in contrast to the baseline AUROC of 0.5. The random prediction will result in the baseline AUPRC. A higher AUPRC value compared to the random prediction value means that the model identifies positive cases well.

The best-performing model in the testing cohort was deployed as a web application with Heroku (San Francisco, California, USA).

RESULTS

Cohort Characteristics and Demographics

A total of 1024 patients met the inclusion criteria for this study. The median age of the cohort was 60 years; 436 (42.6%) patients were female. The most common medical comorbidity in this cohort was diabetes mellitus (19.8%), followed by hypothyroidism (14.1%). The median Charlson comorbidity index was 2. Three hundred and forty-eight patients (34.0%) had a positive smoking history, and 8 had a history of intravenous drug use. Two hundred and sixty-one patients (25.5%) who had depression and/or anxiety, and 13 (1.3%) who had bipolar disorder. Eight hundred and thirty-seven patients (81.7%) had preoperative non-motor neurologic symptoms. Cohort demographics and preoperative characteristics are detailed in Table 1.

Five hundred patients (48.8%) underwent isolated posterior fusion and 491 (47.9%) underwent isolated anterior fusion. A staged approach was performed for 33 patients (3.2%).

Corpectomy was performed in 113 patients (11.0%), and an interbody device was placed in 352 patients (34.4%). The most common indication for instrumented cervical fusion in this cohort was degenerative disease (48.1%), followed by herniated nucleus pulposus (29.8%) and cervical trauma (11.3%). Forty-eight cases (4.7%) were revision procedures. Fusion for a spinal fracture was performed in 33 patients (3.2%). Fifty-two patients (5.1%) developed postoperative C5 palsy. The time to C5 palsy from index fusion ranged from 0 to 15 days. A plurality of C5 palsy cases (36.5%) were identified on postoperative day 1. Eight cases were present in the recovery unit on postoperative day 0, 9 were identified on postoperative day 2, and 16 were identified on post-operative day 3 or later. Surgical characteristics and outcomes are detailed in Table 2.

Model Performances

Ensemble ML and logistic regression models were used to build predictive algorithms for postoperative C5 palsy. Additionally, 4 standard ML models were built using XGBoost, AdaBoost, gradient boosting, and random forest. The ensemble model demonstrates high discrimination with an AUROC of 0.773 ± 0.050 and an AUPRC of 0.188 ± 0.050 (Table 3). The receiver-operating characteristic and precision-recall curves for the ensemble model are depicted in Figures 1 and 2, respectively. The model was well-calibrated with a calibration slope of 0.918 and a calibration intercept of −0.022. While the logistic regression model displays similar discrimination (AUROC 0.747 ± 0.063, AUPRC 0.154 ± 0.060), it is very poorly calibrated with a calibration slope of 119.08 and a calibration intercept of −6.058.

Feature Importance

To obtain feature importance for each model, we applied a partial dependence function on the cross-validation fold in which the performance of the ensemble model was the greatest.[34] The importance of each feature to the performance of the ensemble model is displayed in Table 4. The binary features most important for the ensemble model include diabetes mellitus, bipolar disorder, surgical level of C5 or C4, surgical approach, preoperative presence of non-motor neurologic symptoms, intravenous drug use, and a surgical indication of degenerative disease. The most important continuous features are the number of fused levels, age, and BMI.

Risk Calculator

The ensemble algorithm was used to build a web-based risk calculator that is available as a tool for clinicians. The web application can be accessed at: https://risk-calculator-c5-palsy.herokuapp.com/. Users may input values for each explanatory feature and observe the updated risk for C5 palsy.

DISCUSSION

Initially reported in the context of ossification of the posterior longitudinal ligament and cervical laminoplasty, C5 palsy is a well-documented complication of cervical spine surgery for a wide range of indications.[5,18,42] Although C5 palsy is usually self-limited, patients who develop this complication have a reduced capacity for activities of daily living and report worse outcomes as well as increased costs of hospitalization and rehabilitation.[5,11,12]

While a rapid and transient ischemia-reperfusion injury is thought to be the molecular pathophysiology underlying C5 palsy, the intraoperative inciting event remains unclear.[3,43,44] For many years, it was hypothesized that posterior migration of the spinal cord immediately after posterior decompression causes traction of the anatomically shorter C5 nerve root through tethering at the uncovertebral joint and/or foraminal ligaments.[3,14,17,45–47] Recent studies, however, have not determined spinal cord float-back to be a predictor of C5 palsy. In cases of anterior decompression, dural expansion after decompression may also cause traction of the C5 nerve roots.[48,49] Other proposed mechanisms include thermal injury secondary to high-speed burring, preoperative malrotation of the spinal cord, and shoulder depression from taping during positioning.[50–52] It is likely that the clinical entity of C5 palsy may result from a combination of the aforementioned mechanisms.[53] Perhaps due to the many mechanisms potentially responsible for C5 palsy, there have been few independent risk factors consistently identified for the development of this complication.[53] The few models built for preoperative prediction of C5 palsy rely on the measurement of C4-C5 foraminal width on computed tomography (CT).[13,14,54] As CT is not otherwise indicated for most degenerative spinal pathology, routine preoperative CT studies would increase health care costs and subject the patient to otherwise unnecessary additional radiation. Furthermore, there is no uniform definition of foraminal stenosis used in these algorithms.

With a cohort of 1024 consecutive patients from a single institution, we report a model that predicts postoperative C5 palsy after instrumented cervical fusion. The ensemble model displays high discrimination with an AUROC of 0.773 and is dramatically better calibrated than the logistic regression model. The reported ensemble model thus not only effectively stratifies patients with and without C5 palsy but also captures an accurate estimation of risk. This represents the first ML model for the prediction of C5 palsy after instrumented cervical fusion and exceeds the reported discrimination values of multivariable logistic regression algorithms predicting C5 palsy.[13,14,54] We included only preoperative features in the model to facilitate the prediction of C5 palsy prior to surgery. Additionally, we identified the patient features important to ensemble model performance.

We identify diabetes mellitus as the most important feature for the predictive performance of the ensemble model. Diabetes is an established risk factor for multiple adverse outcomes after spinal fusion, including surgical site infection, re-operation, major complications, and readmission.[41,55–60] While diabetes has not been specifically implicated in C5 palsy risk after cervical fusion, it has been linked to neurologic dysfunction in patients with cervical myelopathy.[5,9,19] Through oxidative stress and microvascular disease, diabetes is a cause of focal and diffuse neuropathies involving both the central and peripheral nervous systems.[61,62] Notably, diabetes represents a potentially modifiable risk factor that can be preoperatively optimized for elective cases. BMI is another modifiable patient feature that we identify as important to the ensemble model. Like diabetes, elevated BMI is associated with adverse outcomes after cervical fusion but has not been shown to be associated with the development of postoperative C5 palsy.[53,60,63,64] Increased BMI is associated with insulin resistance, which is a risk factor for neurophysiological changes in the central and peripheral nervous system even in the absence of overt diabetes.[62,65] We additionally find that patient age is an important feature for model performance. Elevated age has been shown

to be associated with C5 palsy.[5,19,44] It has been hypothesized that advanced age may be associated with decreased elasticity of the C5 nerve root, making older patients more susceptible to developing postoperative C5 palsy.[19]

In addition to medical comorbidities, we show that psychiatric comorbidities influence model performance. Bipolar disorder markedly influences the risk of developing C5 palsy after instrumented cervical fusion. Psychiatric comorbidities have been consistently shown to be risk factors for complications following spine surgery, with higher health care costs and patient dissatisfaction.[66–68] Although preoperative optimization of psychiatric comorbidities may reduce the risk of postoperative C5 palsy as well as improve patient well-being, the extent to which diagnosed chronic mental illness can be adequately preoperatively optimized is limited–particularly in urgent or emergent cases (e.g. trauma, malignancy).

Preoperative symptoms were determined to be important for ensemble model performance. The presence of non-motor neurologic symptoms (e.g. radicular pain, bladder/bowel dysfunction, paresthesias) is the seventh most important feature of the ensemble model. Preoperative C5 root compression with accompanying nerve root symptoms has been shown to be associated with the development of C5 palsy after cervical decompression.[15,42]

Surgery-specific characteristics played an important role in the predictive performance of the ensemble model. A surgical indication of degenerative disease was the 10th most important feature of the ensemble model. Stenosis with or without associated myelopathy from long-standing degenerative disease has been reported as a risk factor for the development of C5 palsy after both anterior and posterior cervical decompression, potentially due to reperfusion injury of the spinal cord.[8,15,16,51] Furthermore, these patients may require wider decompression, a risk factor for C5 palsy.[17,69] Similarly, the number of fused levels was the most important continuous feature for the model. The number of decompressed or fused levels has been shown to be associated with C5 palsy in multiple studies.[4,5,44] In addition to the number of vertebral levels operated on, the specific levels matter. Involvement of the C5 level and/or the C4 level is the third and sixth most important features, respectively, for ensemble model performance. This finding lends credence to the theory that an intraoperative local insult plays a role in the development of postoperative C5 palsy. We also find that surgical approach is important for model performance. It has been shown in numerous studies that posterior decompression with or without instrumentation increases the risk of C5 palsy.[15,70–73] Iatrogenic C5 foraminal stenosis from extensive reduction is one proposed mechanism for this.[70,72,73]

This study has limitations, the first of which is its retrospective design. Selection bias likely exists in this cohort as it is comprised of patients for whom it was perceived that the benefits of instrumented cervical fusion would outweigh the risks. The cohort was comprised of patients from multiple attending surgeons at a single institution who may have individual variation in surgical technique, positioning, and perioperative protocols that may influence the risk of developing postoperative C5 palsy. Similarly, there is heterogeneity in the experience of trainees who were involved in these procedures. Additionally, it was not standard practice to perform electrodiagnostic evaluation to differentiate delayed C5 palsy from brachial plexopathy. Although the rate of brachial plexopathy after cervical

spine surgery is exceedingly rare – 0.07% in a recent multicenter study–this represents a potential limitation.[74] Finally, there is a concern about overfitting in any predictive model. In overfitting, the algorithm performs well on the training cohort but poorly on new cohorts. We attempt to protect against overfitting with our model development and validation strategy; however, future validation on external cohorts is necessary to further assess the generalizability of the model.

CONCLUSIONS

With an institutional cohort of 1024 consecutive patients, we report a well-calibrated ensemble model that predicts the development of C5 palsy after instrumented cervical fusion. To our knowledge, this represents the first ML model predicting C5 palsy after cervical fusion. In order to facilitate the use of this tool in the outpatient setting prior to surgery, we only include preoperative features that do not require any additional radiographic measurements. By providing an accurate estimate of C5 palsy risk, this model can facilitate improved preoperative patient counseling and shared decision-making. The features most important to model performance include potentially modifiable factors such as diabetes and BMI. To encourage direct use of this algorithm by health care providers, we incorporated this model into a web-based digital interface. By providing an accurate estimation of C5 palsy risk, we hope to better allow physicians and patients to accurately gauge the risks and benefits of instrumented cervical fusion. For patients with a high predicted risk of C5 palsy, potential intraoperative measures such as continuous neurophysiological monitoring, prophylactic C5 foraminotomy, or perioperative steroids may be implemented to mitigate the risk of postoperative C5 palsy.[14,42,75–77]

Conflict of interest statement:

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Abbreviations and Acronyms

AUROC	Area under the receiver operating characteristic curve
AUPRC	Area under the precision-recall curve
BMI	Body mass index
ML	Machine learning

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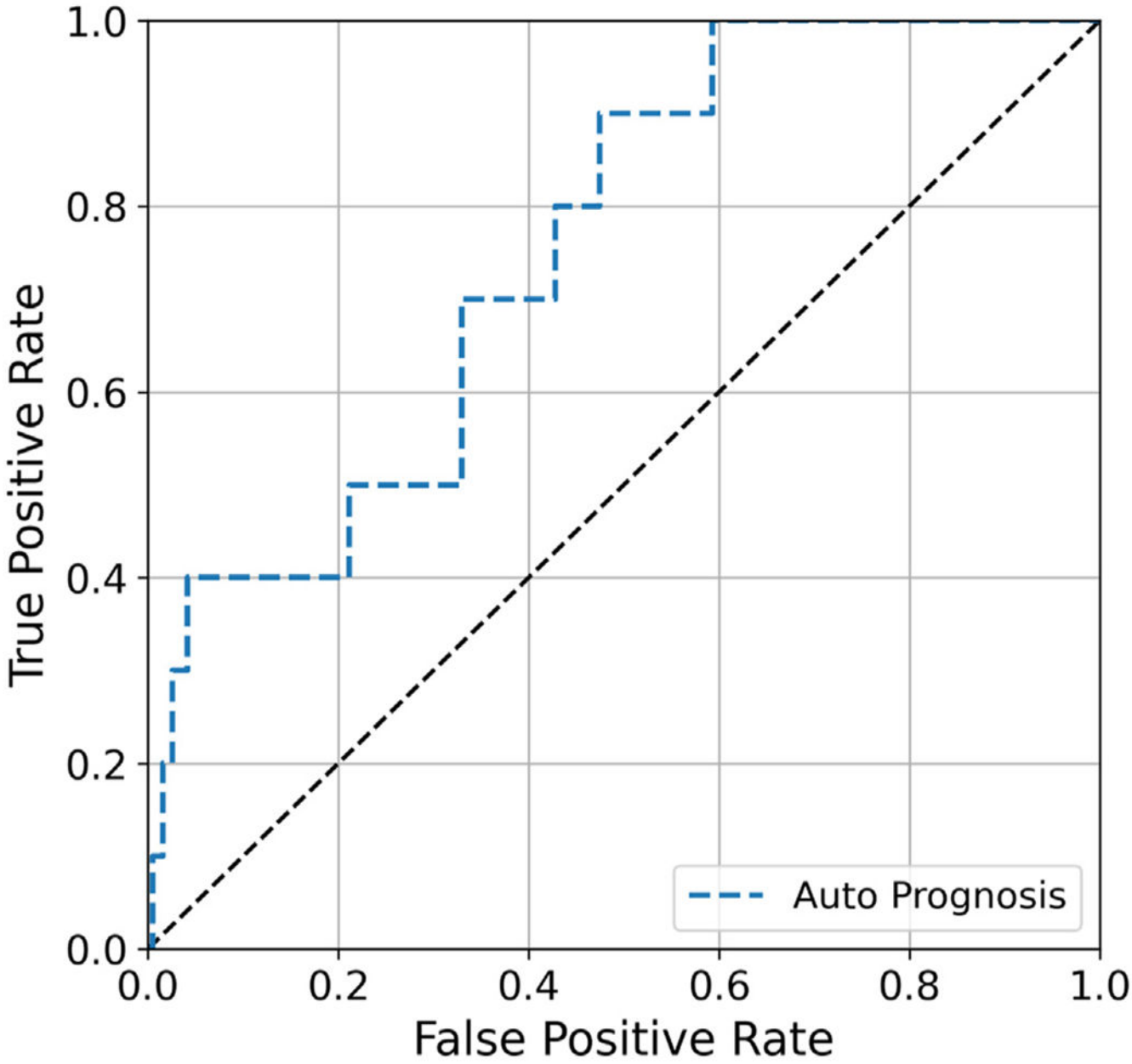

Figure 1.
Receiver operating characteristic curve for the ensemble model predicting postoperative C5 palsy.

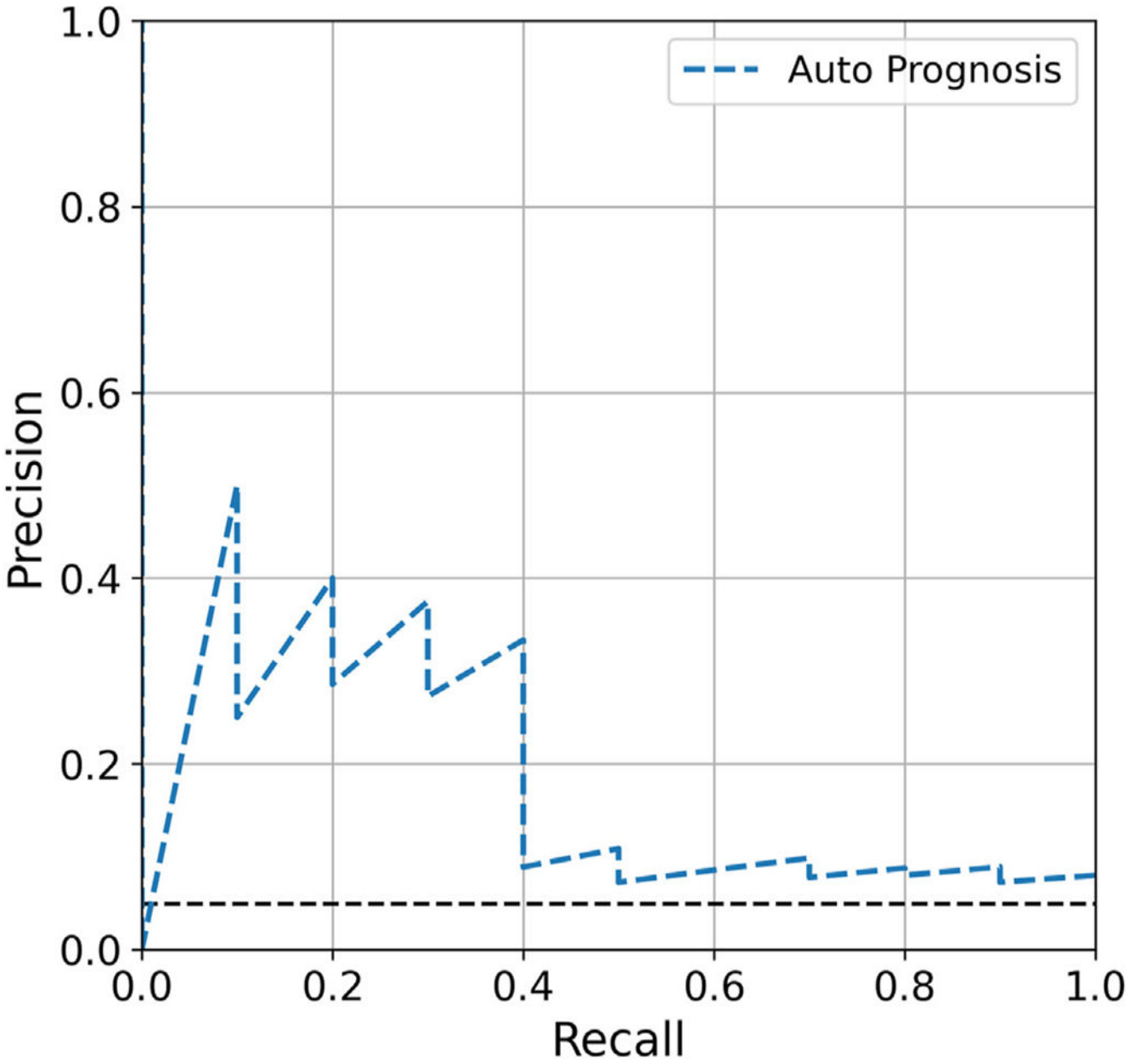

Figure 2.
Precision-recall curve for the ensemble model predicting postoperative C5 palsy.

Table 1.

Cohort Demographics and Preoperative Characteristics

Variable	All Patients (n = 1024) Median (IQR)
Age (years)	60.4 (50.3, 69.6)
Body mass index (kg/m^2) *	26.9 (24.6, 29.2)
Preoperative white blood cell count (1000/mL) *	6.9 (5.6, 8.4)
Preoperative hemoglobin (g/dL) *	13.7 (12.7, 14.8)
Charlson comorbidity index	2 (1, 3)
	Number (%)
Female	436 (42.6)
Medical comorbidities	
Diabetes mellitus	203 (19.8)
Hypothyroidism	144 (14.1)
Immunosuppressed state	107 (10.4)
Malignancy	70 (6.8)
Dialysis dependence	18 (1.8)
Psychiatric comorbidities	
Depression and/or anxiety	261 (25.5)
Bipolar disorder	13 (1.3)
Smoking	348 (34.0)
Intravenous drug use	8 (0.8)
Pre-operative symptoms	
Non-motor neurologic deficit	837 (81.7)
Motor weakness	499 (48.7)
Preoperative medication use	
Opioid	376 (36.7)
Antidepressant	212 (20.7)
Benzodiazepine	178 (17.4)

IQR, Interquartile range; kg, kilograms; m, meter; g, gram; mL, milliliter; dL, deciliter.

*Body mass index, white blood cell count, and hemoglobin had missing values imputed.

Table 2.

Surgical Characteristics and Outcomes

Feature	All Patients(n = 1024) Median (IQR)
Number of fused levels	2 (1, 3)
	Number (%)
Surgical approach	
Isolated posterior fusion	500 (48.8)
Isolated anterior fusion	491 (47.9)
Staged anterior/posterior approach	33 (3.2)
Surgical indications	
Degenerative disease	493 (48.1)
Myelopathy	398 (77.1)
Stenosis	41 (7.9)
Spondylolisthesis	23 (2.2)
Herniated nucleus pulposus	305 (29.8)
Trauma	116 (11.3)
Malignancy	53 (5.2)
Deformity	24 (2.3)
Pseudarthrosis	16 (1.6)
Infection	11 (1.1)
Other	6 (0.6)
Interbody device	352 (34.4)
Corpectomy	113 (11.0)
Revision	48 (4.7)
Fixation for spinal fracture	33 (3.2)
C5 palsy	52 (5.1)
Postoperative day 0	8 (15.4)
Postoperative day 1	19 (36.5)

Feature	All Patients(n = 1024)
	Median (IQR)
Postoperative day 2	9 (17.3)
Postoperative day 3 or later	16 (30.8)
	Median (IQR)
Time to C5 palsy (days)	1 (1, 3)
Hospitalization length (days)	3 (1, 5)

IQR, Interquartile range.

Table 3.

Discrimination of Machine Learning and Logistic Regression Models

Model	AUROC	AUPRC
Ensemble	0.773 ± 0.050	0.188 ± 0.050
XGBoost	0.750 ± 0.063	0.141 ± 0.055
Logistic regression	0.747 ± 0.063	0.154 ± 0.060
Gradient boosting	0.736 ± 0.080	0.127 ± 0.053
Random forest	0.674 ± 0.056	0.104 ± 0.023
AdaBoost	0.669 ± 0.057	0.091 ± 0.026

AUROC, area under the receiver operating characteristic curve, AUPRC, area under the precision-recall curve.

Table 4.

Feature Importance for Ensemble Model Performance

Feature	Rank in Ensemble	Change to Risk Prediction
Binary features		
Diabetes mellitus	1	0.0340
Bipolar disorder	2	0.0161
C5 level	3	0.0146
Anterior approach	4	0.0139
Posterior approach	5	0.0137
C4 level	6	0.0132
Non-motor neurologic symptoms	7	0.0132
Staged approach	8	0.0132
Intravenous drug use	9	0.0129
Degenerative disease	10	0.0127
Continuous features		
Number of fused levels	1	0.0120
Age	2	0.0119
Body mass index	3	0.0062
Preoperative WBC count	4	0.0048
Preoperative hemoglobin	5	0.0021

WBC, White blood cells.