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Investigating risk factors and predicting complications in deep brain stimulation surgery with machine learning algorithms

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ABSTRACT

Background: Deep brain stimulation (DBS) surgery is an option for patients experiencing medically resistant neurological symptoms. DBS complications are rare; finding significant predictors requires a large number of surgeries. Machine learning algorithms may be used to effectively predict these outcomes. The aims of this study were to (1) investigate preoperative clinical risk factors, and (2) build machine learning models to predict adverse outcomes.

Methods: This multicenter registry collected clinical and demographic characteristics of patients undergoing DBS surgery (n=501) and tabulated occurrence of complications. Logistic regression was used to evaluate risk factors. Supervised learning algorithms were trained and validated on 70% and 30%, respectively, of both oversampled and original registry data. Performance was evaluated using area under the receiver operating characteristics curve (AUC), sensitivity, specificity and accuracy.

Results: Logistic regression showed that the risk of complication was related to the operating institution in which the surgery was performed (OR=0.44, confidence interval [CI]=0.25-0.78), BMI (OR=0.94,CI=0.89-0.99) and diabetes (OR=2.33,CI=1.18-4.60). Patients with diabetes were almost three times more likely to return to the operating room (OR=2.78,CI=1.31-5.88). Patients with a history of smoking were four times more likely to experience postoperative infection (OR=4.20,CI=1.21-14.61). Supervised learning algorithms demonstrated high discrimination performance when predicting any complication (AUC=0.86), a complication within 12 months (AUC=0.91), return to the operating room (AUC=0.88) and infection (AUC=0.97). Age, BMI, procedure side, gender and a diagnosis of Parkinson’s disease were influential features.

Conclusions: Multiple significant complication risk factors were identified and supervised learning algorithms effectively predicted adverse outcomes in DBS surgery.
INTRODUCTION

The primary aim of this study was to look at which preoperative clinical factors were related to complications that develop in deep brain stimulation (DBS) therapy. DBS is a safe, effective and common surgical intervention for a range of neurological disorders including Parkinson’s disease and essential tremor. Through electrodes implanted in the brain, DBS therapy stimulates deep subcortical brain structures, including the subthalamic nucleus (STN), the ventral intermedius nucleus (VIM) and the globus pallidus (GPI) to alleviate neurological symptoms like tremor, motor fluctuations, and rigidity. It is a treatment modality that is considered when a patient’s symptoms have not been satisfactorily alleviated by medical management.

DBS therapy requires an initial electrode implantation operation and subsequent surgery to place device generators. Potential complications arising from DBS surgery include infection, intracerebral hemorrhage, seizures and hardware failure, which can lead to unplanned return to the operating room. Post-operative readmission rates range from 1.9% (30-day) to 4.3% (90-day). Factors likely associated with complications include age, smoking history, obesity, diabetes, hypertension and facility surgical volume. Advanced age and hypertension have been associated with the risk of intracranial hemorrhage, and readmission after DBS surgery has been associated with preoperative coronary artery disease, obesity and a history of smoking. Further, there is a seasonal variation in DBS infection, often referred to as the July effect.

Integrating preoperative risk assessment into standard clinical care fosters a shared decision making process between the surgical team, the patient and clinical enablers. Performing pre-operative risk assessment for DBS procedures is challenging due to limited data suggesting the contributions of individual risk factors to post-operative complications. It is arguable that the literature surrounding DBS surgery risk remains inconclusive because the low frequency of complications limits the power and sensitivity of traditional statistical methods. To study this problem, a multi-institutional database of complications and risk factors was compiled, and a pilot study analysed it. Similar to the literature, the only relationship found was an association between smoking and infection risk. The standard statistical methods applied were ineffective at determining significant clinical risk factors related to complications, such as body mass index, diabetes, hypertension, smoking, and age. So, a different
approach to identifying relationships between complications and risk factors, involving the use of
machine learning, was designed and deployed.

Machine learning, a branch of artificial intelligence, represents a powerful set of technologies that
enable three main tasks: classification, regression and clustering. Supervised learning involves
training algorithms with datasets that contain labelled outcomes for each case. Supervised learning (i.e.,
classification and regression) uses input features (X) to predict a defined outcome (Y), while
unsupervised learning (i.e., clustering) involves analyzing input variables (X) to elucidate patterns and
structure in the data. Supervised learning algorithms can predict rare events such as surgical
complications and have the potential to improve patient risk stratification, clinical decision making,
informed consent and health service planning. Supervised learning has been used in DBS surgery
to predict clinical outcomes, surgical targets, side effects, discharge status and
neurophysiological detection of DBS structures.

Extreme gradient boosting machines (XGBM) are a type of supervised learning algorithm. It uses
decision tree-based learning and shows strong performance on a diverse array of problems. It operates
by strategically combining networks of sequential decision trees. Later decision tree models correct
inaccuracies in previous models to improve prediction performance. An XGBM model is comprised
of an ensemble of decision trees. The development of algorithms that incorporate gradient boosting has
produced highly robust regression and classification methods. XGBMs appear to have performed
well in various domains and have been shown to perform particularly well on datasets
characterized by class imbalance. Many supervised learning algorithms perform well as predictive
tools partly because they can estimate complex nonlinear relationships in high volume datasets using
weighted statistical functions in a way that cannot be perceived by linear models or clinicians.
Logistic regression is one such linear classification model. Two advantages it affords are that it is easily
interpretable, and it delivers measures of statistical significance.

Class imbalance describes a situation where the number of one event type (e.g., postoperative DBS
complications) is very low compared to another event type (e.g., no postoperative DBS complications)
A class is a subcategory within a variable in a dataset. For example, within a variable capturing data
on postoperative complications, one class may represent the complication state, while another class may
represent the no-complication state. Class imbalance essentially refers to differences in class probabilities\(^4^9\). Postoperative DBS complications are low probability events. There is a much higher probability that DBS patients will experience no postoperative complications. This imbalanced outcome probability is what is meant by researchers referring to imbalanced classes. Chawla (2010) states that a dataset is imbalanced if the classification categories are not equally represented\(^5^0\). The performance of some supervised learning algorithms is undermined by class imbalance, resulting in output classifications that default simply to the majority class\(^5^1-5^3\). However, class imbalance characterizes many real-world datasets from biomedicine\(^5^2\), to finance\(^5^4\), aviation\(^5^5\) and geoscience\(^5^6\). Class imbalance is one of the main barriers to effectively predicting postoperative complications in neurosurgery\(^1^8,1^9,2^4,3^1\).

Because the class imbalance problem is so prevalent\(^5^3\), much research in the fields of predictive analytics, data mining and machine learning has focused on developing and testing methods to effectively address it, at both the algorithm and data levels\(^4^9,5^1,5^2,5^7-5^9\). The Synthetic Minority Oversampling Technique (SMOTE) has emerged as one effective method of addressing the class imbalance issue at the data level\(^5^9\). It operates by creating additional synthetic cases based upon existing minority cases and the k-nearest neighbor algorithm. It balances the class distribution by synthesizing new additional minority class examples through a process of interpolating between multiple minority class examples that lie together in multidimensional space. In this way, SMOTE has been intentionally designed to avoid the predictive analytics problem of overfitting\(^5^3\). Another strength of employing the SMOTE method is that no cases in the dataset need to be excluded from the predictive analysis, which is particularly useful in neurosurgery where cases are not common and datasets are often not large (i.e., hundreds of cases rather than thousands). The application of SMOTE may effectively facilitate the prediction of DBS complications, which would be of substantial utility to clinicians.

This study sought to answer the following two research questions. Can multivariate logistic regression detect significant associations between preoperative variables and postoperative outcomes? Can DBS complications be accurately predicted by applying the XGBM algorithm and SMOTE?
METHOD

Subjects

This study was approved by Institutional Review Boards at each study site. Due to the retrospective nature of the study, the requirement for informed consent was waived. A combined registry was created comprising 501 adults who underwent initial DBS implantation surgeries between October 1997 and May 2018 at two private practices. Procedures included were performed by five neurosurgeons at two neurosurgical centers over a 22-year period. Patients underwent DBS implantation for Parkinson’s disease (n=348), essential tremor (n=129), dystonia (n=11) and other indications (n=13).

Surgical Technique

The general surgical technique was relatively similar among all surgeons. Primary surgeons at each institution each had >15 years of experience in DBS surgery. A frame-based approach was used in patients with DBS lead placement (unilateral or bilateral) using Medtronic 3389 or 3379 leads. Microelectrode recording was used in all cases. A single microelectrode was used to identify and confirm the target in all cases. The average number of microelectrode passes per lead was 1.4. Intraoperative imaging of lead location with cone beam CT was performed in some cases beginning in 2008. The majority of patients underwent intraoperative bipolar review of clinical efficacy and side effects in an “awake” state. Generator placement was staged one to two weeks after initial lead implantation. All patients underwent postoperative MRI and/or CT scans within a week of lead implantation.

Data

Pre-existing quality assurance databases of DBS patients and their outcomes from both research sites were combined. Additional retrospective data were collected from electronic medical records. Potential risk factors were recorded, including age, gender, BMI, clinical diagnosis, smoking history, immunosuppression, hypertension (medications taken within 90 days of surgery), diagnosis of diabetes mellitus, hypertension, surgical target (VIM, STN, GPi) and procedure side (left, right, bilateral).

Complication categories were intracranial hemorrhage, readmission, ischemic infarction, seizure, lead fracture, electrode migration, loose or flipping battery needing surgical revision, device
malfunction, return to the operating room and infection. An infection was defined as an event requiring surgical removal of hardware, regardless of the time after implantation. This included perioperative infections within 3 months of surgery, as well as delayed infection associated with hardware erosion or other systemic infections and infections after generator replacement surgery that could have been years later. Intracranial hemorrhage was defined as any form of new post-operative bleeding on radiology report, with or without neurological sequelae and not necessarily requiring surgical intervention. Return to the operating room included all surgeries that required a return to the operating room, regardless of time since lead implantation, for indications including haemorrhage, infection, erosion of hardware, fracture of hardware detected on imaging or as open circuit on programming, revision of lead location, revision of flipping or loose generator, or tight extension wires. Four primary outcomes were recorded for each patient: any postoperative complication, a complication within 12 months of surgery, return to the operating room and infection.

Analysis

Unilateral (n=151), simultaneous bilateral (n=296) and staged bilateral lead implantation (n=54) were counted each as a single case. Descriptive statistics, multivariate logistic regression and supervised learning model development were performed using Python 3.6.

**Neural network development for BMI data imputation**

Missing data can create problems for some supervised learning algorithms and may necessitate dropping entire cases. Further, missing data can adversely affect the validity of results \(^{61}\). Out of 501 cases, there were 51 missing BMI values. Given the scarce nature of DBS case data and the resources required to collect it, the research team was motivated to retain as many cases as possible for analysis. Data imputation addresses this issue and various methods can be used \(^{61-65}\). Four neural network regression models were developed to impute BMI for the cases with missing data. BMI values were imputed using all pre- and post-operative variables in the dataset. One neural network was selected for imputation regression because it demonstrated the best performance. Mean BMI before and after imputation did not differ significantly (27.57, SD=5.06 and 27.39, SD=5.98, respectively; p=0.58).

**Feature selection**
Three criteria were used when selecting input features for the models: (1) existing evidence in the literature suggesting a relationship between the feature and the outcome, (2) availability of the feature in the dataset; and (3) clinical expert approval that the feature under consideration was clinically related to the outcome variable.

**Multivariate logistic regression to detect associations**

Multivariate logistic regression was conducted using the statsmodels [53] and scikit-learn [54] packages. Multivariate model performance, odds ratios (OR) and confidence intervals (CI) were calculated for each risk factor. Features with negligible statistical contribution to multivariate models (z-score <0.02) were excluded and models were subsequently retrained.

**XGBM model development for postoperative complication prediction**

Multiple classifiers were tested and compared to predict postoperative complication outcomes, including logistic regression, random forests, decision trees and support vector machines. Algorithm performance statistics were compared using multiple metrics including area under the receiver operating characteristic curve (AUC), accuracy, sensitivity, specificity, positive predictive value and negative predictive value. XGBM was among the highest performing classifiers. Because of this and previous literature demonstrating strong performance on imbalanced datasets, multiple XGBM models were developed using the XGBoost package. For each of the four primary outcome variables, three XGBM models were created: one using the original dataset, one using the SMOTE dataset, and one using a SMOTE training dataset with a non-SMOTE validation dataset.

Each model was trained on a 70% sample of the dataset and validated on the remaining 30%. In the original dataset, this resulted in 350 training cases and 151 validation cases. In the SMOTE oversampled datasets, ratios of training:validation case numbers were as follows: any complication, 585:251; complication within 12 months, 618:266; return to the operating room, 627:269; and infection, 663:285. SMOTE was selected over other techniques to address class imbalance because (1) it allowed retention and use of all cases in the DBS dataset, (2) it was designed to avoid overfitting, and (3) it has been implemented as an accessible Python package.
Hyperparameter tuning involving grid-search with 5-fold cross-validation was used to find optimal XGBM parameters. Grid-search employed 1512 hyperparameter combinations, resulting in 7560 fit cycles for each of the XGBM models. Using the optimal hyperparameters found in the grid-search process, internal cross-validation was conducted with the number of boosting rounds set at 50 and the number of early stopping rounds set at 10. AUC was used as the performance metric in this process.

Predictions were made using the optimized model and the validation test sets. Confusion matrices and performance statistics were computed. Performance metrics included AUC, accuracy, sensitivity, specificity, positive predictive value and negative predictive value. Feature importance was calculated, decision trees were visualized and receiver operating characteristics (ROC) curves developed. Figure 1 outlines the analysis process overall.
RESULTS

Descriptive statistics are displayed in Table 1. Mean age at implant was 64±10.3 years. The majority of patients were male (63%), were diagnosed with Parkinson’s disease (70%), had a BMI of 25 or more (67%) and underwent a simultaneous bilateral (59%) STN procedure (70%). Patient characteristics did not differ significantly between institutions.

Complication Rates

There were 27 (5.4%) infections over the period of observation (mean 455 days). These infections were either perioperative, occurring within 3 months of lead implantation in 13 (2.6%) patients, or delayed in 14 (2.8%) patients. The median time to onset of all infections was 3.3 months. Delayed infections were typically related to hardware erosion, systemic infections, generator replacement, or appeared spontaneously.

Surgical revision of hardware occurred in 26 (5.2%) patients, on average 28 months after initial implantation. These revisions were for lead or extension wire fracture in 18 (3.6%) patients, loose hardware in seven (1.4%), or repositioned leads due to side effects or poor efficacy in eight (1.6%).

Intracranial hemorrhage occurred in 15 (3.0%) patients, all associated with lead implantation. This included intraparenchymal hemorrhage along the lead and subdural hematoma. No deaths occurred in any of these cases. Of these hemorrhages, 2 of 501 patients (0.4%) had substantial morbidity requiring surgical intervention. Other hemorrhages, 13 (2.6%), were observed on imaging, and resolved without surgical treatment or neurological sequelae.

Risk factors identified using logistic regression

Logistic regression demonstrated statistically significant relationships between risk factors and complications (Table 2). Diabetic patients were nearly three times more likely to return to the operating room than those without diabetes (OR=2.78, CI=1.31-5.88, p<0.01). Postoperative infection was associated with a history of smoking (OR=4.20, CI=1.21-14.61, p<0.05). It appeared that patients with a history of smoking were more than four times more likely to experience postoperative infection.

Experiencing any type of complication was associated with operating institution (OR=0.44, CI=0.25-0.78, p<0.01), BMI (OR=0.94, CI=0.89-0.99, p<0.05) and diabetes (OR=2.33, CI=1.18-4.60, p<0.05).
Operating institution was also significantly associated with experiencing a complication within 12 months (OR=0.36, CI=0.18-0.70, p<0.01). The institution with slightly higher complication rates appeared to have operated on a patient sample with higher comorbidity rates (Table 3).

**Complication prediction with XGBM models**

XGBM models coupled with the SMOTE dataset demonstrated strong predictive performance (Table 4). These models demonstrated higher performance (validation AUC: 0.86-0.97) compared to models trained and validated on the original dataset (validation AUC: 0.57-0.69). Models based on the SMOTE dataset predicted high numbers of true positives and true negatives. Models trained on the SMOTE training dataset and validated on the non-SMOTE holdout sample demonstrated performance that was not substantially superior to the models trained on the original dataset.

ROC curves were generated by running the trained models on the holdout validation datasets. The ROC curves and corresponding AUC associated with the four SMOTE XGBM models showed strong performance (Figure 2).

**Plotting feature importance**

Feature importance metrics were plotted for each of the SMOTE XGBM models (Figure 3). Age, BMI, procedure side, gender, a diagnosis of Parkinson’s disease, institution and comorbidities appeared to be the most influential predictive features associated with complications. Feature importance appeared to vary slightly by model. When plotting complicated cases in the original dataset according to BMI and age, cases clustered at approximately age 70 and a BMI of 24 (Figure 4).

**Carrying out predictions on hypothetical patient data**

A set of hypothetical patients is shown to demonstrate the output of the XGBM predictive models (Table 5). Risk thresholds similar to those developed in cardiology risk stratification research were applied to facilitate interpretation of model output (low=<10%, moderate=10-15%, high=16-50%, very high= >50%) 69.
DISCUSSION

This study found multiple clinical predictors of complications in DBS surgery using supervised machine learning algorithms. Logistic regression showed that patient BMI, diabetes and operating institution were significantly associated with all complications grouped together. Diabetics were almost three times more likely to return to the operating room. A history of smoking was significantly associated with postoperative infection.

The XGBM supervised learning algorithm demonstrated strong predictive performance. The results of this study suggested that XGBMs, coupled with a SMOTE oversampling method, may be employed to successfully overcome the class imbalance problem and effectively predict complication outcomes in DBS surgery. This method may be used to estimate any individual patient’s risk of complications. Plotting feature importance demonstrated that age, BMI, gender, procedure side, a diagnosis of Parkinson’s disease, the operating institution and preoperative comorbidities were influential predictors of postoperative complications. The results of this study that suggested associations between preoperative risk factors and postoperative adverse outcomes are supported by previous research demonstrating that many of these same factors are significantly associated with complication outcomes in DBS surgery \(^{31,70,71}\) and in other forms of neurosurgery \(^{18,23,24,72,73}\).

Surgeons often perceive patterns in their clinical practice. Machine learning algorithms seem to approximate well the intuition of the surgeon. Postoperative complications are likely to arise as a result of complex interactions between many risk factors \(^{74}\). While logistic regression has been deployed in the past to predict surgical outcomes \(^{18,24}\), other supervised learning algorithms, including XGBM, may be better suited to modeling these complex nonlinear relationships \(^{44,48,75}\).

This study has demonstrated one potential approach to addressing the class imbalance problem, which is a major issue in surgical risk stratification \(^{18,19,24,31}\). The approach employed here, applying SMOTE oversampling in conjunction with the XGBM supervised learning algorithm, produced encouraging results.

Simple linear relationships between risks and outcomes are intuitive. Linear and logistic regression generate statistical weights associated with each predictor and can be represented with a linear equation. These approaches offer rapid interpretability and an impression of understandability. In contrast,
advanced supervised machine learning algorithms are often more complex, inscrutable and opaque.

Surgeons are likely to have a lower level of trust in, and therefore may demonstrate weaker adoption of, opaque machine learning algorithms as decision support tools. The XGBM performance statistics, feature importance plots and hypothetical cases generated help to address this issue by providing some insight into the mechanics of the XGBM models developed. More work on developing the “explainability” of these models is required.

A collection of hypothetical cases was presented to demonstrate the risk stratification outputs of the supervised learning models developed. There may be a tendency to attempt to identify patterns in the hypothetical patient data displayed and the corresponding risk evaluation output statistics. However, this tendency is fraught because the number of hypothetical cases displayed is small and the algorithms are able to model complex nonlinearities in the data, based on hundreds of training cases, which are likely to evade human judgement. Similar to previous research¹⁸, these examples provide a random selection of cases and patient characteristics to offer clinicians a general sense of the predictive risk outputs of the models trained. They are not intended to offer a systematic demonstration of the complex relationships modeled by the trained algorithms.

These machine learning models have the potential to facilitate patient safety improvements ⁷⁶. They may be used to stimulate a deeper conversation about complications with a patient prior to surgery, more attention throughout the process from the surgeon and surgical team, closer patient follow-up and activation of other organizational patient support processes postoperatively. Models of this nature should form part of a broader comprehensive approach to clinical risk stratification and patient safety improvement. As an example from another domain of neurosurgery, the Seattle Spine Team has developed a systematic and standardised approach that incorporates multidisciplinary patient review conferences, specialized clinical teams, intraoperative monitoring protocols and multi-surgeon operating practices, in addition to the development of experimental decision support systems underpinned by machine learning methods ²⁴,⁷⁷–⁸⁴.

The advantages of using machine learning methods to stratify risk in neurosurgery are numerous. Machine learning methods are more capable of capturing complex nonlinearities in very large datasets
than traditional statistical techniques and can be deployed to production using cloud computing services for potential use by clinicians and patients globally. These tools are well-suited to high-volume complex data processing, they facilitate access to information, they save time and they have the potential to augment the clinical functioning of the neurosurgeon. Incorporating machine learning tools into the neurosurgical workflow may assist in reducing the likelihood of clinical error and positively engaging the patient. Supervised machine learning models can provide accurate and individualized outcome predictions, which are likely to be beneficial as healthcare progresses toward a future that is more precise and value based. Prediction datapoints may feed into and influence perioperative care processes and decisions or intraoperative treatment by human and robotic systems. On the other hand, it may not be suitable to apply machine learning methods to datasets that are erroneous, exceedingly noisy, obsolete or biased. In these cases, it may be preferable to rely on the unassisted judgment of the expert surgeon and an experienced clinical team.

**Limitations and future research**

The performance metrics using SMOTE oversampling and extreme gradient boosting were strong. Such high performance of the XGBM algorithms suggests that some degree of overfitting may have occurred, despite built-in overfitting mitigation. This, however, is difficult to assess, particularly in the context of limited case data. Caution and appropriate clinical judgement should be exercised if deploying and using these models to make predictions on new patient data. Further validation on new data from other institutions and larger datasets would be beneficial.

While assessing the effects of the use of intraoperative CT on complication rates and patient outcomes was beyond the scope of this study, it may have been beneficial to control for its use in the analysis. Per patient labelling of this variable was not captured in the dataset and this is therefore a limitation of this study. Similarly, it would be beneficial for future predictive modeling studies to control for additional preoperative clinical variables in multivariate analyses. These may include pre- and post-operative functional status, anemia, operating time, the number of electrode passes, passage through the ventricle and a patient history of coronary artery disease or stroke.
A primary aim of this study was to develop models capable of stratifying patient complication risk in DBS surgery. To achieve this and to mitigate the limitations of the dataset, complication subcategories were amalgamated into a superordinate variable representing general clinical risk and adverse outcomes. This approach allowed the development of a set of useful and applicable models. However, it must be noted that these models are broad in their risk predictions and that to predict specific types of complications, which would enable the implementation of specific clinical risk mitigation tactics (e.g., augmented infection prevention or operating room preparation for a returning patient), larger datasets and more modeling work are required. The variables included in the superordinate complication outcome variable fall logically under the banner of adverse postoperative clinical events. While the specific outcomes that make up this variable may be considered diverse, amalgamating them remains clinically useful because together they broadly indicate high risk patients that may require additional critical clinical thought and discussion, resources and careful perioperative management.

Future research may deploy the methods applied here for the prediction of complications associated with other surgical procedures that are characterized by a similar class imbalance problem. Studies may also develop supervised learning models to predict positive functional outcomes and the degree of functional improvement associated with various neurosurgical procedures. Future work may focus on the development of clinical decision support systems to be applied in clinical practice and to deliver decision-support benefits directly to patients via application to patient consultations in the clinics.  

Conclusion

Significant complication risk factors were detected and supervised machine learning algorithms effectively predicted adverse outcomes in DBS surgery. These supervised learning models can be used for the improvement of risk stratification, preoperative patient informed consent and clinical planning to make DBS surgery safer for patients. XGBMs and SMOTE appear to be useful tools for the prediction of complication outcomes and risk stratification in DBS surgical practice.
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Figure legend:

- **Figure 1:** Schematic outline of the two main phases of the analysis process.

- **Figure 2:** ROC curves for each of the SMOTE XGBM models, derived from the holdout test validation datasets.

- **Figure 3:** Feature importance plots for each of the SMOTE XGBM models. BMI = body mass index. DM = diabetes mellitus. GPi = globus pallidus. HB = hemiballismus. HTN = hypertension. L = left. PD = Parkinson’s Disease. R = right. STN = subthalamic nucleus. VIM = ventral intermedius nucleus.

- **Figure 4:** Joint plots of complicated cases (any complication; A) and uncomplicated cases (B) in our sample according to age and BMI. Complicated cases clustered at approximately age=70 and BMI=24, whereas uncomplicated cases clustered at approximately age=69 and BMI=28. Histograms plot age and BMI frequency distributions.
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<td></td>
<td>Age 75 and over</td>
<td>70 (14%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Under 75</td>
<td>431 (86%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gender Male</td>
<td>318 (63%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>183 (37%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diagnoses Parkinson’s disease</td>
<td>349 (70%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Essential tremor</td>
<td>129 (26%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dystonia</td>
<td>11 (2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>12 (2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>BMI ≥25</td>
<td>335 (67%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18 to 24.9</td>
<td>157 (31%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;18</td>
<td>9 (2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comorbidities and risk factors</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Smoking history</td>
<td>25 (5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Immune Suppressed</td>
<td>25 (5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Diabetes</td>
<td>67 (13%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertension</td>
<td>231 (46%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Procedure type</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subthalamic (STN)</td>
<td>349 (70%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thalamic (VIM)</td>
<td>128 (26%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Globus Pallidus Internus (Gpi)</td>
<td>22 (4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>2 (0%)</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Intracranial hemorrhage</td>
<td>15 (3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Readmission</td>
<td>17 (3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ischemic infarction</td>
<td>3 (1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Seizure</td>
<td>3 (1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lead fractures</td>
<td>18 (4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Electrode migration</td>
<td>8 (2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Battery loose or flipping</td>
<td>7 (1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Device malfunction</td>
<td>26 (5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Return to operating room</td>
<td>53 (11%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Infection</td>
<td>27 (5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hemiparesis</td>
<td>5 (1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Facial droop</td>
<td>6 (1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sensory change</td>
<td>4 (1%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complication other</td>
<td>8 (2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complication any</td>
<td>83 (17%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Complication within 12 months</td>
<td>59 (12%)</td>
<td></td>
</tr>
</tbody>
</table>

*Table 1: Descriptive statistics displaying the classes of each of the predictors and outcome features in the dataset of 501 DBS patients. Other diagnoses included cluster headache, Holmes tremor and Tourette Syndrome.*
### Table 2: Multivariate logistic regression modelling results. These results are based on analysis of the original (non-SMOTE) dataset. CI = confidence interval. LLR = log likelihood ratio. OR = odds ratio. The reference categories were: female, Parkinson’s Disease, age <75, institution 01, an operation conducted on both sides and an STN procedure. *p<0.05, **p<0.01.
Institution 01 | Institution 02
---|---
Number of cases | 201 | 300
Demographics | |  
Age (mean, SD) | 62.12 (10.52) | 66.28 (9.94)  
BMI (mean, SD) | 27.71 (5.47) | 27.17 (4.62)  
Female | 41% | 34%  
Diagnosis | |  
Parkinson’s disease | 68% | 71%  
Essential tremor | 24% | 27%  
Dystonia | 1% | 3%  
Clinical features | |  
Smoking history | 5% | 5%  
Immune suppressed | 9% | 2%  
Diabetes mellitus | 13% | 13%  
Hypertension | 70% | 30%  
Target | |  
STN | 69% | 70%  
VIM | 27% | 24%  
GPi | 3% | 5%  
Procedure side | |  
Left | 36% | 25%  
Right | 17% | 8%  
Both | 47% | 67%  
Complication outcomes | |  
Any complication | 22% | 13%  
Complication at 12 months | 18% | 7%  
Return to the operating room | 11% | 10%  
Infection | 6% | 5%  

Table 3: A comparison of case characteristics between institutions, demonstrating a notable difference in the prevalence of patients with hypertension and immune suppression.
<table>
<thead>
<tr>
<th>Data</th>
<th>Original Dataset</th>
<th>SMOTE Dataset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model</td>
<td>Any complication</td>
<td>Complication at 12 months</td>
</tr>
<tr>
<td>Performance on validation holdout datasets</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accuracy</td>
<td>0.66</td>
<td>0.86</td>
</tr>
<tr>
<td>AUC</td>
<td>0.58</td>
<td>0.69</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>0.07</td>
<td>0.00</td>
</tr>
<tr>
<td>Specificity</td>
<td>0.81</td>
<td>0.88</td>
</tr>
<tr>
<td>PPV</td>
<td>0.08</td>
<td>0.00</td>
</tr>
<tr>
<td>Confusion matrices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predicted</td>
<td>Actual</td>
<td>Actual</td>
</tr>
<tr>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>-</td>
<td>2</td>
<td>23</td>
</tr>
<tr>
<td>+</td>
<td>29</td>
<td>97</td>
</tr>
<tr>
<td>-</td>
<td>28</td>
<td>97</td>
</tr>
</tbody>
</table>

Table 4: Predictive performance metrics of XGBM models predicting (1) any complication, (2) complication within 12 months, (3) return to the operating room and (4) infection; using (a) the original dataset, and (b) the SMOTE oversampled training and validation datasets.
<table>
<thead>
<tr>
<th>Institution</th>
<th>1</th>
<th>1</th>
<th>1</th>
<th>1</th>
<th>2</th>
<th>2</th>
<th>2</th>
<th>2</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at implant</td>
<td>33</td>
<td>48</td>
<td>63</td>
<td>75</td>
<td>33</td>
<td>48</td>
<td>54</td>
<td>78</td>
<td>57</td>
<td>76</td>
</tr>
<tr>
<td>Gender</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>M</td>
</tr>
<tr>
<td>BMI</td>
<td>18</td>
<td>24</td>
<td>30</td>
<td>27</td>
<td>28</td>
<td>35</td>
<td>22</td>
<td>29</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>PD</td>
<td>Dyst</td>
<td>PD</td>
<td>PD</td>
<td>PD</td>
<td>ET</td>
<td>PD</td>
<td>PD</td>
<td>PD</td>
<td>ET</td>
</tr>
<tr>
<td>Smoking history</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Yes</td>
<td>Normal</td>
<td>Normal</td>
<td>Yes</td>
<td>Normal</td>
<td>Yes</td>
<td>Normal</td>
</tr>
<tr>
<td>Diabetes status</td>
<td>--</td>
<td>DM</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>DM</td>
<td>--</td>
<td>DM</td>
<td>DM</td>
<td>DM</td>
</tr>
<tr>
<td>Hypertension status</td>
<td>--</td>
<td>--</td>
<td>HTN</td>
<td>--</td>
<td>HTN</td>
<td>--</td>
<td>--</td>
<td>HTN</td>
<td>HTN</td>
<td>--</td>
</tr>
<tr>
<td>Procedure target</td>
<td>STN</td>
<td>GPi</td>
<td>GPi</td>
<td>STN</td>
<td>STN</td>
<td>VIM</td>
<td>STN</td>
<td>STN</td>
<td>STN</td>
<td>VIM</td>
</tr>
<tr>
<td>Procedure side</td>
<td>Left</td>
<td>Both</td>
<td>Left</td>
<td>Right</td>
<td>Both</td>
<td>Both</td>
<td>Left</td>
<td>Both</td>
<td>Both</td>
<td>Right</td>
</tr>
</tbody>
</table>

### Predicted probabilities of complication outcomes (likelihood shown in parentheses)

<table>
<thead>
<tr>
<th>Infection</th>
<th>M (11%)</th>
<th>H (25%)</th>
<th>L (7%)</th>
<th>H (29%)</th>
<th>H (17%)</th>
<th>L (4%)</th>
<th>M (10%)</th>
<th>M (12%)</th>
<th>H (16%)</th>
<th>H (19%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Return to the operating room</td>
<td>M (12%)</td>
<td>VH (64%)</td>
<td>L (7%)</td>
<td>L (5%)</td>
<td>H (28%)</td>
<td>M (13%)</td>
<td>M (13%)</td>
<td>M (11%)</td>
<td>H (22%)</td>
<td>L (7%)</td>
</tr>
<tr>
<td>Any postoperative complication</td>
<td>H (43%)</td>
<td>VH (61%)</td>
<td>L (2%)</td>
<td>M (13%)</td>
<td>H (39%)</td>
<td>M (10%)</td>
<td>M (13%)</td>
<td>M (10%)</td>
<td>H (22%)</td>
<td>H (16%)</td>
</tr>
<tr>
<td>Postoperative complication within 12 months</td>
<td>M (14%)</td>
<td>H (19%)</td>
<td>L (2%)</td>
<td>H (32%)</td>
<td>L (6%)</td>
<td>L (8%)</td>
<td>H (17%)</td>
<td>L (3%)</td>
<td>H (23%)</td>
<td>H (31%)</td>
</tr>
</tbody>
</table>

*Table 5: Hypothetical patient characteristics and corresponding predicted complication likelihood. Risk thresholds are based on decision boundaries developed in cardiology: Low = <10%; Moderate = 10-15%; High = 16-50%; Very high = >50%. Dyst = dystonia. ET = essential tremor. GPi = globus pallidus. H = high. L = low. M = moderate. PD = Parkinson’s Disease. STN = subthalamic nucleus. VH = very high. VIM = ventral intermedius nucleus.*
Phase 1: Statistical Analysis
Purpose: Detect hypothesis-driven statistically significant associations
- Logistic regression
- Feature selection
- 100% of original dataset used in the analysis
- Significant associations detected

Phase 2: Supervised Learning
Purpose: Train XGBM classifiers to enable complication prediction

Approach 01
- Original dataset
- 70% training set
- 30% validation set
- XGBM hyperparameter tuning
- Training

Approach 02
- SMOTE oversampled dataset
- 70% training set
- 30% validation set
- XGBM hyperparameter tuning
- Training

Approach 03
- Original dataset
- 70% SMOTE training set
- 30% validation set
- XGBM hyperparameter tuning
- Training

Performance evaluation
- AUC
- ACC
- SEN
- SPC
- PPV
- NPV
# Abbreviations list

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Expansion / Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC</td>
<td>area under the receiver operating characteristics curve</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>DBS</td>
<td>deep brain stimulation</td>
</tr>
<tr>
<td>Dyst</td>
<td>dystonia</td>
</tr>
<tr>
<td>ET</td>
<td>essential tremor</td>
</tr>
<tr>
<td>GBM</td>
<td>gradient boosting machine</td>
</tr>
<tr>
<td>Gpi</td>
<td>globus pallidus</td>
</tr>
<tr>
<td>H</td>
<td>High</td>
</tr>
<tr>
<td>L</td>
<td>Low</td>
</tr>
<tr>
<td>LLR</td>
<td>log likelihood ratio</td>
</tr>
<tr>
<td>M</td>
<td>Moderate</td>
</tr>
<tr>
<td>NPV</td>
<td>negative predictive value</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
</tr>
<tr>
<td>PD</td>
<td>Parkinson’s disease</td>
</tr>
<tr>
<td>PPV</td>
<td>positive predictive value</td>
</tr>
<tr>
<td>ROC</td>
<td>receiver operating characteristics</td>
</tr>
<tr>
<td>SMOTE</td>
<td>Synthetic Minority Oversampling Technique</td>
</tr>
<tr>
<td>STN</td>
<td>subthalamic nucleus</td>
</tr>
<tr>
<td>VH</td>
<td>Very high</td>
</tr>
<tr>
<td>VIM</td>
<td>ventral intermedius nucleus</td>
</tr>
<tr>
<td>XGBM</td>
<td>extreme gradient boosting machine</td>
</tr>
</tbody>
</table>