Machine Learning-Based Predictive Modeling of Surgical Intervention in Glaucoma Using Systemic Data From Electronic Health Records

SALLY L. BAXTER, CHARLES MARKS, TSUNG-TING KUO, LUCILA OHNO-MACHADO, AND ROBERT N. WEINREB

• PURPOSE: To predict the need for surgical intervention in patients with primary open-angle glaucoma (POAG) using systemic data in electronic health records (EHRs).
• DESIGN: Development and evaluation of machine learning models.
• METHODS: Structured EHR data of 385 POAG patients from a single academic institution were incorporated into models using multivariable logistic regression, random forests, and artificial neural networks. Leave-one-out cross-validation was performed. Mean area under the receiver operating characteristic curve (AUC), sensitivity, specificity, accuracy, and Youden index were calculated for each model to evaluate performance. Systemic variables driving predictions were identified and interpreted.
• RESULTS: Multivariable logistic regression was most effective at discriminating patients with progressive disease requiring surgery, with an AUC of 0.67. Higher mean systolic blood pressure was associated with significantly increased odds of needing glaucoma surgery (odds ratio [OR] = 1.09, $P < .001$). Ophthalmic medications (OR = 0.28, $P < .001$), non-opioid analgesic medications (OR = 0.21, $P = .002$), antihyperlipidemic medications (OR = 0.39, $P = .004$), macrolide antibiotics (OR = 0.40, $P = .03$), and calcium blockers (OR = 0.43, $P = .03$) were associated with decreased odds of needing glaucoma surgery.
• CONCLUSIONS: Existing systemic data in the EHR has some predictive value in identifying POAG patients at risk of progression to surgical intervention, even in the absence of eye-specific data. Blood pressure-related metrics and certain medication classes emerged as predictors of glaucoma progression. This approach provides an opportunity for future development of automated risk prediction within the EHR based on systemic data to assist with clinical decision-making. (Am J Ophthalmol 2019;208:30–40. Published by Elsevier Inc.)

GLAUCOMA IS A PROGRESSIVE OPTIC NEUROPATHY and the world's leading cause of irreversible blindness.[1] Intraocular pressure (IOP) is the only documented modifiable risk factor, and lowering IOP is the current mainstay of glaucoma therapy. However, not all patients with glaucoma have high IOP, and many patients progress to significant visual impairment despite IOP lowering. In addition, even though IOP lowering has demonstrated effectiveness in delaying disease progression, prior large clinical studies have shown that disease progression is still inevitable.[2–4] Thus, there has been increasing interest in identifying other therapeutic targets besides IOP.

Vascular conditions such as hypertension, diabetes, and coronary artery disease have been hypothesized to have a role in glaucoma development and progression.[5] The relationship between systemic hypertension and primary open-angle glaucoma (POAG) is of particular interest, as both are age-related chronic diseases that are increasing in prevalence. Several population-based cross-sectional studies, such as the Rotterdam Eye Study[6] and the Egna-Neumarkt Glaucoma Study,[7] have demonstrated an association between elevated blood pressure (BP), elevated IOP, and glaucoma. The Blue Mountains Eye Study[8] also demonstrated that systemic hypertension is related to an increased risk of glaucoma, and this elevated risk was independent of the effect of elevated BP on raising IOP. However, the relationship between BP and glaucoma is multifaceted, as the Barbados Eye Studies showed that *lower* systolic BP was also associated with risk of developing glaucoma.[9] Several subsequent studies found that hypotension is a risk factor for glaucoma, and, specifically, reduction of BP at night, known as nocturnal dipping, appears to make the optic nerve more susceptible to damage.[10–15] However, many of these prior analyses did not account for coexisting vascular conditions, such as diabetes mellitus, which could also potentially influence the

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From the Viterbi Family Department of Ophthalmology, Hamilton Glaucoma Center and Shiley Eye Institute, University of California, San Diego (S.L.B., R.N.W.), La Jolla, California, USA; UCSD Health Department of Biomedical Informatics, University of California, San Diego, (S.L.B., C.M., T.-T.-K., L.O.-M.), La Jolla, California, USA; Interdisciplinary Research on Substance Use Joint Doctoral Program, University of California, San Diego and San Diego State University (C.M.), San Diego, California, USA; Division of Health Services Research and Development, Veterans Administration San Diego Healthcare System (L.O.-M.), La Jolla, California, USA.
Inquiries to Robert N. Weinreb, MD, UCSD Shiley Eye Institute, 9415 Campus Point Drive, Mail Code 0946, La Jolla CA, 92093-0946; e-mail: rweinreb@ucsd.edu

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perfusion of the optic nerve. Moreover, the medical treatment of systemic hypertension, which may have a major confounding effect, was not always rigorously examined in the population-based studies. Some of the clinical studies were limited by small sample size. Finally, these studies used an expert-driven approach to create models incorporating only a modest number of risk variables and thus were not able to perform a comprehensive analysis of systemic risk factors in relation to glaucoma progression.

With the wide adoption of electronic health records (EHRs), vast quantities of systemic data are readily available that can potentially be leveraged to better understand the relationship between systemic conditions and POAG. Since surgical intervention is a discrete event that is clearly defined and captured in the EHR, we used glaucoma surgery in this study as a surrogate for progressive disease. We hypothesized that machine-learning models trained with systemic data in the EHR may offer predictive value in classifying patients at high risk of glaucoma progression, as represented by need for glaucoma surgery within 6 months. This could potentially enhance the ability to practice precision medicine in the management of glaucoma patients. Furthermore, by identifying clinical features that are associated with risk of progression, these models may help us better understand glaucoma pathophysiology and identify novel therapeutic targets for future investigation.

METHODS

• **STUDY POPULATION AND DATA SOURCE:** This study entailed development and evaluation of machine-learning models based on retrospective data. We obtained EHR data from patients with glaucoma from the University of California, San Diego (UCSD) Clinical Data Warehouse with clinical encounters during a 5-year period from September 2013 to September 2018. The EHR used in both inpatient and ambulatory settings was Epic (EpicCare, Verona, WI, USA). Institutional review board/ethics committee approval was obtained at UCSD before the study began, and waiver of informed consent was also granted by the institutional review board. The study adhered to the tenets of the Declaration of Helsinki and was compliant with the Health Insurance Portability and Accountability Act and all federal and state laws.

Inclusion criteria consisted of the following: diagnosis of POAG (International Classification of Disease [ICD]-9 code of 365.11 or ICD-10 code of H40.11), age 18 years or older, diagnosis date between September 1, 2013, and September 1, 2018, and presence of systemic data in the UCSD EHR. Patients were excluded if the timespan of systemic data in the UCSD EHR was less than 6 months' duration. With this exclusion criterion, patients who were seen by ophthalmology and sent to a primary care provider for preoperative clearance shortly before surgery (such as those with advanced glaucoma who were referred to UCSD specifically for glaucoma surgical intervention) but lacked any other systemic data in the EHR were excluded. This helped ensure that the two groups (patients with surgery and those without surgery) would be similarly derived and helped mitigate potential bias from our institution serving as a tertiary referral center. By excluding these patients specifically referred for surgery, the training data for our models consisted of only patients who had undergone routine monitoring and had systemic data within our health system for at least 6 months. The final cohort that met these inclusion and exclusion criteria consisted of 385 patients, 174 of whom underwent glaucoma surgery within 6 months (cases) and 211 who did not (controls). All patients who underwent surgery did so at our institution's ambulatory/outpatient surgical center. None of the patients required hospitalization for their glaucoma surgery.

• **OUTCOME DEFINITION:** The primary outcome of interest was defined as need for any type of glaucoma-related surgical intervention within 6 months of presentation, with initial presentation defined as date of first encounter within the EHR. Similar to a recent study by Zheng et al,[16] the following Current Procedural Terminology codes were used to classify incisional and laser glaucoma surgery: 66160, 66170, 66172, 66174, 66175, 66179, 66180, 66183, 66184, 66185, 66710, 66711, and 65855. In addition to these, 65850, 65820, 0191T, and 0449T were also included as qualifying codes to represent minimally invasive glaucoma surgeries.

• **DATA PROCESSING:** Figure 1 depicts the overall workflow for data processing and model construction and evaluation. First, data were extracted from the UCSD EHR Clinical Data Warehouse for the defined patient cohort. These included structured data pertaining to patient demographics, medications, information about admissions/hospitalizations, social history, vital signs, laboratory results, disease diagnoses, and procedures/surgeries. All records in the data sources were indexed by a unique patient identifier and timestamp. Free text clinical narrative notes and radiology images and reports were not included. A summary of the source data is provided in Supplemental Table 1 (available at AJO.com).

The raw data were abstracted from the Clinical Data Warehouse into encrypted, password-protected Microsoft Excel files, which were placed on a secure Health Insurance Portability and Accountability Act-compliant server.[13] The data were exported to R (version 3.5.1, R Core Team, www.r-project.org) for processing and analysis on the secure server. The following libraries were used: *tidyverse*, *icd*, *varhandle*, *tableone*, *PerformanceAnalytics*, *ROCR*, *randomForest*, *nnet*, *cutpointr*, and *psych*. All codes for data cleaning, processing, and analysis are released on

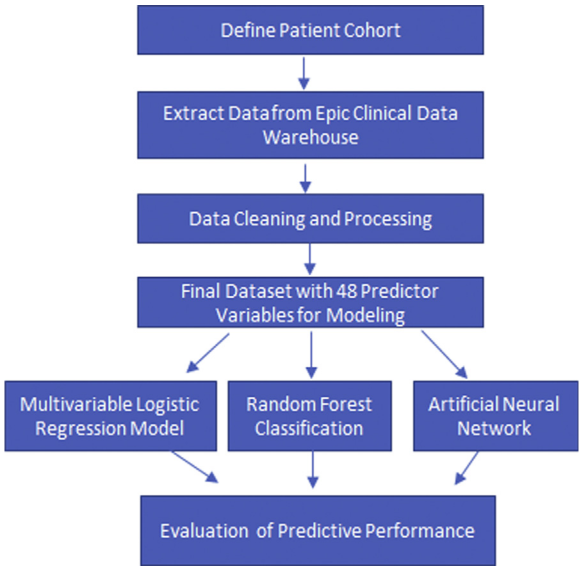

FIGURE 1. Overall workflow diagram. This diagram depicts the workflow for machine learning-based predictive modeling to classify patients with POAG who need glaucoma surgery within 6 months. After defining the patient cohort, systemic data were extracted from the UCSD EHR Clinical Data Warehouse, cleaned and processed, and then used for training and testing three different machine-learning models: logistic regression, random forests, and artificial neural networks. We employed LOOCV and compared predictive performance between models.

GitHub (https://github.com/cmarkymark/Baxter_Marks_Kuo_Ohno-Machado_Weinreb/tree/1.0.0).[17]

To decrease the risk of overfitting, we processed the data to reduce feature dimensionality. For medications, individual medications were coded into pharmacologic classes based on RxNorm ontologies,[18] and any medication used for fewer than 2 weeks was excluded. For hospitalizations, a binary variable was created to characterize any history of hospitalization as well as a continuous variable to define total number of days hospitalized during the observed study period. Vital signs were processed to define features such as maximum, minimum, and mean for both systolic BP, diastolic BP, and heart rate. Body mass index was calculated based on height and weight information. Mapping of individual ICD-9 and ICD-10 codes into disease categories was performed using the *icd* package in R.[19] We excluded categorical variables with too few unique responses to include in the cross-validation procedure described below. At the conclusion of data cleaning and processing, we reduced the features to a total of 48 predictor variables (11 continuous and 37 categorical) for training the subsequent predictive models.

• **STATISTICAL ANALYSIS AND PREDICTIVE MODELING METHODS:** We generated summary statistics to describe both cases and controls. Univariate analyses were performed to investigate for potential associations between a) *Demographic Characteristics* and b) *Clinical Features*, individually with the primary outcome. For predictive modeling, we exploited the following three binary classification methods:

Multivariable Logistic Regression. Logistic regression is a classification model widely used for predictive modeling in the medical literature that learns a direct map from the input data to the response labels and predicts risk using a monotonically increasing or decreasing function.[20] We initially adopted a bidirectional stepwise variable selection using the *step* function in R based on the Akaike information criterion (AIC) before training a multivariable logistic regression model. This function uses the AIC value to choose whether to add or remove variables from the model starting from the null model; its first direction is always forward. Details of the methodology underlying bidirectional stepwise variable selection have been previously described by Hastie and Pregibon.[21] We chose this method over modern tree-based methods because classic regression-based variable selection methods, such as those based on AIC, have been demonstrated to achieve better parsimony in clinical prediction problems in relatively smaller datasets similar in size to our cohort.[22] We also trained a full model with all predictor variables to evaluate its performance without stepwise regression.

Random Forests. The random forests method classifies data based on an ensemble of many binary decision trees, which are trained by splitting the dataset into subsets on a value at a node and repeating this process on each subset.[23–25] A forest reduces the risk of overfitting by averaging over multiple decision trees.[23] Here we used the *randomForest* package[26] in R to build a random forest model.

Artificial Neural Networks. Artificial neural networks were implemented using the *nnet* package in R.[27] We compared a variety of neural network architectures (e.g., one hidden layer versus two hidden layers, different numbers of nodes within each layer) using a grid search method. We used a gradient descent learning algorithm with an exponential learning rate decay starting at 1. Complete batches were used. For each neural network, the maximum iteration variable was set to 1000 epochs. The stopping criteria were either 1000 iterations or if the maximum conditional likelihood fell below 0.0001, or if the change in the optimizer (Broyden-Fletcher-Goldfarb-Shanno algorithm[28]) fell below $1x10^{-9}$.

• **EVALUATION AND SETTINGS FOR PREDICTIVE MODELS:** For model evaluation, we used a leave-one-out cross-validation (LOOCV) approach, also known as the jackknife method,[29] in which the model is trained on all observations except one, which then serves as the test set. Accordingly, in our dataset we predicted each case based on a model trained on the remaining 384 cases. That is, the following process is repeated 385 times for each of the 385 test cases: each case was removed, the model was trained on the remaining 384 cases, and then we applied the model to the single test case to collect the prediction score for that specific case. In LOOCV, the overall predictive performance consists of summative measures (i.e., computed using the prediction scores collected from the test cases).[30] We used five evaluation metrics of predictive performance: area under the receiver operating characteristic curve (AUC), sensitivity, specificity, accuracy, and the Youden index. Advantages to the LOOCV approach include the capacity to provide a direct assessment of predictive ability, being intuitive, and lack of randomness in the training/validation set splits, and its general nature lends compatibility for use with any kind of predictive modeling.[29,30] Although LOOCV is computationally expensive in general,[30,31] this method was feasible for our study given the manageable sample size.

For the *Multivariable Logistic Regression* model, we additionally developed a model using the entire dataset to examine the relative contribution of various predictor variables. For the *Random Forest* model, we computed the mean decrease in accuracy (MDA or permutation importance) and the mean decrease in impurity (MDI or Gini importance) for all variables using the entire dataset to determine important variables for predicting need for glaucoma surgery. For the *Artificial Neural Network*, there were four hyper-parameters: the number of layers, the nodes of the output layer, the nodes of the hidden layer (if used), and the number of epochs for training. The last hyper-parameter (i.e., epochs) was determined by evaluating for occurrence of overfitting based on the AUC, with a predefined maximum of 1000 epochs.

RESULTS

WE IDENTIFIED 385 ADULT PATIENTS WITH POAG IN OUR Clinical Data Warehouse with clinical encounters between 2013 and 2018 and at least 6 months of longitudinal systemic data captured in the EHR. Of these, 174 had undergone surgical intervention for glaucoma within 6 months of presentation (cases), and 211 had not undergone surgical intervention (controls). Surgical intervention included any type of glaucoma-related procedural intervention, including incisional surgery, minimally invasive glaucoma surgery, and laser surgery.

Table 1 shows the baseline characteristics of both cases and controls. No statistically significant differences were observed in demographic characteristics between cases and controls. Mean age in both groups was approximately 73 years. Patients undergoing surgery were approximately equally split between males and females. There was a slight female predominance (53.5%) among those without any surgical intervention, but this was not statistically significant ($P = .414$). Most patients self-identified as white (52.9% of cases, 57.8% of controls), with "Other Race or Mixed Race" being the next most highly represented racial category (19.0% of cases, 17.1% of controls). About 15% of patients in both groups self-identified as Hispanic.

Univariate analyses of potential predictor variables with the outcome of glaucoma surgical intervention showed that cases and controls in this cohort were similar with respect to age, gender, body mass index, smoking status, pulse, BP, a range of comorbidities

TABLE 1. Demographic Characteristics of Patients with Primary Open-Angle Glaucoma Included in Predictive Models Using Systemic Data from the Electronic Health Record to Predict Need for Glaucoma-Related Surgical Intervention

	Patients Without Any Glaucoma Surgery (n = 211)	Patients Undergoing Glaucoma Surgery Within 6 Months of Presentation (n = 174)	P Value[a]
Age (Mean, SD)	73.24 (11.88)	73.09 (12.60)	.905
Male Gender (n, %)	98 (46.4)	89 (51.1)	.414
Self-Reported Race (n, %)			.228
American Indian or Alaska Native	0 (0.0)	1 (0.6)	
Asian	29 (13.7)	20 (11.5)	
Black or African American	7 (3.3)	16 (9.2)	
Native Hawaiian or Other Pacific Islander	0 (0.0)	0 (0.0)	
Other Race or Mixed Race	36 (17.1)	33 (19.0)	
Unknown (Patient cannot or refuses to declare race)	17 (8.1)	12 (6.9)	
White	122 (57.8)	92 (52.9)	
Self-Reported Ethnicity (n, %)			.695
African American	0 (0.0)	1 (0.6)	
Asian/Pacific Islander	0 (0.0)	1 (0.6)	
Caucasian	1 (0.5)	0 (0.0)	
Hispanic	32 (15.2)	25 (14.4)	
Multi-Racial	1 (0.5)	2 (1.1)	
Non-Hispanic	156 (73.9)	128 (73.6)	
Unknown (Patient cannot or refuses to declare ethnicity)	20 (9.5)	15 (8.6)	

n = number; SD = standard deviation.
[a]The threshold for statistical significance was $P < .05$.

TABLE 2. Univariate Analyses of Clinical Features Captured in the Electronic Health Record with Need for Glaucoma Surgery			
	Patients Without Any Glaucoma Surgery (n = 211)	Patients Undergoing Glaucoma Surgery Within 6 Months of Presentation (n = 174)	*P* Value[a]
Vital Signs (Mean, SD)			
Systolic Blood Pressure (mmHg)			
Minimum recorded value	118.75 (22.66)	115.02 (17.12)	.074
Maximum recorded value	152.14 (21.76)	153.99 (19.71)	.385
Mean of recorded values	134.47 (17.46)	133.65 (14.58)	.624
SD of recorded values	11.73 (5.36)	12.92 (6.24)	.059
Diastolic Blood Pressure (mmHg)			
Minimum recorded value	62.95 (11.96)	61.99 (10.24)	.405
Maximum recorded value	83.23 (12.65)	84.08 (9.80)	.468
Mean of recorded values	73.03 (9.41)	73.10 (7.54)	.936
SD of recorded values	7.06 (2.88)	7.11 (2.87)	.861
Heart Rate (beats/minute)			
Minimum recorded value	63.07 (10.91)	63.04 (9.43)	.977
Maximum recorded value	84.86 (16.30)	86.37 (15.89)	.360
Mean of recorded values	72.43 (9.81)	73.47 (9.83)	.304
Body Mass Index (Mean, SD)	27.86 (6.19)	27.92 (5.71)	.922
Smoking Status (n, %)			.530
Current	69 (32.7)	51 (29.5)	
Former	15 (7.1)	9 (5.2)	
Never	127 (60.2)	113 (65.3)	
Comorbid Diagnoses (n, %)			
Pulmonary disease	44 (20.9)	30 (17.2)	.444
Cancer	25 (11.8)	22 (12.6)	.936
Renal disease	24 (11.4)	18 (10.3)	.874
Peripheral vascular disease	20 (9.5)	8 (4.6)	.101
Congestive heart failure	19 (9.0)	11 (6.3)	.432
Diabetes mellitus	18 (8.5)	15 (8.6)	1.000
Stroke	17 (8.1)	12 (6.9)	.814
Hospitalization Status			
Ever hospitalized (n, %)	184 (87.2)	149 (85.6)	.765
Number of days hospitalized (mean, SD)	11.46 (22.9)	7.11 (10.5)	.021
Prescribed Medications[b] (n, %)			
Ophthalmic	128 (60.7)	58 (33.3)	<.001
Non-opioid analgesics	35 (16.6)	8 (4.6)	<.001
Anti-viral	21 (10.0)	5 (2.9)	.011
Antidepressants	38 (18.0)	17 (9.8)	.031
Anti-hyperlipidemic	61 (28.9)	35 (20.1)	.062
Anti-hypertensive	52 (24.6)	34 (19.5)	.283
Dermatological	52 (24.6)	33 (19.0)	.225
Opioid analgesics	41 (19.4)	33 (19.0)	1.000
Ulcer drugs	46 (21.8)	29 (16.7)	.256
Laxatives	39 (18.5)	28 (16.1)	.631
Beta blockers	38 (18.0)	26 (14.9)	.505
Diuretics	32 (15.2)	26 (14.9)	1.000
Calcium blockers	41 (19.4)	24 (13.8)	.182
Anticonvulsants	24 (11.4)	21 (12.1)	.959
Anti-asthmatic	28 (13.3)	20 (11.5)	.711
Fluoroquinolones	22 (10.4)	19 (10.9)	1.000
Anti-diabetic	19 (9.0)	18 (10.3)	.787
Corticosteroids	21 (10.0)	18 (10.3)	1.000
Decongestants	34 (16.1)	16 (9.2)	.063
Anti-rheumatic	29 (13.7)	15 (8.6)	.158
Cold/cough	20 (9.5)	15 (8.6)	.910

Continued on next page

TABLE 2. Univariate Analyses of Clinical Features Captured in the Electronic Health Record with Need for Glaucoma Surgery (*Continued*)

	Patients Without Any Glaucoma Surgery (n = 211)	Patients Undergoing Glaucoma Surgery Within 6 Months of Presentation (n = 174)	*P* Value[a]
Laboratory values (mean, SD)			
Sodium (mEq/L)	139.40 (2.76)	139.20 (2.51)	.565
Anion gap	13.40 (1.73)	13.54 (2.12)	.599
Creatinine (mg/dL)	1.07 (0.80)	1.10 (0.97)	.805
Hemoglobin (g/dL)	13.07 (1.78)	13.22 (1.70)	.513
HDL Cholesterol (mg/dL)	59.56 (18.24)	59.03 (20.03)	.850
Non-HDL Cholesterol (mg/dL)	119.30 (31.50)	129.69 (43.56)	.067
Triglycerides (mg/dL)	121.48 (78.84)	130.67 (72.11)	.410
A1c (%)	6.00 (1.05)	6.25 (1.36)	.172
Erythrocyte sedimentation rate (mm/hr)	20.89 (22.27)	21.84 (19.69)	.845
Lactate (mg/dL)	4.17 (6.70)	4.49 (5.83)	.890

HDL = high-density lipoprotein; n = number; SD = standard deviation.

[a]The threshold for statistical significance was $P < .05$.

[b]Medication categories based on mapping individual medication orders from the clinical data warehouse with RxNorm ontologies for pharmacologic classes.

(history of myocardial infarction, congestive heart failure, peripheral vascular disease, stroke, dementia, pulmonary disease, rheumatic disease, peptic ulcer disease, liver disease, diabetes, renal diseases, cancer, metastatic disease, and HIV), most medication classes, and laboratory values (Table 2). Several factors were associated with need for glaucoma surgical intervention based on the univariate analyses. These included fewer days hospitalized and not having been prescribed ophthalmic medications, non-opioid analgesics, anti-viral agents, or anti-depressant medications during the study period (Table 2).

• **PREDICTIVE MODELING:** The overall performance of the three predictive models based on LOOCV are shown in Table 3; the AUC curves are depicted in Figure 2. Results for logistic regression are reported for the full model incorporating all predictor variables. The logistic regression model had the highest mean AUC at 0.67, followed closely by random forests and artificial neural networks at 0.65. Logistic regression and artificial neural networks were more sensitive than the random forests. However, random forests demonstrated better specificity than the other two models. All three methods had similar accuracy, ranging from 0.60 (artificial neural networks) to 0.62 (logistic regression and random forests). The logistic regression model had the highest Youden index at 0.26 (Table 3). Additional results are described below.

Results of Multivariable Logistic Regression. For relative contribution of the various predictor variables, Table 4 lists the important coefficients in the model. Factors that were significantly protective against needing glaucoma surgery were greater number of days hospitalized (odds ratio [OR] = 0.97, $P = 0.006$), higher values for minimum systolic BP (OR = 0.92, $P < .001$), and being prescribed ophthalmic medication (OR = 0.28, $P < 0.001$), non-opioid analgesic medication (OR = 0.21, $P = .002$), anti-hyperlipidemic medication (OR = 0.39, $P = 0.004$), macrolide antibiotics (OR = 0.40, $P = .034$), or calcium blockers (OR = 0.43, $P = .025$). Factors associated with significantly increased risk of glaucoma surgery was higher mean systolic BP (OR = 1.09, $P < .001$) and use of anti-coagulant medication (OR = 2.75, $P = .042$).

Results of Random Forests. The top variables of importance for predicting need for glaucoma surgery, determined using MDA and MDI, are shown in Figures 3A and 3B, respectively. The five features with the greatest MDA were ophthalmic medications, minimum systolic BP, number of days hospitalized, maximum diastolic BP, and non-opioid analgesic medication use (Figure 3A). There were 12 features associated with relatively larger MDI: systolic BP (minimum, maximum, and mean), diastolic BP (minimum, maximum, and mean), heart rate (minimum, maximum, and mean), age, number of days hospitalized, and ophthalmic medications (Figure 3B).

Results of Artificial Neural Networks. We found the best-performing model to be a two-layer neural network with one hidden layer of five nodes and an output layer with one node. Although more sensitive than random forests, for all other measures of predictive performance the neural networks did not yield superior results compared to logistic regression or random forests.

TABLE 3. Comparison of Predictive Performance of Various Machine Learning Models for Predicting Need for Surgical Intervention Within 6 Months Among Patients with Primary Open-Angle Glaucoma

Predictive Model	AUC	Sensitivity	Specificity	Accuracy	Youden Index
Multivariate Logistic Regression	0.67	0.75	0.50	0.62	0.26
Random Forests	0.65	0.55	0.68	0.62	0.24
Artificial Neural Networks	0.65	0.71	0.51	0.60	0.22

AUC = area under the receiver operating characteristic curve.

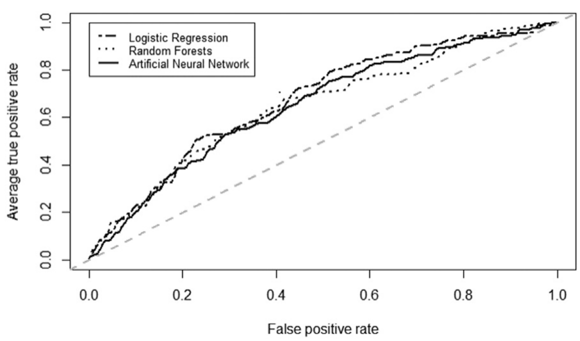

FIGURE 2. Average receiver operating characteristic curves for machine-learning models predicting need for glaucoma surgery within 6 months in patients with POAG using systemic data in the EHR.

TABLE 4. Relative Contribution of Various Predictor Variables in the Multivariable Logistic Regression Model Predicting Need for Surgical Intervention Within 6 Months Among Patients with Primary Open-Angle Glaucoma

Variable	Adjusted Odds Ratio (95% Confidence Interval)	*P* Value[a]
Ophthalmic medication	0.28 (0.17, 0.46)	< .001
Minimum systolic blood pressure	0.92 (0.89, 0.95)	< .001
Mean systolic blood pressure	1.09 (1.06, 1.13)	< .001
Non-opioid analgesic medication	0.21 (0.07, 0.52)	.002
Anti-hyperlipidemic medication	0.39 (0.21, 0.73)	.004
Number of days hospitalized	0.97 (0.94, 0.99)	.006
Calcium blocker medication	0.43 (0.21, 0.89)	.025
Macrolide antibiotic medication	0.40 (0.17, 0.93)	.034
Anticoagulant medication	2.75 (1.05, 7.46)	.042
Male gender	1.52 (0.94, 2.47)	.089
Cold/cough medication	2.22 (0.83, 6.06)	.115
Minimum diastolic blood pressure	0.98 (0.95, 1.01)	.117
Dementia	0.26 (0.04, 1.38)	.141
Antidepressant medication	0.56 (0.50, 1.21)	.143
Metastatic disease	0.31 (0.06, 1.43)	.149

[a]The threshold for statistical significance was $P < .05$.

DISCUSSION

IN THIS STUDY, WE DEVELOPED AND COMPARED MACHINE-learning models to predict the need for glaucoma surgical intervention within 6 months for patients with POAG based on their existing systemic data in the EHR. The rationale for this was rooted in increasing evidence that systemic conditions and medications have a role in glaucoma pathophysiology.[5,7,16,32] This may be important in understanding why some patients experience glaucoma progression leading to debilitating visual impairment, despite seemingly adequate control of IOP.

We generated predictive models using statistical and machine-learning methods trained with systemic data from the EHR in the absence of eye-specific data such as visual acuity, IOP, and structural and functional testing such as optical coherence tomography images or visual field test results, which are the conventional data points ophthalmologists use to determine whether a patient will need surgery. By doing so, we used a data-driven approach that could encompass a wide range of potential predictor variables and additionally quantify the effect of systemic factors on glaucoma progression. The performance of our models supports the hypothesis that systemic data captured in the EHR during routine clinical care have some predictive value.

The statistical and machine-learning approaches employed here demonstrated similar predictive performance overall; neural networks did not yield superior results. Furthermore, both logistic regression and random forests offered interpretable results. The logistic regression equation clearly delineated coefficients and ORs that described the relative weights of various clinical features in making the prediction, whereas we used MDA and MDI to assess variable importance in random forests. This interpretability allowed identification of features with the most predictive value, and that may represent future areas of investigation to better understand pathophysiology or to develop new treatments. In this way, predictive modeling may provide a tool to explore data captured in the EHR to generate hypotheses for future studies. Although artificial neural networks have been previously employed to perform highly accurate clinical predictions based on EHR data,[33] one of their key limitations is that the underlying process driving their predictions is opaque.[34] Hence, their "black box" nature may limit their usefulness in driving future clinical research, although various approaches to overcome this limitation exist. In this study, the artificial neural networks did not demonstrate superior performance. This may be due to the relatively small number of samples and high number of parameters that needed to be estimated.

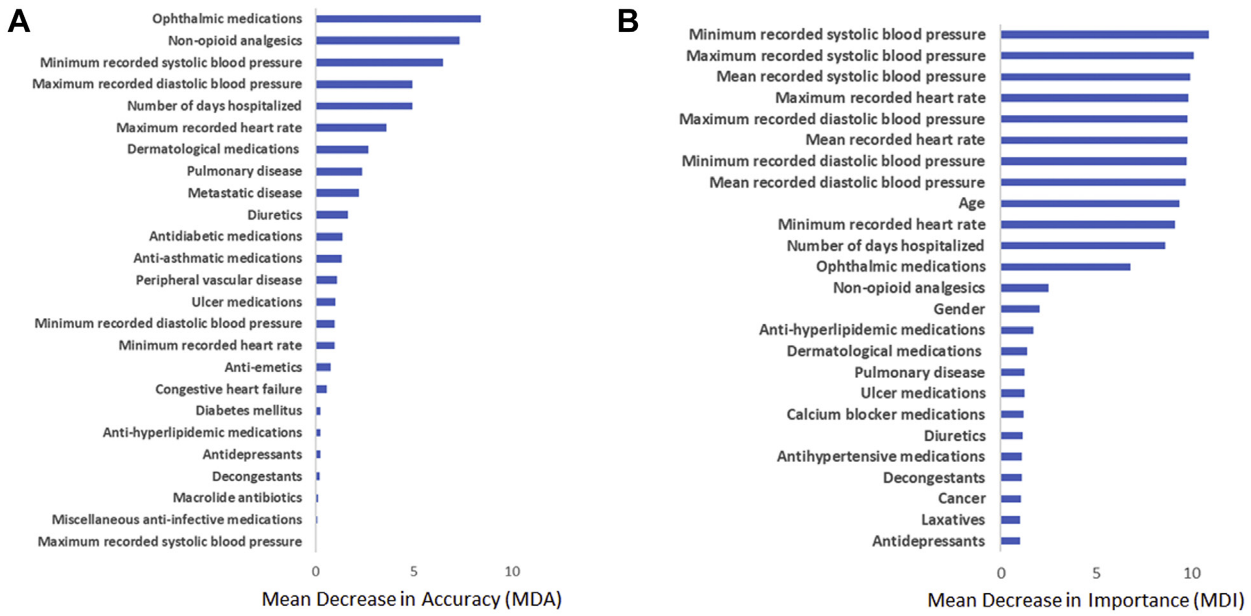

FIGURE 3. Importance of top clinical predictors based on (A) MDA (or permutation importance) and (B) MDI (or Gini importance) for the random forests model predicting need for glaucoma surgery in patients with POAG using systemic data in the EHR.

Our models provided further support for some of the findings from prior studies examining the relationship between hypertension and glaucoma. In our logistic regression model, higher mean systolic BPs (e.g., chronic hypertension) were associated with increased risk of needing glaucoma surgery. Interestingly, our logistic regression model revealed that lower values for the minimum recorded systolic BP (e.g., episodes of relative hypotension) also were associated with increased risk of needing surgery. This supports previously reported studies that have associated hypotension with glaucoma progression.[10–12,14] Measures related to systolic BPs (e.g., minimum, maximum, and mean) also emerged as important variables in driving the random forests classification. Diastolic BP has also been linked with IOP[6] and is a critical component of the calculation of mean ocular perfusion pressure,[35] but its significance in glaucoma progression is not well understood. Similarly, diastolic BP did not have any significant predictive value in our logistic regression model, but measures related to diastolic BP did emerge as variables of importance in the random forest classification.

Several classes of medications emerged as having predictive value in our models. In our logistic regression model, patients who had been prescribed ophthalmic medications, non-opioid analgesics, anti-hyperlipidemic medications, macrolide antibiotics, and calcium blockers were significantly less likely to need glaucoma surgery. The random forests classification also identified ophthalmic medications and non-opioid analgesics as variables of importance. The fact that use of ophthalmic medications would have predictive value is unsurprising. However, the finding that these other classes of medications (non-opioid analgesics, anti-hyperlipidemic medications, macrolide antibiotics, and calcium blockers) helped successfully predict patients who did not need glaucoma surgery could support further investigation of possible new therapeutic targets in these drug classes. Of note, the non-opioid analgesics category included a variety of formulations of acetaminophen and aspirin. Outside of aspirin, the RxNorm codes categorized other non-steroidal anti-inflammatory drugs as "anti-rheumatic" medications, which did not exhibit significant predictive value in our models.

The potential effects of some of these medication classes on glaucoma progression have been explored in prior studies, with mixed results. For non-opioid analgesics, aspirin has been hypothesized to have potential applications in glaucoma by increasing blood flow to the optic nerve, acting as a neuroprotective agent to prevent retinal ganglion cell death, and regulating IOP via upregulating prostaglandin receptors.[36] However, a retrospective analysis showed that aspirin use had no association with progression of optic nerve parameters in POAG suspects,[37] and another analysis showed that aspirin use was actually associated with optic disc hemorrhages,[38] which have been linked with glaucoma progression.[39–41] The case for anti-hyperlipidemic medications such as statin therapies is more compelling, with several retrospective studies demonstrating an association between statin use and decreased risk of developing POAG and decreased risk of POAG progression.[42–45] The finding of macrolide antibiotics having a potentially protective effect may provide some support for the hypothesis that the bacterium *Helicobacter pylori* plays a causative role in glaucoma.[46–48] Although some studies have suggested that eradication of *H. pylori* with antibiotic therapy may positively influence glaucoma parameters,[49] others have not demonstrated a clear beneficial effect.[46,50,51] Our findings support the need for further study of possible therapeutic effects of systemic medications in glaucoma. Generating definitive evidence will require large, well-powered, prospective clinical trials in the future.

Interestingly, calcium blockers had a protective effect in our analysis but were associated with increased risk of POAG in a different study using claims data.[16] These conflicting results stem from one of the key limitations of both EHR and claims data, which is that they do not capture real-world medication use. Having a medication order in the EHR indicates that the treating physician recommended the patient take the medication but does not demonstrate whether the patient filled the prescription. Although claims data may capture whether the pharmacy dispensed the medication, they still do not show whether the patient subsequently took the medication at home as prescribed. Efforts to effectively link EHR data with claims data regarding medication use are ongoing.[52] Given that medication adherence in glaucoma remains a key challenge,[53] incorporating data that more directly represent patients' medication use, such as using data from personal health records or even medication adherence sensors, will likely strengthen predictive models in the future.

We used glaucoma surgery as a proxy for glaucoma progression because it was a clearly defined event in the EHR, thereby reducing the risk of misclassification. In addition, the exact definition of glaucoma progression (and even of glaucoma itself) is not necessarily uniform across clinical research studies.[53] However, our analysis demonstrated that need for glaucoma surgery was not a perfect surrogate for disease progression. For example, more days hospitalized was found to be protective against needing surgery. This was likely due to the fact that patients with illnesses requiring prolonged hospitalizations are usually not ideal candidates for elective surgery, rather than hospitalization itself actually being protective against glaucoma progression.

Despite the limitations of working with data obtained from real-world clinical practice, our analysis demonstrated the potential value of machine-learning models using clinical features captured in the EHR to identify patients at greater risk of glaucoma progression. Evaluation of systemic data in the EHR is likely an underused resource, as ophthalmologists tend to be high-volume providers with little time spent during each individual patient encounter.[54,55] Based on national data collected in the Signal Efficiency Portal by the Epic UserWeb, as of December 2018, the median time in clinical chart review per appointment among ophthalmologists nationwide using Epic was 0.8 minutes (25th percentile, 0.5 minutes; 75th percentile, 1.1 minutes).[56] In conjunction with the complexity of the EHR and this kind of time pressure, thorough and detailed chart review of systemic data is unlikely to be performed by ophthalmologists. Therefore, another potential application of EHR-based predictive models would be to extract relevant systemic data and assist clinicians in real time to efficiently estimate the risk of disease progression in individual patients. This may help ophthalmologists advise patients and their families regarding prognosis and also help them make decisions about appropriate follow-up intervals to reevaluate patients before progression occurs. With automated risk prediction within the EHR incorporating each individual patient's systemic data, ophthalmologists would be better equipped to deliver precision management and reduce patients' risk of irreversible blindness from glaucoma.

In conclusion, systemic data in the EHR offer some predictive value in classifying patients at risk of glaucoma progression (indicated by need for glaucoma surgery within 6 months) even in the absence of eye-specific endpoints. These predictive models are hypothesis generating by identifying conditions and medications that may serve as novel therapeutic targets for future investigation. Although real-world data present some limitations, ultimately this type of predictive modeling has the potential to facilitate automated risk prediction within the EHR, which would help ophthalmologists more efficiently review systemic data and incorporate this information into their clinical decision-making for glaucoma patients.

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