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Prediction of myasthenia gravis crisis events by a machine learning algorithm

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INTRODUCTION

- Myasthenia gravis (MG) is a rare, chronic autoimmune disease of the neuromuscular junction characterized by fatigable muscle weakness.[1,2]
- Approximately 15% to 20% of patients with MG experience myasthenic crisis, defined as respiratory failure necessitating either noninvasive positive pressure ventilation or mechanical ventilation.[2-4]
  - Treatment of MG crises often requires admission to an intensive care unit and usually involves additional acute care and supportive therapy, such as plasmapheresis, intravenous immunoglobulin, and/or corticosteroids.[2,3]
- MG crisis is more likely to occur early in the disease course, usually within 3 years of diagnosis, and the mortality rate is ~ 5%, primarily resulting from comorbidities.[2,4]
- Identifying characteristics of patients at high-risk for MG crisis can guide treatment decisions and help avoid critical MG disease progression to MG crisis.[5]

OBJECTIVE

- To identify key patient characteristics, disease symptoms, and comorbidities associated with an increased risk of MG crisis using a machine learning (ML) algorithm.

CONCLUSIONS

- In this novel analysis, the application of an ML algorithm identified several key patient-relevant characteristics, disease symptoms, and comorbidities as risk factors significantly associated with a higher probability of experiencing an MG crisis.
  - Variables related to the respiratory and bulbar domains of the Myasthenia Gravis Activities of Daily Living scale, including cough, shortness of breath, dyspnea, aphasia/speech disturbance, and dysphagia, appeared to be more important for MG crisis prediction than variables related to the ocular and limb domains.
- Collectively, these results suggest that more aggressive treatment strategies with novel medications may be necessary for patients deemed at higher risk of MG crises.

References

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NS has served as a speaker for Alexion and Catalyst. **KSY** is an employee of Alexion, AstraZeneca Rare Disease, and holds stock or stock options in AstraZeneca and Takeda. **JL** is an employee of Alexion, AstraZeneca Rare Disease, and holds stock or stock options in AstraZeneca. **NJS** has served on a scientific advisory or data safety monitoring board for Alexion, argenx, Avilar, Immunovant, Regeneron, Sarepta, Strongbridge, and UCB and on speakers bureaus for Alexion and argenx; has served as consultant or on a data safety monitoring board for Alexion, Amgen, Annexon, argenx, Immunovant, Johnson & Johnson, Regeneron, and UCB; and has received publishing royalties from a publication relating to healthcare.

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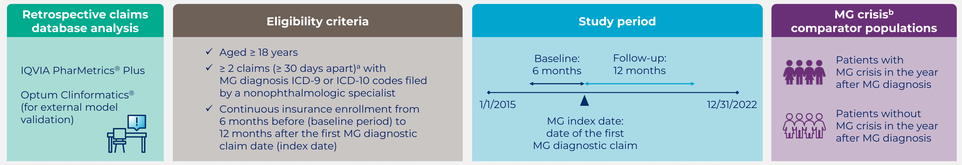
METHODS

- The IQVIA PharMetrics® Plus and Optum Clinformatics® claims databases were retrospectively analyzed (**Figure 1**).

Figure 1. Study design



[a]Patients who had an MG crisis within 7 days of the first MG diagnostic claim date were excluded. [b]MG crisis was defined as an inpatient claim with a code for acute respiratory failure (ICD-10-CM 396.x; ICD-9-CM 158.81) or a Current Procedural Terminology code for mechanical intubation or ventilation (31500, 94660, 94662).
ICD, International Classification of Disease; MG, myasthenia gravis.

- A regularized logistic regression model was applied to identify MG crisis risk factors using the H2O AutoML package.
  - Variables for examination included demographic characteristics and baseline symptoms, comorbidities, pre-index medications, and hospitalization events.
  - For symptom/comorbidity variables, International Classification of Disease codes were converted into Phecode categories.
  - Highly correlated variables (correlation coefficient ≥ 0.3) were combined to control for multicollinearity.
  - Model performance was evaluated using receiver operating characteristic (ROC) analysis.
- Survival analysis was performed on several selected risk factors with high variable importance to demonstrate how they influence the likelihood of MG crisis.

RESULTS AND INTERPRETATION

Patient characteristics

- Of the 205,142,792 patients in the IQVIA PharMetrics® Plus database, 7609 met the study eligibility criteria.
  - 7277 patients had not experienced an MG crisis within 1 year of MG diagnosis, and 332 patients had an MG crisis within that time.
- Certain characteristics (**Table 1**), comorbidities (**Table 2**), and pre-index medications (**Table 3**) were more common in patients with MG crisis than those without.

Table 1. Patient demographics and clinical characteristics

Characteristic	Without MG crisis (n = 7277)	With MG crisis (n = 332)
Sex, n (%)		
Female	3730 (51.3)	139 (41.9)**
Male	3547 (48.7)	193 (58.1)**
Age at index date, mean (SD), years	57.1 (14.8)	61.5 (14.5)**
Insurance payer, n (%)		
Commercial	5886 (80.9)	230 (69.3)**
Medicare	1364 (18.7)	101 (30.4)**
Other	27 (0.4)	1 (0.3)**
MG diagnosis at inpatient service, n (%)	371 (5.1)	57 (17.2)**
Hospitalizations,[a] number/patient (SD)	0.2 (0.6)	0.5 (1.0)**

**P ≤ 0.001. *P* values (chi-square test) for comparison of patients with MG crisis vs without.
[a]During 6-month baseline period.
MG, myasthenia gravis.

Table 2. Comorbidities

Characteristic, n (%)	Without MG crisis (n = 7277)	With MG crisis (n = 332)
Essential hypertension	2376 (32.7)	156 (47.0)**
Diplopia, disorders of binocular vision	1800 (24.7)	71 (21.4)
Ptosis of eyelid	1708 (23.5)	100 (30.1)*
Malaise and fatigue	1246 (17.1)	101 (30.4)**
Type 2 diabetes	1110 (15.3)	79 (23.8)**
Pain in joint	1008 (13.9)	68 (20.5)**
Hyperlipidemia	913 (12.5)	47 (14.2)
Back pain	747 (10.3)	49 (14.8)*
Hypothyroidism NOS	715 (9.8)	35 (10.5)
Obstructive sleep apnea	702 (9.6)	47 (14.2)*
Shortness of breath	677 (9.3)	70 (21.1)**
Nonspecific chest pain	673 (9.2)	62 (18.7)**
Abdominal pain	686 (9.4)	38 (11.4)
Dysphagia	653 (9.0)	66 (19.9)**
Senile cataract	671 (9.2)	40 (12.0)
Paralytic strabismus	645 (8.9)	26 (7.8)
Pain in limb	606 (8.3)	44 (13.3)*
Muscle weakness	581 (8.0)	46 (13.9)**
Cough	562 (7.7)	58 (17.5)**
Dizziness and giddiness[a]	580 (8.0)	38 (11.4)*
Other headache syndromes	585 (8.0)	27 (8.1)
Visual disturbances	565 (7.8)	32 (9.6)
Cervicalgia	541 (7.4)	41 (12.3)**
Osteoarthrosis (localized, primary)	517 (7.1)	41 (12.3)**
Aphasia/speech disturbance	466 (6.4)	63 (19.0)**
Other dyspnea	465 (6.4)	64 (19.3)**
Spondylosis without myelopathy	483 (6.6)	36 (10.8)*
Coronary atherosclerosis	489 (6.7)	27 (8.1)
GERD	485 (6.7)	29 (8.7)
Strabismus[b]	490 (6.7)	24 (7.2)
Respiratory failure	90 (1.2)	28 (8.4)**
Orthopnea	4 (0.1)	5 (1.5)**

*P ≤ 0.05. **P ≤ 0.001. *P* values (chi-square test) for comparison of patients with MG crisis vs without.
[a]Includes lightheadedness and vertigo. [b]Not specified as paralytic.
GERD, gastroesophageal reflux disease; MG, myasthenia gravis; NOS, not otherwise specified.

Table 3. Pre-index medications

Medication, n (%)	Without MG crisis (n = 7277)	With MG crisis (n = 332)
Pyridostigmine bromide	1541 (21.2)	66 (19.9)
Prednisone	880 (12.1)	56 (16.9)*
Levothyroxine sodium	749 (10.3)	28 (8.4)
Atorvastatin calcium	654 (9.0)	37 (11.1)
Lisinopril	492 (6.8)	24 (7.2)
Metformin HCL	459 (6.3)	27 (8.1)
Amlodipine besylate	410 (5.6)	38 (11.4)**
Omeprazole	386 (5.3)	26 (7.8)
Hydrocodone-acetaminophen	381 (5.2)	18 (5.4)
Albuterol sulfate	359 (4.9)	39 (11.7)**
Azithromycin	358 (4.9)	29 (8.7)*
Gabapentin	325 (4.5)	33 (9.9)**
Amoxicillin and potassium clavulanate	330 (4.5)	13 (3.9)
Amoxicillin	324 (4.5)	18 (5.4)
Losartan potassium	325 (4.5)	17 (5.1)
Fluticasone propionate (nasal)	289 (4.0)	16 (4.8)
Methylprednisolone	281 (3.9)	21 (6.3)*
Metoprolol succinate	262 (3.6)	22 (6.6)*
Pantoprazole sodium	257 (3.5)	19 (5.7)
Hydrochlorothiazide	250 (3.4)	12 (3.6)

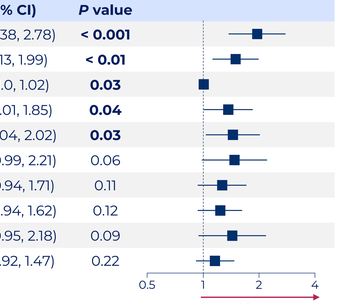
*P ≤ 0.05 **P ≤ 0.001. *P* values (chi-square test) for comparison of patients with MG crisis vs without.
HCL, hydrochloride; MG, myasthenia gravis.

Variables predicting MG crisis

- Based on the claims data analysis, initial variables selected for the prediction model were
  - Age at MG index date and sex
  - Top 30 baseline symptoms/comorbidities by prevalence and respiratory failure
  - Top 20 pre-index medications by prevalence
  - Number of prior all-cause hospitalizations and the place of service (inpatient vs noninpatient) where the first MG diagnosis occurred
- Significant model-identified MG crisis risk factors were MG diagnosis at inpatient service, baseline presence of aphasia/speech disturbance or dysphagia, older age at diagnosis, baseline presence of shortness of breath or other dyspnea, and baseline presence of cough (**Figure 2**).

Figure 2. Odds ratio of variables predicting MG crisis

Variable	Variable importance	Odds ratio (95% CI)	*P* value
MG diagnosis at inpatient service	1.00	1.96 (1.38, 2.78)	**< 0.001**
Aphasia/speech disturbance or dysphagia	0.87	1.5 (1.13, 1.99)	**< 0.01**
Age at MG diagnosis	0.86	1.01 (1.0, 1.02)	**0.03**
Shortness of breath or other dyspnea	0.68	1.37 (1.01, 1.85)	**0.04**
Cough	0.66	1.45 (1.04, 2.02)	**0.03**
Albuterol sulfate	0.56	1.48 (0.99, 2.21)	0.06
Respiratory failure or prior hospitalization	0.53	1.27 (0.94, 1.71)	0.11
Malaise and fatigue	0.53	1.24 (0.94, 1.62)	0.12
Gabapentin	0.50	1.44 (0.95, 2.18)	0.09
Essential hypertension	0.46	1.16 (0.92, 1.47)	0.22

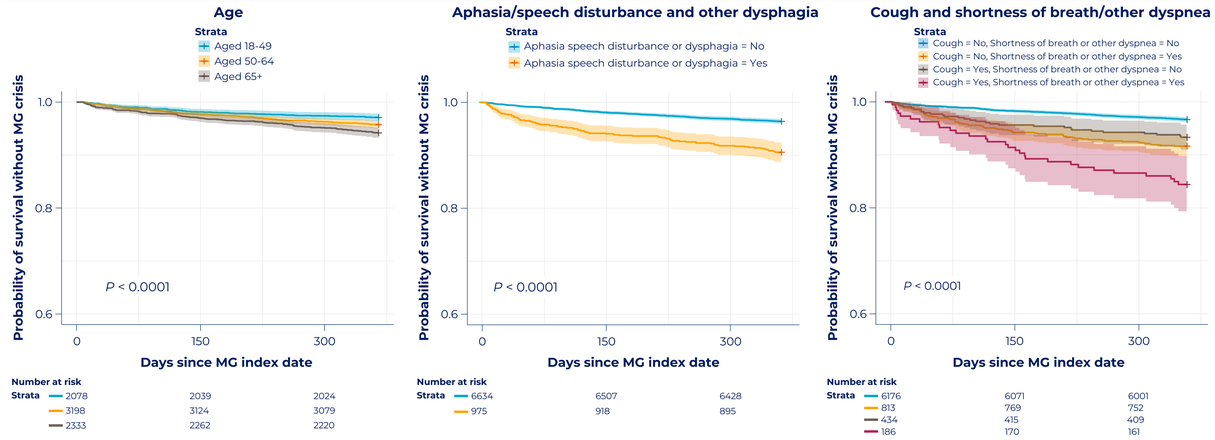


Variable importance was derived based on the magnitude of standardized coefficients. Bolded values indicate significance (*P* ≤ 0.05).
MG, myasthenia gravis.

Risk factors predicting MG crisis

- Survival analyses confirmed significant associations between select risk factors and the likelihood of MG crises, with higher probabilities observed for patients with multiple risk factors (**Figure 3**).
  - Older patients, patients with aphasia/speech disturbance or dysphagia claims at baseline, and patients with multiple risk factors, such as cough and/or shortness of breath/other dyspnea, have a significantly higher probability of experiencing MG crisis at follow-up.

Figure 3. Survival analysis stratified by MG crisis risk factors

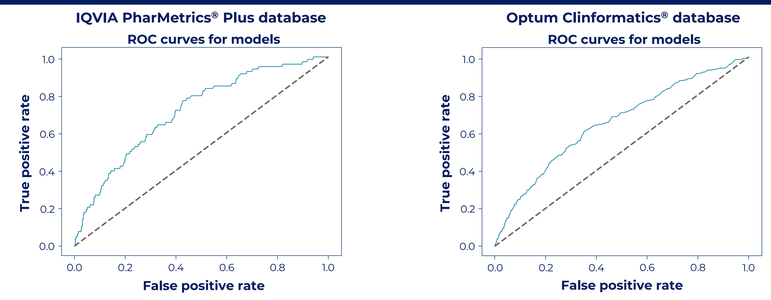


P values derived by *t* test.
MG, myasthenia gravis.

Measure of ML model performance

- Internal validation of the model by ROC curve yielded an area under the curve (AUC) of 0.71 (95% CI: 0.69, 0.72), indicating fair overall predictive performance; external model validation yielded a similarly acceptable AUC (0.65) (**Figure 4**).
  - Factors such as demographic differences, data collection and coding practice differences, variations in healthcare resource utilization patterns, and external validation challenges influenced the AUC difference between the internal and external validation datasets.

Figure 4. Machine learning model performance



For internal model (IQVIA PharMetrics® Plus database) performance assessment, 20 bootstrapping runs were performed.
ROC, receiver operating characteristic.

Limitations

- The IQVIA PharMetrics® Plus database only contains claims data; electronic medical records data, such as lab measurements, are not available.
- The first MG diagnostic claims date in the IQVIA PharMetrics® Plus database may not be the actual initial MG diagnosis date.
- Mild multicollinearity issues exist because of the nature of the claims data, even after the combination of variables was used; this can influence the interpretation of odds ratios.