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Identification of High-Risk Population for Mortality and Severe Clinical Outcomes Among Patients With Myasthenia Gravis: A Nationwide Population-Based Cohort Study in Korea

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ABSTRACT

Background: Myasthenia gravis (MG) is a rare chronic neurological condition characterized by skeletal muscle weakness and fatigue. Some patients with MG have poorly controlled symptoms with conventional treatments. While new treatments could be considered in patients with poorly controlled MG, their costs are considerably higher and may impose a financial burden on patients and the national health insurance system. Therefore, we sought to identify high-risk populations for mortality and severe clinical outcomes among MG patients to effectively allocate health resources.
Methods: A population-based cohort study was conducted using the Health Insurance Review and Assessment database from South Korea (2007–2023). Among patients with incident MG, we defined six clinical criteria expected to be associated with poor prognosis of MG. Separate study cohorts were constructed for the history of each criterion within two years of the first MG diagnosis to compare the risk of mortality, myasthenic crisis (MC), intensive care unit (ICU) admission, and MG-related hospitalization between patients. To adjust for any potential confounding, each covariate was assessed for inclusion in a multivariate Cox proportional hazards model, and findings were presented using hazard ratios (HRs) and 95% confidence intervals (CIs).
Results: We identified 10,458 patients with incident MG (54.2% aged over 60 years; 56.8% female), of whom 361 and 319 were defined as MG patients with history of MC and refractory MG, respectively. Among MG patients, patients with history of any of the predefined clinical criteria showed worse prognosis than those without. Patients with a history of MC had a significantly higher risk of mortality compared to those without (54.0 vs. 17.9 per 1,000 person-year; HR, 2.33; 95% CI, 1.87–2.89). Similarly, across six different criteria, including refractory MG, the risk of serious clinical outcomes, defined MC, ICU admission, and MG-related hospitalization were increased in patients who met the criteria versus those who didn't.

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Disclosure

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Data Sharing Statement

Data from non-interventional studies are outside of UCB's data sharing policy and are unavailable for sharing.

Author Contributions

Conceptualization: Woo J, Kim SW, Kim JH, Yuk J, Jung K, Cho Y, Park Y, Shin JY, Shin HY; Data curation: Woo J, Shin JY, Shin HY; Formal analysis: Woo J, Yuk J; Funding acquisition: Park Y, Shin JY, Shin HY; Methodology: Woo J, Kim SW, Kim JH, Yuk J, Jung K, Cho Y, Park Y, Shin JY, Shin HY; Supervision: Shin JY, Shin HY;

Conclusion: Our study identified high-risk populations among patients with MG. Patients with a history of certain clinical criteria, including MC or refractory MG, had elevated risk of mortality and severe clinical outcomes. These findings may be utilized to establish the reimbursement strategy by identifying MG patients with a priority need for new treatments.

Keywords: Myasthenia Gravis; Population-Based Study; Clinical Outcomes; Myasthenic Crisis; Refractory Myasthenia Gravis; Mortality; Korea

INTRODUCTION

Myasthenia gravis (MG) is a rare, chronic autoantibody mediated neuromuscular disorder, characterized by skeletal muscle weakness and fatigue.[1] Global incidence and prevalence of MG have steadily increased over the past decades.[2] A similar trend has been observed in Korea, where the standardized incidence rates were 1.18 and 1.81 per 100,000 person-years in 2010 and 2018, respectively.[3]

Task Force of the Myasthenia Gravis Foundation of America recommends acetylcholinesterase inhibitors as a first-line therapy, supplemented by corticosteroids (CSs) or non-steroidal immunosuppressant (NS-IST).[4] In South Korea, there is an increasing shift toward using tacrolimus and mycophenolate mofetil,[3] which are reimbursed for patients intolerant to azathioprine or CS. This indicates that a significant number of MG patients experience difficulties with first-line therapies. Moreover, about 10–20% of patients with MG experience poorly controlled symptoms due to inadequate response or intolerance to conventional therapies, or require chronic treatment with intravenous immunoglobulin or plasma exchange.[5,6]

Patients with poorly controlled MG generally have a negative prognosis and are susceptible to symptom exacerbations, myasthenic crisis (MC), emergency department visits, and hospitalizations.[6-8] For these patients, new treatments including complement inhibitors, neonatal Fc receptor antagonists, and B cell modulators could be considered.[5,9-11] However, the higher cost of new treatments versus conventional therapies[12,13] may impose a substantial financial burden to patients and national health insurance systems. Therefore, it is important to identify patients with MG who are at high-risk of poor prognoses to prioritize the reimbursement of new treatments.

In this population-based cohort study, we aimed to identify high-risk groups among patients with MG by evaluating mortality and severe clinical outcomes, including MC, intensive care unit (ICU) admissions, and MG-related hospitalizations, across different predefined clinical criteria. Identifying high-risk groups and prioritizing new treatments for these patients may mitigate the reimbursement burden on allocated healthcare resources.

METHODS

Data source and study design

We conducted a nationwide retrospective cohort study using the Health Insurance Review and Assessment (HIRA) database from January 2007 to February 2023. The HIRA database represents approximately 98% of the entire population in South Korea with all reimbursable

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healthcare services. This database includes individuals' anonymized identifiers with comprehensive information on demographic characteristics (e.g. 10-year band age groups, sex, and health insurance type) and medical records such as diagnoses, treatments, procedures, drug prescriptions, and in-hospital records of death. The diagnoses are recorded based on the Korean Standard Classification of Diseases-8 which is a modified code based on the International Classification of Disease, 10th revision (ICD-10). HIRA database also includes generic name, amount, duration, and the route of administration of prescribed drugs, which are recorded based on the National Drug Codes mapped to the Anatomical Therapeutic Chemical classification.

Study population and operational definitions of clinical criteria

We identified all patients with MG between January 1, 2008 and December 31, 2020. MG was defined as having at least 2 diagnosis codes for MG (ICD-10: G70.0) in primary or secondary diagnoses positions, separately encountered at least 3 months apart within 1 year of the initial diagnosis of MG by a neurologist, pediatrician, or ophthalmologist. We excluded patients with history of MG in a 1-year wash-out period (i.e., January 1–December 31, 2007) to include only incidence cases. The first diagnosis date of MG was defined as cohort entry date (CED) and index date was defined as 2 years after the CED, with follow-up starting from the index date. The 2-year interval was used to determine whether there was a sufficient response to conventional treatments, requiring a minimum period of 1 year per NS-IST to reflect the real-world clinical situation. We also excluded patients who died during the exposure assessment period (i.e., the 2-year interval between CED and index date) for exposure ascertainment (**Supplementary Fig. 1**).

Based on previous reports,[14-16] history of MC and/or status of MG requiring excessive immunosuppressive therapies were assumed to be associated with poor prognosis of MG. Therefore, we constructed six different operational definitions of clinical criteria: 1) record of using CS and at least 2 distinct NS-ISTs; 2) refractory MG, defined as using at least 2 distinct NS-IST and an average prednisolone-equivalent dose of over 15 mg/day of CS; 3) MC, defined as having a procedure code for intubation, and ventilation with diagnosis code of MG; 4) MC and the use of either CS or at least 1 NS-IST; 5) MC and the use of CS and at least 1 NS-IST; and 6) MC and refractory MG (**Supplementary Table 1**). In general, refractory MG is defined as uncontrolled MG despite treatment with CS and at least 2 NS-IST of adequate dose and duration.[4] Although Myasthenia Gravis Foundation of America classification or MG Activities of Daily Living score is generally used to determine whether MG is being well-controlled, these variables are not included in our database. Separate study cohorts were constructed for each clinical criterion, classifying patients with and without a history of each clinical criterion during the exposure assessment period. The flow chart is outlined in **Supplementary Fig. 2**, and the study design is presented in **Fig. 1**.

Outcome

The primary outcome was mortality defined as the date of in-hospital death record or the date of the last record with no further claims within the next 365 days.[17] The secondary outcome was severe clinical outcomes including MC, ICU admission, and MG-related hospitalization (**Supplementary Table 1**). We compared the risk of mortality and severe clinical outcomes between patients with and without a history of each clinical criterion. Patients were followed from the index date to the occurrence of study outcomes, date of death, or end of the study period (December 31, 2022). All outcomes were restricted to the first occurrence in the follow-up period.

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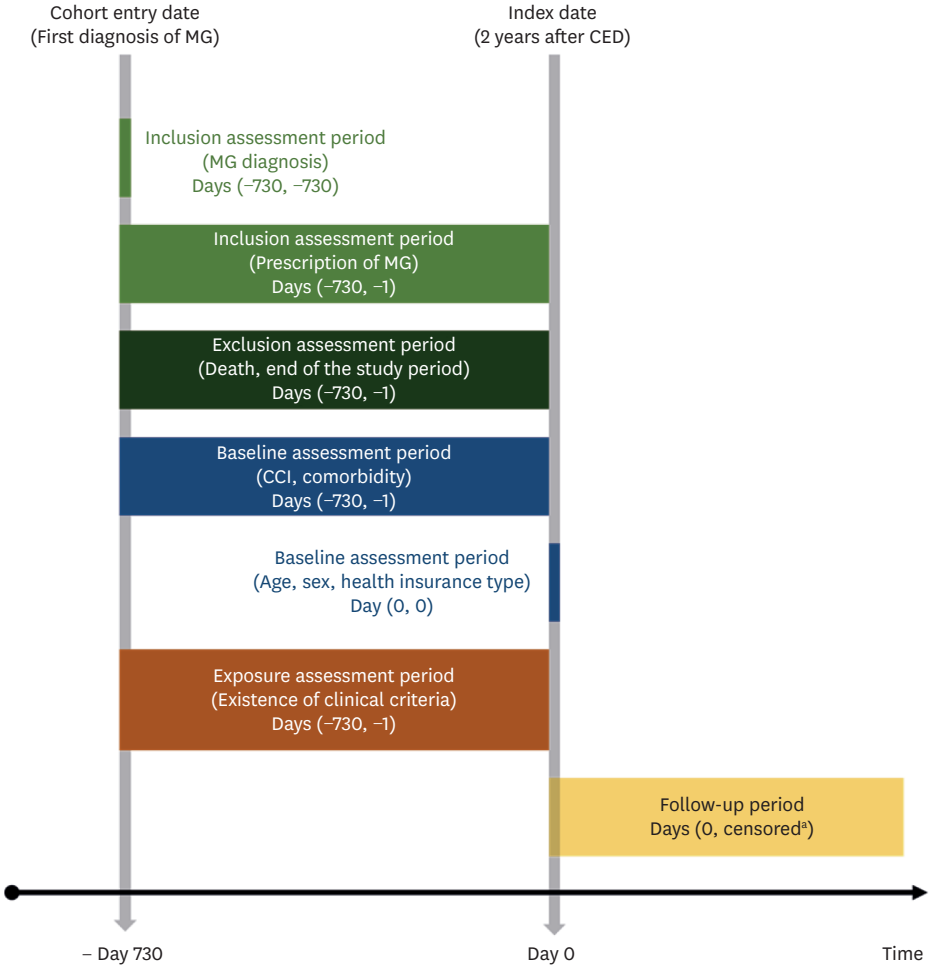

Fig. 1. Study design.
MG = myasthenia gravis, CED = cohort entry date, CCI = Charlson Comorbidity Index.
[a]Censored until the occurrence of a study outcome, date of death or end of the study period (December 31, 2022), whichever occurred earlier.

Covariates

Demographic characteristics, including age group, sex, and type of health insurance were measured at the index date. Clinical characteristics were measured during the 2-year interval between CED and index date, including comorbidities such as pneumonia, atrial fibrillation, heart failure, hypertension and solid tumor. The Charlson Comorbidity Index (CCI) was calculated based on the comorbidities.[18] Detailed definitions of comorbidities and CCI are available in **Supplementary Tables 1** and **2**.

Statistical analysis

We compared baseline characteristics of MG patients classified based on each clinical criterion, presented as mean and standard deviation (SD) for continuous variables, and frequencies with percentages for categorical variables. Differences between patients with or without history of the criteria were assessed using the χ^2 test for categorical variables and the two-sided *t*-test for continuous variables. The *P* values below 0.05 were considered statistically significant.

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To assess the incidence and compare the risk of mortality and severe clinical outcomes in MG patients with or without history of the clinical criteria, we calculated incidence rate based on Poisson distribution, dividing the number of outcomes by 1,000 person-years. To adjust for potential confounding, multivariable Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). Each covariate was evaluated in the Cox proportional hazard model by including it with the exposure and outcome variables, and if the inclusion of that single covariate changed the estimate of HR for exposure by more than 10%, then the covariate was included in the final multivariable Cox proportional hazard model.[19] Comorbidities included in CCI were excluded from the model and were only considered for adjustment by CCI score. All statistical analyses were performed using SAS Enterprise Guide version 9.4 (SAS Institute Inc, Cary, NC, USA), and a two-sided α value less than 0.05 was considered statistically significant.

Sensitivity analyses

Sensitivity analyses were conducted to assess the robustness of the main findings. First, to improve the accuracy of capturing the study outcome, we redefined mortality as 1) having an in-hospital death record or the last record with no claims filed within the next 180 days, or 2) having an in-hospital death record only. Second, we restricted the follow-up period to 1, 3, 5, and 10 years from the index date to observe the risk of mortality at different time points. Third, to assess exposure misclassification, we explored different average doses of CS (10 mg/day or 20 mg/day) used to define refractory MG.

Exploratory analyses

We performed exploratory analyses of the risk of mortality and severe clinical outcomes to identify additional high-risk groups among MG patients. We further considered MG patients based on the following operational definitions of clinical criteria: 1) MC and the use of at least 2 distinct NS-IST; 2) MC and the use of an average dose of over 15 mg/day of CS; and 3) the use of an average dose of over 15 mg/day of CS.

Ethics statement

The study protocol was approved by the Institutional Review Board of Sungkyunkwan University and the requirement for informed consent was waived (SKKU 2023-10-019).

RESULTS

Study population and baseline characteristics

Between January 1, 2008, and December 31, 2020, 10,458 patients were identified as incident MG patients. Of these, 54.2% were aged over 60 years, 43.2% were male, and the mean CCI was 1.25 (SD, 1.3). Median follow-up duration was 5.1 and 5.0 years in the analyses of death and occurrence of MC, respectively. In terms of treatment, 3,367 patients (32.2%) used NS-IST and 6,123 patients (58.6%) used CS at least once during the exposure assessment period. Of these, 778 (7.4%) patients had used CS and at least 2 distinct NS-ISTs, 319 (3.1%) patients satisfied the definition of refractory MG, 361 (3.5%) patients had MC, 330 (3.2%) patients had MC and used either CS or at least 1 NS-IST, 221 (2.1%) patients had MC and used CS and at least 1 NS-IST, and 55 (0.5%) patients had MC and satisfied the definition of refractory MG (**Table 1**).

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Table 1. Baseline characteristics in patients with MG

Baseline characteristics	Patients with MG (N = 10,458)
Age group, yr	
0–9	0 (0.0)
10–19	279 (2.7)
20–29	400 (3.8)
30–39	896 (8.6)
40–49	1,330 (12.7)
50–59	1,877 (17.9)
60–69	2,293 (21.9)
70–79	1,865 (17.8)
80 and more	1,518 (14.5)
Sex	
Male	4,516 (43.2)
Female	5,942 (56.8)
Health insurance type	
National Health Insurance	9,798 (93.7)
Medical aid	660 (6.3)
Comorbidities	
Asthma	1,269 (12.1)
Atrial fibrillation	174 (1.7)
Cerebrovascular disease	1,162 (11.1)
Chronic kidney disease	154 (1.5)
Chronic pulmonary disease	1,137 (10.9)
Diabetes mellitus	2,416 (23.1)
Dyslipidemia	3,184 (30.5)
Heart failure	222 (2.1)
Hematologic cancer	38 (0.4)
Hypertension	3,335 (31.9)
Ischemic heart disease	762 (7.3)
Myocardial infarction	60 (0.6)
Pneumonia	1,396 (13.4)
Solid tumor	1,607 (15.4)
Stroke	605 (5.8)
CCI	1.25 ± 1.29
CCI group	
0	2,631 (25.2)
1	5,325 (50.9)
2	518 (5.0)
≥ 3	1,984 (19.0)
Follow-up period, yr, median (IQR)	
Mortality	5.1 (6.3)
MC	5.0 (6.3)
ICU admission	4.7 (6.1)
MG-related hospitalization	4.1 (6.1)
MG patients with history of clinical criteria	
CS and at least 2 NS-IST	778 (7.4)
Refractory MG[a]	319 (3.1)
MC	361 (3.5)
MC and either CS or at least 1 NS-IST	330 (3.2)
MC and CS and at least 1 NS-IST	221 (2.1)
MC and refractory MG	55 (0.5)

Values are presented as mean ± standard deviation or number (%).
MG = myasthenia gravis, CCI = Charlson Comorbidity Index, IQR = interquartile range, MC = myasthenic crisis, ICU = intensive care unit, CS = corticosteroid, NS-IST = nonsteroidal immunosuppressant.
[a]Refractory MG defined as using at least 2 distinct NS-IST and an average prednisolone-equivalent dose of over 15 mg/day of CS.

A lower proportion of patients with refractory MG than those without were aged 60 years or older (42.6% vs. 54.6%). The patients with refractory MG had a higher mean ± SD CCI score than those without (1.79 ± 1.8 vs. 1.23 ± 1.3; $P < 0.001$) (**Supplementary Table 3**). The patients

with history of MC more frequently had diabetes mellitus (33.0% vs. 22.8%; $P < 0.001$), heart failure (6.4% vs. 2.0%; $P < 0.001$), pneumonia (26.6% vs. 12.9%; $P < 0.001$), and solid tumor (43.2% vs. 14.4%; $P < 0.001$) than those without (**Supplementary Table 4**). A similar trend was observed when patients were compared based on the combination of MC and use of immunosuppressive medications (**Supplementary Tables 5-8**).

Risk of mortality

Of the six clinical criteria that were analyzed, patients with history of MC had the highest mortality rate compared to those without (54.0 vs. 17.9 per 1,000 person-year), corresponding to the adjusted HR of 2.33 (95% CI, 1.87–2.89). Mortality rate was also higher in patients with MC and either CS or at least 1 NS-IST (HR, 1.98; 95% CI, 1.56–2.51) or patients with MC and CS and at least 1 NS-IST (2.03; 1.52–2.71) than those without, respectively. In contrast, mortality rate was not significantly different between the patients with refractory MG compared to those without (17.1 vs. 19.0 per 1,000 person-year; HR, 1.07; 95% CI, 0.74–1.55) (**Table 2**).

Risk of severe clinical outcomes

Risk of severe clinical outcomes were notably higher in patients with a history of each clinical criterion compared with those without, across all criteria (**Fig. 2**). The risk of MC after the exposure assessment period was significantly higher among the patients with previous MC than those without (HR, 5.75; 95% CI, 4.15–7.96) with the highest incidence rate (30.6;

Table 2. Risk of mortality in MG patients with clinical criteria compared to the MG patients without clinical criteria

Exposure[a]	No. of patients	No. of events[b]	Incidence rate[c] (95% CI)	Crude HR (95% CI)	Adjust HR[d] (95% CI)
CS and at least 2 NS-IST					
MG patients with the use of CS and at least 2 NS-IST	778	76	19.6 (15.6–24.5)	1.04 (0.83–1.32)	1.12 (0.89–1.42)
MG patients without the use of CS and at least 2 NS-IST	9,680	1,032	18.9 (17.8–20.1)	1.00 (Reference)	1.00 (Reference)
Refractory MG[e]					
MG patients with history of refractory MG	319	29	17.1 (11.9–24.6)	0.90 (0.62–1.30)	1.07 (0.74–1.55)
MG patients without history of refractory MG	10,139	1,079	19.0 (17.9–20.1)	1.00 (Reference)	1.00 (Reference)
MC					
MG patients with history of MC	361	92	54.0 (44.0–66.2)	3.03 (2.45–3.75)	2.33 (1.87–2.89)
MG patients without history of MC	10,097	1,016	17.9 (16.8–19.0)	1.00 (Reference)	1.00 (Reference)
MC and either CS or at least 1 NS-IST					
MG patients with history of MC and either CS or at least 1 NS-IST	330	76	46.5 (37.2–58.2)	2.57 (2.04–3.25)	1.98 (1.56–2.51)
MG patients without history of MC and either CS or at least 1 NS-IST	10,128	1,032	18.1 (17.1–19.3)	1.00 (Reference)	1.00 (Reference)
MC and CS and at least 1 NS-IST					
MG patients with history of MC with CS and at least 1 NS-IST	221	49	44.3 (33.5–58.6)	2.41 (1.81–3.21)	2.03 (1.52–2.71)
MG patients without history of MC with CS and at least 1 NS-IST	10,237	1,059	18.4 (17.4–19.6)	1.00 (Reference)	1.00 (Reference)
MC and refractory MG					
MG patients with history of MC and refractory MG	55	9	28.5 (14.8–54.8)	1.51 (0.78–2.90)	1.86 (0.96–3.59)
MG patients without history of MC and refractory MG	10,403	1,099	18.9 (17.8–20.0)	1.00 (Reference)	1.00 (Reference)

MG = myasthenia gravis, CI = confidence interval, HR = hazard ratio, NS-IST = nonsteroidal immunosuppressant, CS = corticosteroid, MC = myasthenic crisis.
[a]Exposure, clinical criteria, defined during the exposure assessment period, that is a 2-year time span between the initial MG diagnosis and the index date.
[b]Outcome occurred in follow-up period, from the index period (2 years after first diagnosis of MG).
[c]Per 1,000 person-years.
[d]Each covariate was evaluated by including it in a Cox proportional hazards model with the exposure and outcome variables. If the inclusion of that single covariate changed the HR estimate for exposure by more than 10%, it was included in the final multivariate Cox proportional hazards model to estimate the adjusted HR and 95% CI.
[e]MG patients who were prescribed at least 2 distinct NS-ISTs and an average of over 15 mg/day prednisolone-equivalent dose of CS.

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Exposure[a]	With the history of clinical criteria: No. of events[b] /No. of patients	With the history of clinical criteria: Incidence rate[c] (95% CI)	Without the history of clinical criteria: No. of events[b] /No. of patients	Without the history of clinical criteria: Incidence rate[c] (95% CI)	Forest plot	Adjust HR[d] (95% CI)
MC[e]						
CS and at least 2 NS-IST	30/778	7.9 (5.5–11.3)	241/9,680	4.5 (3.9–5.1)		1.57 (1.07–2.30)
Refractory MG[f]	15/319	9.2 (5.6–15.3)	256/10,139	4.6 (4.0–5.1)		1.88 (1.11–3.19)
MC	48/361	30.6 (23.0–40.5)	223/10,097	4.0 (3.5–4.5)		5.75 (4.15–7.96)
MC and either CS or at least 1 NS-IST	36/330	23.6 (17.0–32.7)	235/10,128	4.2 (3.7–4.7)		4.16 (2.89–5.98)
MC and CS and at least 1 NS-IST	24/221	23.0 (15.4–34.4)	247/10,237	4.3 (3.8–4.9)		3.94 (2.56–6.06)
MC and refractory MG	7/55	24.6 (11.7–51.6)	264/10,403	4.6 (4.1–5.2)		4.66 (2.18–9.97)
					0 1 2 3 4 5 6	
ICU admission						
CS and at least 2 NS-IST	105/778	29.6 (24.5–35.9)	978/9,680	18.9 (17.8–20.2)		1.46 (1.19–1.78)
Refractory MG[f]	54/319	36.5 (27.9–47.6)	1,029/10,139	19.2 (18.0–20.4)		1.88 (1.43–2.48)
MC	70/361	47.1 (37.3–59.5)	1,013/10,097	18.9 (17.7–20.1)		1.80 (1.41–2.31)
MC and either CS or at least 1 NS-IST	63/330	44.2 (34.5–56.5)	1,020/10,128	19.0 (17.8–20.2)		1.69 (1.30–2.19)
MC and CS and at least 1 NS-IST	45/221	47.3 (35.3–63.4)	1,038/10,237	19.1 (18.0–20.3)		1.87 (1.38–2.53)
MC and refractory MG	10/55	38.9 (20.9–72.3)	1,073/10,403	19.5 (18.4–20.7)		1.76 (0.94–3.30)
					0 1 2 3 4 5 6	
MG-related hospitalization						
CS and at least 2 NS-IST	244/778	85.4 (75.4–96.8)	1,571/9,680	32.8 (31.2–34.5)		2.23 (1.94–2.55)
Refractory MG[f]	127/319	113.4 (95.3–135.0)	1,688/10,139	34.0 (32.4–35.7)		2.89 (2.41–3.47)
MC	147/361	133.4 (113.5–156.8)	1,668/10,097	33.6 (32.0–35.3)		2.74 (2.30–3.27)
MC and either CS or at least 1 NS-IST	145/330	139.9 (118.9–164.7)	1,670/10,128	33.6 (32.0–35.2)		2.93 (2.46–3.50)
MC and CS and at least 1 NS-IST	102/221	153.0 (126.0–185.7)	1,713/10,237	34.2 (32.6–35.9)		3.09 (2.52–3.79)
MC and refractory MG	27/55	184.6 (126.6–269.1)	1,788/10,403	35.3 (33.7–37.0)		3.35 (2.28–4.91)
					0 1 2 3 4 5 6	

Fig. 2. Risk of severe clinical outcomes in MG patients with clinical criteria compared to the MG patients without clinical criteria.
CI = confidence interval, HR = hazard ratio, MC = myasthenic crisis, CS = corticosteroid, NS-IST = nonsteroidal immunosuppressant, MG = myasthenia gravis.
[a]Exposure, clinical criteria, defined during the exposure assessment period, that is a 2-year time span between the initial MG diagnosis and the index date.
[b]Outcome occurred in follow-up period, from the index period (2 years after first diagnosis of MG).
[c]Per 1,000 person-years.
[d]Each covariate was evaluated by including it in a Cox proportional hazards model with the exposure and outcome variables. If the inclusion of that single covariate changed the HR estimate for exposure by more than 10%, it was included in the final multivariate Cox proportional hazards model to estimate the adjusted HR and 95% CI.
[e]All prior MC events were resolved before the index date.
[f]MG patients who were prescribed at least 2 distinct NS-ISTs and an average of over 15 mg/day prednisolone-equivalent dose of CS.

23.0–40.5). The risk of MC was also high with the patients with MC and either CS or at least 1 NS-IST (4.16; 2.89–5.98), and MC and refractory MG (4.66; 2.18–9.97). The risk of ICU admission and MG-related hospitalization were similarly high across all patients with history of the predefined criteria. Adjusted HR for ICU admission was 1.88 (1.43–2.48) in patients with refractory MG and 1.80 (1.41–2.31) in patients with MC, and adjusted HR for MG-related hospitalization was 2.89 (2.41–3.47) in patients with refractory MG and 2.74 (2.30–3.27) in patients with previous MC.

Sensitivity analyses

The results of sensitivity analyses using the modified definition for death or restricting the follow-up period were generally consistent with the main findings (**Supplementary Tables 9-14**). Using the alternative definition of average CS dose, an elevated HR was also observed in

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patients with refractory MG, but with a 95% CI that included the null value, suggesting some imprecision in the estimate (1.12; 0.83–1.52 for average CS dose of over 10 mg, 1.06; 0.69–1.64 for average CS dose of over 20 mg) (**Supplementary Tables 15** and **16**).

Exploratory analyses

Exploratory analyses identified additional high-risk groups among patients with MG. Patients who had MC and used at least 2 NS-IST, and those who had MC and used over 15 mg/day of CS showed significant risks of mortality and severe clinical outcomes, whereas the risks were non-significant in patients who had used over 15 mg/day of CS (**Supplementary Tables 17-20**).

DISCUSSION

In this nationwide population-based cohort study, we sought to explore patients with MG who are at higher risk of mortality and severe clinical outcomes. We found that patients with MC during the 2-year period after the diagnosis of MG had significantly higher mortality than those without, regardless of whether immunosuppressive therapies were used. The risk of severe clinical outcomes including MC, ICU admission and MG-related hospitalization was higher across six different predefined clinical criteria compared to those without. These findings were consistently observed throughout various sensitivity analyses, indicating that certain group of patients with MG are at high-risk of worse clinical outcome. Newly developed therapies could be prioritized for consideration in these subgroups of MG patients.

A previous study identified several risk factors for mortality in patients with MG, including MC, high MGFA classification, elevated acetylcholine receptor antibody, and presence of chronic obstructive pulmonary disease, myocardial infarction, atrial fibrillation, or malignant tumor.[20] This association is consistent with our findings on elevated mortality rate in patients with previous MC, which may suggest that MC impacts mortality in ways beyond merely complicating long-term disease control. Our study population included patients with varying comorbidities, among whom those with MC were more likely to have chronic pulmonary disease or heart disease, and pulmonary infarction or cardiac arrhythmia.[21] These comorbidities have also been reported as the cause of death in patients with MC, supporting the significant role of comorbidities in mortality.[20] However, the association between MC and mortality was still significant after adjusting for comorbidities, and the underlying mechanism should be studied further.

Patients who experienced MC within the first two years of MG diagnosis also had a higher risk of MC, ICU admission, and hospitalization. Although the difference in the incidence of ICU admission was lower than other outcomes, considering the baseline characteristics of MG patients, more than 50% of patients were older than 60 years old and had various comorbidities such as pneumonia, solid tumor, and heart failure which could be related to ICU admissions.[22,23] Previous studies similarly demonstrated that 29% to 50% of the patients with MC experienced recurrent MC.[15,16] Mück et al.[24] also showed that patients who had experienced severe exacerbation of MG requiring rescue therapy were more likely to undergo additional hospitalization and had higher quantitative MG score during the follow-up period than those without. These results, along with our findings, indicated that highly active MG, represented by MC, during the early phase of the disease could negatively affect the long-term prognosis.

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Refractory MG is generally defined as an insufficient response despite the conventional treatment including CS and NS-IST for a sufficient duration.[4,5,14,25] Although the treatment response cannot be determined from our database, patients treated with CS and two or more NS-IST in the present study, especially those treated with high-dose CS, were likely to be defined as refractory MG. These patients had a significantly higher risk of MC, ICU admission, and MG-related hospitalization than the remaining patients, aligning with the known clinical course of refractory MG. Rath et al.[14] demonstrated that patients with refractory MG experienced more frequent exacerbation, required higher level of immunosuppression or frequent rescue therapies, and were likely to have higher disease severity. Similarly, Jeong et al.[7] showed that patients with refractory MG had a higher risk for MC and hospitalization than those with non-refractory MG. However, in contrast to MC, the risk of mortality did not differ between patients with and without a history of refractory MG.

Early escalation of treatment or early attempt of newly-developed biologics, including complement inhibitors, FcRn modulators, or B cell depletion therapies, could be considered for patients having refractory MG or MC. A recent German guideline supported this approach and recommended these therapies for patients with highly active or refractory MG, defined by persistent symptoms despite adequate disease-modifying therapy or recurrent severe exacerbations within one year of diagnosis.[10] The guideline proposed the use of FcRn modulators, complement inhibitors, and rituximab as first-line treatments for these patients. Mück et al.[24] also suggested early escalation of therapy for patients with highly active MG to prevent exacerbation that could negatively affect the long-term prognosis.

The main strength of this nationwide cohort study is the comprehensive coverage of patients with MG in South Korea for over 10 years. Also, our study evaluated the risk of mortality and severe clinical outcomes for the various clinical criteria among patients with MG with sufficient follow-up time.

This study also has limitations. First, as our retrospective population-based cohort study was based on an administrative claims data, there was no information on clinical information such as electrodiagnostic testing or antibody testing that MG patients may have received for diagnosis, so there may be limitations in identifying MG patients. Second, although we adjusted measured confounders using the Cox proportional hazards model, unmeasured or residual confounders may still exist. Third, as only in-hospital death records were available in the HIRA database, there is a possibility of misclassification of mortality. Therefore, we defined mortality as the in-hospital record of death or 365 days without medical utilization from the most recent claims, which was validated with a positive predictive value of 96.68%.[17] Also, we conducted sensitivity analyses with various definitions of mortality, which were consistent with the main findings. Lastly, changes in treatment and covariates during the follow-up period were not addressed in this study. These limitations should be considered when interpreting the study findings as these factors may have influenced the results.

In this nationwide population-based cohort study among MG patients in South Korea, patients with a history of MC had elevated risk of mortality. Patients with a history of all six clinical criteria defined in the present study, including MC and refractory MG, had an elevated risk of severe clinical outcomes including ICU admission and MG-related hospitalization compared to those without. Healthcare providers could prioritize the reimbursement of newly targeted treatments by utilizing these findings, thereby alleviating the clinical and economic burden of high-risk patients with MG.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Definitions and codes

Supplementary Table 2
List of ICD-10 codes and the corresponding scores used to define CCI

Supplementary Table 3
Baseline characteristics of the MG patients with and without a history of refractory MG

Supplementary Table 4
Baseline characteristics of the MG patients with and without a history of MC

Supplementary Table 5
Baseline characteristics of the MG patients with and without a history of receiving CS and at least 2 NS-IST

Supplementary Table 6
Baseline characteristics of the MG patients with and without a history of MC and either CS or at least 1 NS-IST

Supplementary Table 7
Baseline characteristics of the MG patients with and without a history of MC and CS and at least 1 NS-IST

Supplementary Table 8
Baseline characteristics of the MG patients with and without a history of refractory MG with MC

Supplementary Table 9
Sensitivity analysis of the risk of mortality in MG patients with and without a history of clinical criteria: redefine the definition of mortality to recorded in-hospital death

Supplementary Table 10
Sensitivity analysis of the risk of mortality in MG patients with and without a history of clinical criteria: redefine the definition of all-cause mortality to recorded in-hospital death or 180 days without medical utilization

Supplementary Table 11
Sensitivity analysis of the risk of mortality in MG patients with and without a history of clinical criteria: restrict 1 year follow-up period

Supplementary Table 12
Sensitivity analysis of the risk of mortality in MG patients with and without a history of clinical criteria: restrict 3 years follow-up period

Supplementary Table 13
Sensitivity analysis of the risk of mortality in MG patients with and without a history of clinical criteria: restrict 5 years follow-up period

Supplementary Table 14
Sensitivity analysis of the risk of mortality in MG patients with and without a history of clinical criteria: restrict 10 years follow-up period

Supplementary Table 15
Sensitivity analysis of the risk of mortality in MG patients with and without a history of clinical criteria: redefine CS as an average dose of over 10 mg/day prednisolone-equivalent of CS within 2 years

Supplementary Table 16
Sensitivity analysis of the risk of mortality in MG patients with and without a history of clinical criteria: redefine CS as an average dose of over 20 mg/day prednisolone-equivalent of CS within 2 years

Supplementary Table 17
Exploratory analyses of the risk of mortality in MG patients with a history of clinical criteria compared to the those without

Supplementary Table 18
Exploratory analysis of the risk of MC in MG patients with a history of clinical criteria compared to the those without

Supplementary Table 19
Exploratory analysis of the risk of intensive care unit admission in MG patients with a history of clinical criteria compared to the those without

Supplementary Table 20
Exploratory analysis of the risk of MG-related hospitalization in MG patients with a history of clinical criteria compared to the those without

Supplementary Fig. 1
Study period.

Supplementary Fig. 2
Flow chart of the study participants selection.

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