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The characteristics of new-onset myasthenia gravis after COVID-19 outbreak: a cross-sectional study

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Abstract

Background Little research has been conducted on new-onset myasthenia gravis (MG) patients following the coronavirus disease 2019 (COVID-19) pandemic. COVID-19 surged in China on December 7th, 2022. This study aimed to explore the clinical characteristics of new-onset MG patients after COVID-19 and analyze factors affecting their disease improvement.

Methods All new-onset MG patients before (December 1st, 2021 to December 7th, 2022) and after COVID-19 outbreak (December 8th, 2022 to November 30th, 2023) were included in this study. Data was collected through the electronic medical record system and follow-up. Multivariate logistic regression was used to identify independent predictors of clinical improvement in patients with new-onset MG.

Results 359 new-onset MG patients (165 before COVID-19 outbreak and 194 after COVID-19 outbreak) were enrolled in this study. After COVID-19 outbreak, there was an increase in new-onset MG patients, with more cases occurring within the first three months. The rates of pulmonary inflammation (40.28%), COVID-19 vaccination (88.14%), and treatment with tacrolimus (15.98%) and MG duration (15 weeks, IQR: 5.75, 32) were higher, while rates of thymectomy (13.92%), baseline MG-ADL (3, IQR: 3, 6), and QMGS (7, IQR: 5,8) were lower compared to new-onset MG patients before COVID-19 outbreak. Multivariate logistic regression analysis showed that age at onset (OR 0.964, $p < 0.001$), baseline MG-ADL (OR 1.611, $p < 0.001$), and ocular MG (OR 0.401, $p = 0.041$) were independent predictors of clinical improvement in new-onset MG after the COVID-19 outbreak.

Conclusion In this single-center cross-sectional study, new-onset MG patients following the COVID-19 outbreak showed altered seasonal onset patterns, milder disease severity, and higher OMG onset age. Age at onset is an independently negative predictor of improvement in new-onset MG patients after the COVID-19 outbreak. Whereas baseline MG-ADL is an independently positive predictor.

Keywords New-onset, Myasthenia gravis, COVID-19, Clinical characteristics, Clinical improvement

Background

The Coronavirus disease 2019 (COVID-19) pandemic has profoundly impacted global public health systems while simultaneously posing novel challenges in the diagnosis and management of neurological autoimmune disorders. Previous evidence suggests that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with the development of multiple

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autoimmune neurological disorders [1], with proposed mechanisms primarily involving immune system hyperactivation and molecular mimicry. The first reported case of COVID-19-associated new-onset myasthenia gravis (MG), reported in Italy in 2020, provided clinical evidence for this association, with the patient demonstrating high serum titers of anti-acetylcholine receptor (AChR) antibodies [2]. MG is an autoimmune disorder characterized by autoantibody-mediated impairment of neuromuscular transmission. The disease manifests as fluctuating muscle weakness, with ptosis and diplopia are the common symptoms. The most common pathogenic antibodies identified in MG target three key proteins: the antibodies against AChR, muscle-specific tyrosine kinase (MuSK), and low-density lipoprotein receptor-associated protein 4 (LRP4). However, some patients test negative for these antibodies but may still have other autoantibodies, such as those against ryanodine receptor (RyR) and/or titin. Genetic susceptibility, an abnormal thymus, and viral infections are associated with MG pathogenesis [3, 4]. In addition, psychological and mental disorders also have been found to be related to the development or aggravation of MG [5]. Notably, accumulating case reports suggest that COVID-19 or its vaccine might increase the risk of triggering or exacerbating MG [6–9]. Several potential mechanisms have been proposed to explain this association. First, SARS-CoV-2 exhibits direct neurotoxic effects through structural mimicry, as its receptor has a similar structure to the acetylcholine receptor [10]. Second, SARS-CoV-2 infection may induce excessive T-lymphocyte activation and thymic germinal center hyperplasia [8], consequently disrupting immune homeostasis—an important mechanism in triggering autoimmune responses. Third, SARS-CoV-2 infection could potentially accelerate the progression from subclinical MG to overt clinical manifestations [7, 11]. The antibodies induced by the vaccine may cross-react with neuromuscular junction proteins. Additionally, COVID-19 caused by the SARS-CoV-2 has increased the emotional and psychological stress of patients [12]. Nevertheless, whether the COVID-19 pandemic has influenced the clinical presentation of new-onset MG remains uncertain.

The global COVID-19 pandemic began in 2020, but its impact in China was relatively limited due to strict prevention and control measures. However, after the policies were relaxed on December 7, 2022, the situation worsened significantly. A widespread outbreak occurred over the following 1–2 months, during which the infection rate of COVID-19 increased sharply in China. This distinct epidemiological context offers unique opportunities to investigate the potential association between COVID-19 and the clinical features of new-onset MG. Moreover, as COVID-19 continues to mutate and infect more individuals, its impact on MG patients has also evolved over time. Many existing studies have focused on patients with pre-existing MG, such as how COVID-19 exacerbates MG symptoms [13]. However, well-controlled studies comparing MG clinical data before and after the COVID-19 outbreak remain scarce. It remains unclear whether the COVID-19 outbreak altered the demographic, immunological, or clinical severity profiles of new-onset MG cases.

In this study, we compared the clinical characteristics of newly diagnosed MG patients before and after the outbreak of COVID-19 in Guangxi, China. We hypothesized that certain clinical characteristics of these new-onset MG patients might have changed following the COVID-19 outbreak. Furthermore, we investigated potential independent factors affecting clinical improvement in new-onset MG patients. The findings of this study will provide valuable insights for the management of new-onset MG patients in the post-pandemic era.

Methods

Patients

This single-center, retrospective study was conducted at the First Hospital of Guangxi Medical University, Guangxi, China. This study was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (2024-E420-01), and informed consent was obtained from all patients. Patients diagnosed with MG after the COVID-19 outbreak (December 8th, 2022–November 30 th, 2023) and before the COVID-19 outbreak (December 1st, 2021–November 7th, 2022) were enrolled. According to the International Consensus Guidance for Management of Myasthenia Gravis (2020 Update) and the Chinese Guidelines for the Diagnosis and Treatment of MG (2020), the diagnosis of MG is based on clinical muscle weakness and at least one positive test, including the neostigmine test, repetitive nerve stimulation (RNS), and MG-related autoimmune antibodies. With low stimulation rate (2 or 3 Hz), the amplitude of compound muscle action potential decreases by more than 10% after RNS in MG patients. Some patients with MG also show thymus abnormalities on Computed Tomography (CT) or Magnetic Resonance (MR) imaging, including thymoma and thymic hyperplasia. MG can be classified into ocular myasthenia gravis (OMG) and generalized myasthenia gravis (GMG), based on clinical phenotypes. A total of 1277 MG patients (706 before the COVID-19 outbreak and 571 after the COVID-19 outbreak) visited the outpatient clinic of neurology, 359 of whom were new-onset MG patients and enrolled in the study (165 before the COVID-19 outbreak and 194 after the COVID-19 outbreak). The study population was

divided into two groups based on the patient-reported date of symptom onset: the"before group"(i.e. patients with new-onset MG before the COVID-19 outbreak) and the"after group"(i.e. patients with new-onset MG after the COVID-19 outbreak). Patients with MG were classified into five groups based on the Myasthenia Gravis Foundation of America (MGFA) clinical classification. The MG-ADL and Quantitative MG Score (QMGS) were used to assess disease severity. A relative improvement indicator (post-treatment MG-ADL score pre-treatment MG-ADL score) * 100/pre-treatment MG-ADL score) was also calculated to evaluate clinical improvement. MG-ADL is commonly used in evaluating treatment response, with a decrease of at least two points indicating significant clinical improvement [14]. Clinical improvement of MG in our study was defined as a reduction of at least two points in MG-ADL and a relative improvement indicator more than 25% after approximately six months of treatment, compared to baseline MG-ADL. Thymoma subtypes were classified according to the World Health Organization (WHO) criteria for thymoma histology. Winter was defined as December to February, spring as March to May, summer as June to August, and autumn as September to November. COVID-19 was confirmed by a nasopharyngeal swab polymerase chain reaction test for SARS-CoV-2, a nasopharyngeal swab that tested positive for the SARS-CoV-2 antigen, or by typical clinical symptoms after close contact with COVID-19 patients.

Clinical data collection

The data of patients with MG were obtained from the electronic medical record system. Data included demographic information, vaccination status, MG duration, time of onset, MG symptoms, MGFA, clinical phenotype, thymus status, thymus pathology, baseline MG-ADL, baseline QMGS, and antibody status. MG duration is the duration of disease prior to therapy. The data was collected from March 1st to May 30 th, 2024, including records from the first visit, the most recent visit, and about six months after treatment. Patients were contacted by phone or face-to-face during this period. None of the questionnaires were anonymous. The questionnaire included questions regarding demographics, smoking history, vaccination status, COVID-19 status, treatment status, thymus status, MG-ADL, QMGS, and outcomes.

Statistical analysis

Categorical variables were described as n (%), and data was analyzed using the chi-squared test, Yates' correction, or Fisher's exact test. Numerical variables that fit the normal distribution were described as means and standard deviations; otherwise, they were described as medians and interquartile ranges (IQR). These numerical data was analyzed using either the independent samples t-test or the Mann–Whitney test. Statistical significance was set at $p < 0.05$. Multivariate logistic regression analysis was conducted to assess clinical improvement in patients with new-onset MG after the COVID-19 outbreak. Significant factors associated with clinical improvement were used as predictors to determine which variables were the independent predictors of clinical improvement. Statistical analyses were performed using SPSS version 21.

Results

Clinical characteristics of new-onset MG patients after COVID-19 outbreak

The clinical characteristics of patients with new-onset MG after the COVID-19 outbreak were shown in Table 1. There were 165 new-onset MG patients in the before group, and194 new-onset MG patients in the after group. This represented an increase (194 vs. 165). There were no statistically significant differences in demographics, smoking history, COVID-19 infection rate, MG associated antibodies, and RNS between the two groups. Among the OMG patients, the age at onset (37, IQR: 18, 54) in patients in the after group was older than that in the before group (33, IQR: 14.5, 53.75, $p = 0.014$). More patients (88.14%) in the after group were vaccinated and the duration of MG was longer (15, IQR: 5.75, 32, $p = 0.024$). The after group also had 107 (55.15%) patients who were classified as MGFA type I, 44 (22.68%) as type II, and 43 (22.17%) as more than type II. In the before group, the classification of MGFA I, II, and more than II was 72 (43.64%), 55 (33.33%), and 38 (23.03%), respectively. There was a significant difference in the MGFA classification between the two groups ($p = 0.048$). Compared to the before group, the number of new-onset MG patients with type I was increased ($p = 0.030$), but type II was decreased ($p = 0.024$). The number of patients with GMG in the after group was lower (44.85% vs. 56.36%, $P = 0.030$) than that in the before group, and there was less involvement of the bulbar or respiratory muscles ($p = 0.017$). 69 patients (35.75%, 69/193) in the after group had an abnormal thymus. Thymus surgery was performed in 27 patients (13.92%), including 22 with thymoma and 5 with thymic hyperplasia, which was a lower percentage compared to the before group (13.92% vs. 21.82%, $p < 0.05$). In addition, 22 patients with thymoma in the before group underwent immunohistochemical examination of the thymus, 3 patients (13.63%, 3/22) with type A or AB and 19 patients (86.37%, 19/22) with type B. 16 patients with thymoma in the after group, of which 8 (50.00%, 8/16) patients were type A or AB and 8 patients (50.00%) were type B. The histological distribution of thymomas

Table 1 Clinical characteristics of new-onset MG patients after COVID-19 outbreak

Variables	Before COVID-19 outbreak (*n* = 165)	After COVID-19 outbreak (*n* = 194)	*P* value
Gender, female, n (%)	94 (56.97)	105 (54.12)	0.589
BMI (mean ± SD)	21.94 ± 4.36	21.78 ± 3.75	0.706
Vaccination, ≥ 1, n (%)	133 (80.61)	171 (88.14)	0.048*
Infection rate, n (%)	158 (95.76)	185 (95.36)	0.856
Age at onset (y), median (IQR)	43 (24, 55)	41 (23, 55)	0.916
Ocular MG	33 (14.5, 53.75)	37 (18, 54)	0.014*
Generalized MG	48 (31.5, 56)	43 (35, 55)	0.605
Age at time of diagnosis (y), median (IQR)	44 (26, 55)	42 (24.75, 55)	0.880
MG duration (w), median (IQR)	12 (5, 23)	15 (5.75, 32)	0.024*
Smoking, n (%)	33 (20)	30 (15.46)	0.260
Hospitalized, n (%)	65 (39.39)	72 (37.11)	0.658
MGFA			0.048*
I, n (%)	72 (43.64)	107 (55.15)	0.030*
II, n (%)	55 (33.33)	44 (22.68)	0.024*
≥ III, n (%)	38 (23.03)	43 (22.17)	0.845
Clinical phenotype			0.030*
Ocular, n (%)	72 (43.64)	107 (55.15)	
Generalized, n (%)	93 (56.36)	87 (44.85)	
Affect bulbar or respiratory muscles, n (%)	58 (35.15)	46 (26.74)	0.017*
Affect limb muscles, n (%)	35 (21.21)	41 (23.84)	0.986
Antibody status (missed 5)			0.161
AChRab +, n (%)	113 (69.33)	137 (71.73)	
MuSKab +, n (%)	11 (6.74)	16 (8.38)	
LRP4ab + or RyR ab + or Titin ab +, n (%)	0 (0)	4 (2.09)	
Seronegative, n (%)	39 (23.93)	34 (17.80)	
Abnormal thymus (missed 1), n (%)	63 (38.18)	69 (35.75)	0.635
Thymectomy, n (%)	36 (21.82)	27 (13.92)	0.0498
Thymoma histology (22 = before and 16 = after), n (%)			0.028
A or AB	3 (13.63)	8 (50)	
B	19 (86.37)	8 (50)	
RNS + (missed 22), n (%)	73 (46.79)	88 (48.62)	0.738
MG treatment			
Pyridostigmine, n (%)	155 (93.94)	187 (93.39)	0.276
Prednisolone, n (%)	85 (51.52)	136 (70.10)	< 0.001*
Immunosuppressants, n (%)	30 (18.18)	47 (24.23)	0.164
AZA, n (%)	10 (6.06)	6 (3.09)	0.174
MMF, n (%)	6 (3.64)	10 (5.15)	0.487
Tacrolimus, n (%)	14 (8.48)	31 (15.98)	0.033*
Baseline MG-ADL, median (IQR)	5 (3, 7)	3 (3, 6)	0.003*
Baseline QMGS, median (IQR)	9 (6, 12)	7 (5, 8)	< 0.001*
Clinical improvement, n (%)	125 (75.76)	123 (63.40)	0.012*
CT lung inflammation of inpatients (before = 65 and after = 72), n (%)	13 (20.00)	29(40.28)	0.010*
Pyridostigmine in outpatient treatment (before = 100 and after = 122), n (%)	91 (91.00)	119 (97.54)	0.032*
Antibody status of outpatients (missed 2, before = 100 and after = 122), Seronegative, n (%)	27 (27.00)	19 (15.83)	0.043*

Note: **P*-value < 0.05 is significant. Seronegative MG indicates that all five antibodies are negative

Abbreviations MG myasthenia gravis, *COVID-19* Coronavirus disease 2019, *IQR* Interquartile range, *SD* Standard deviation, *BMI* Body mass index, *MGFA* Myasthenia Gravis Foundation of America, *AChRab* + anti-acetylcholine receptor antibody positive, *MuSKab* + anti-muscle-specific tyrosine kinase positive, *LRP4ab* + anti-low-density lipoprotein receptor-related protein 4 positive, *RyRab* + anti- ryanodine receptor positive, *Titin ab* + anti-Titin antibody positive, *RNS* + Repetitive nerve stimulation positive, *AZA* Azathioprine, *MMF* Mycophenolate mofetil, *MG-ADL* MG activities of daily living profile, *QMGS* Quantitative MG Score

between the two groups was significantly different ($p=$ 0.028). For treatment of MG, the number of using prednisolone in the after group was significantly higher than that in the before group (70.10% vs. 51.52%, $p<$ 0.001). Furthermore, a greater number of MG patients in the after group (15.98% vs. 8.48%, $p=$ 0.033) used tacrolimus. The baseline MG-ADL (3, IQR: 3, 6) and QMGS (7, IQR: 5, 8) scores in the after group were lower than those in the before group ($p<$ 0.05). Most patients with MG were admitted specifically due to a worsening of myasthenic symptoms. The inpatient rates (37.11%) of MG patients in the after group were slightly lower compared to those in the before group (39.39%). CT scans showed more lung inflammation in inpatients (40.28% vs. 20%, $p=$ 0.010) of the after group. Of the 122 MG outpatients in the after group, 119 (97.54%) individuals used pyridostigmine and 19 (15.82%, 19/120) were antibody-negative MG, which were significantly different from those in the before group.

The season of onset for patients with new-onset MG before and after the COVID-19 outbreak was different (Fig. 1). Among new-onset MG patients after the outbreak of COVID-19, 65 (33.51%) had a new onset of MG in winter, 43 (22.16%) in spring, 46 (23.71%) in summer, and 40 (20.62%) in autumn. In the before group, there were 32 (19.39%), 26 (15.76%), 56 (33.94%), and 51 (30.91%) patients, respectively. The difference in the seasonal distribution of incidence of MG between the two groups was significant ($p=$ 0.001). Approximately 55.67% (108/194) of patients' new onset of MG occurred in winter or spring, which was significantly higher than that in the before group (35.15%, 58/165, $p<$ 0.001). The most notable increase was observed in winter (33.51% vs. 19.39%, $p=$ 0.003). Additionally, the proportion of patients was increased significantly near the time of the COVID-19 outbreak.

Predictors for prognosis of new-onset MG patients before and after COVID-19 outbreak

The clinical improvement rate in patients with MG in the after group (63.40% vs. 75.76%, p< 0.002) was significantly lower than that in the before group. Univariate logistic regression analysis showed that MG-ADL, medical treatment using prednisolone, MGFA type III or higher, muscle involvement in the bulbar or respiratory muscles, and GMG were related factors affecting the clinical improvement of MG patients in the before group; however, only MG-ADL (OR 1.687, 95% CI: 1.282–2.220, $p<$ 0.001) was identified as an independent predictor in the multivariate logistic analysis (Table 2).

The clinical improvement features in patients with new-onset MG after the outbreak of COVID-19 were shown in Table 3. There were no significant differences between the patients with improvement and without improvement in demographics, COVID-19 vaccination, infection rate, MG duration, season of onset, antibody status, thymus status, and RNS. More MG patients with improvement (29.27% vs. 9.86%, $p=$ 0.002) were classified as having an MGFA III or more. The improved group had approximately 51.22% of patients with GMG, almost twice as many as the non-improved group (33.80%; $p=$ 0.019). In addition, more patients with improvement (30.08%) were affected by the bulbar or respiratory muscles than the non-improved group (11.26%, $p=$ 0.003). Patients with improvement were younger at onset (36, IQR: 20, 52, $p=$ 0.001) and were more likely to use pyridostigmine (99.19%) or tacrolimus (20.33%). The difference between baseline MG-ADL (5, IQR: 3, 6) in patients with improvement and baseline MG-ADL (3, IQR: 3, 3) in patients without improvement was statistically significant ($p<$ 0.001).

Furthermore, multivariate logistic regression analysis showed that age at onset (OR 0.964, 95% CI: 0.947–0.982,

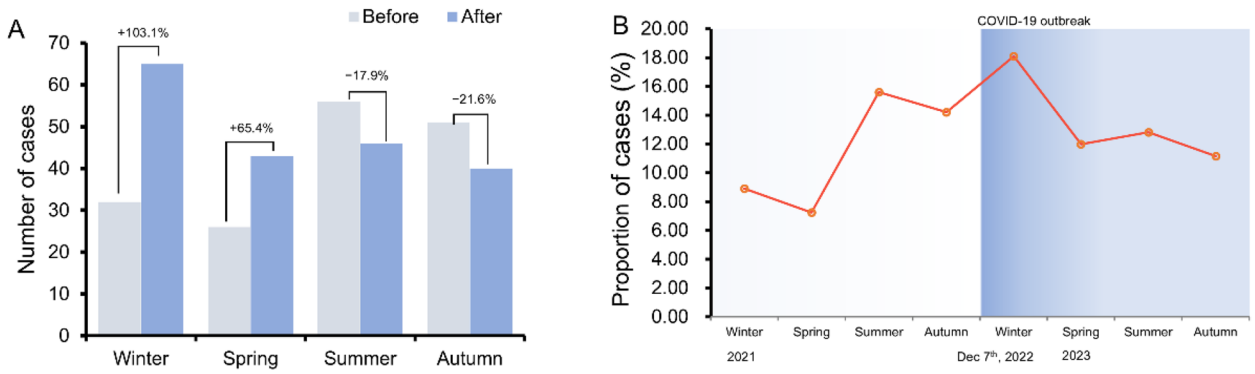

Fig. 1 Season of onset in MG patients before and after the outbreak of COVID-19. **A** Number of MG patients in each season. **B** Proportion of MG patients by season. Changes of cases between the patients before and after COVID-19 outbreak are indicated. The graph shows the impact of COVID-19 outbreak

Table 2 Logistic regression analysis of predictors for clinical improvement in new-onset MG patients before COVID-19 outbreak

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Baseline MG-ADL	1.720 (1.339, 2.211)	< 0.001*	1.687 (1.282, 2.220)	< 0.001*
Age at the onset	1.004 (0.986, 1.022)	0.697	0.987 (0.976, 1.008)	0.216
Vaccine	1.561 (0.666, 3.655)	0.305		
Pyridostigmine	2.204 (0.589, 8.241)	0.240	1.422 (0.275, 7.365)	0.675
Immunosuppressant	1.616 (0.572, 4.567)	0.365		
Prednisolone	2.442 (1.165, 5.117)	0.018*	1.667 (0.679, 4.091)	0.265
RNS-positive	1.925, (0.928, 3.396)	0.079	1.233 (0.506, 3.000)	0.645
Abnormal thymus	0.904 (0.436, 1.873)	0.786		
Antibody status	1.171 (0.592, 2.316)	0.650		
Smoking	1.561 (0.594, 4.105)	0.366		
Season of onset	1.215 (0.840, 1.756)	0.301	1.187 (0.788, 1.786)	0.412
MGFA ≥ III	4.796 (1.388, 16.568)	0.013*	1.382 (0.256, 7.465)	0.707
Generalized MG	3.189 (1.515, 6.715)	0.002*	0.917 (0.312, 2.697)	0.875
Affect bulbar or respiratory muscles	4.037 (1.580, 10.312)	0.004*	1.558 (0.341, 6.160)	0.616
Infection rate	2.453 (0.525, 11.459)	0.254		
MG duration	1.000 (0.976, 1.024)	0.972		
Gender, male	1.179 (0.571, 2.432)	0.657		

Note: **P*-value < 0.05 is significant. $n = 165$ (125 for clinical improvement, 40 for without clinical improvement)

Abbreviations: *MG* Myasthenia gravis, *MG-ADL* MG activities of daily living profile, *MGFA* Myasthenia Gravis Foundation of America, *RNS* Repetitive nerve stimulation

$p < 0.001$), baseline MG-ADL (OR 1.611, 95% CI: 1.279–2.208, $p < 0.001$), lack of medical treatment with pyridostigmine (OR 0.083, 95% CI: 0.008–0.903, $p = 0.041$) and OMG (OR 0.401, 95% CI: 0.167–0.962, $p = 0.041$) were independent predictors of clinical improvement in new-onset patients after the COVID-19 outbreak (Table 4).

Features of new-onset GMG patients following COVID-19 outbreak

The features of new-onset OMG and GMG patients following the COVID-19 outbreak were shown in Table 5. GMG patients were more frequently female (62.07% vs. 47.66%, $p = 0.045$) and older at onset (43 vs. 37, $p = 0.013$). In addition, their MG duration (16, IQR: 7, 36) was longer than that of OMG patients (14, IQR: 5, 27, $p = 0.065$), although the difference was not statistically significant. 14 patients with GMG underwent thymectomy; the pathological types of all 14 thymuses (100.00%) were thymomas, which was significantly higher than that in patients with OMG (61.54%, 8/13, $p = 0.016$). Positive rates of RNS (60.00%, 48/80, $p = 0.013$) and anti-MuSK (18.60%, 16/86, $p < 0.001$) were higher in patients with GMG than in those with OMG. The decremental responses of RNS in patients with OMG were exclusively observed in the facial nerve, with no similar findings detected in other tested nerves (accessory, axillary, or median nerves). The antibody negative rate (11.63%, 10/86) was significantly lower than that in patients with OMG (22.86%, 24/105, $p = 0.044$). Among the 87 patients with GMG, 76 (87.36%, $p < 0.001$) patients were treated with prednisolone. 36 (41.38%, $p < 0.001$) were treated with immunosuppressants, including 23 (26.44%, $p < 0.001$) with tacrolimus and 8 (9.20%, $p = 0.022$) with MMF. Baseline MG-ADL (5, IQR: 3, 6, $p = 0.027$) and QMGS (9, IQR: 6, 14, $p < 0.001$) in GMG patients were significantly higher than in those with OMG patients. Moreover, a logistic analysis was conducted for patients with OMG and GMG, respectively (Table 6). Baseline MG-ADL, MG occurring in March, COVID-19 vaccination, and age at onset were associated with clinical improvement in patients with OMG, but only age at onset (OR 0.963, $p < 0.001$) and baseline MG-ADL (OR 1.843, $p < 0.001$) were independent factors. Muscle involvement in the limbs, prednisolone use, and baseline MG-ADL were associated with clinical improvement in patients with GMG, but only MG-ADL (OR 1.495, $p = 0.002$) was an independent factor.

Discussion

This study is the first to analyze the characteristics and predictors of clinical improvement in new-onset MG one year before and one year after the COVID-19 outbreak. Our study found that the total number of MG outpatient

Table 3 Features of MG clinical improvement in new-onset MG patients after COVID-19 outbreak

Variables	MG Clinical Improvement		*P* value
	NO (n = 71)	YES (n = 123)	
Gender, female, n (%)	33 (46.48)	72 (58.54)	0.104
BMI (mean ± SD)	22.01 ± 3.61	22.64 ± 3.83	0.511
Smoking, n (%)	14 (19.72)	16 (13.01)	0.213
Vaccination, ≥ 1, n (%)	64 (90.14)	107 (86.99)	0.513
Infection rate, n (%)	68 (95.77)	117 (95.12)	0.835
Age at onset (y), median (IQR)	49 (35, 60)	36 (20, 52)	0.001*
MG duration (w), median (IQR)	14 (6, 32)	15 (5, 32)	0.969
Season of onset, Winter and Spring, n (%)	40 (56.34)	68 (55.28)	0.887
MGFA,			0.002*
< III, n (%)	64 (90.14)	87 (70.73)	
≥ III, n (%)	7 (9.86)	36 (29.27)	
Clinical phenotype			0.019*
Ocular, n (%)	47 (66.20)	60 (48.78)	
Generalized, n (%)	24 (33.80)	63 (51.22)	
Affect bulbar or respiratory muscles, n (%)	8 (11.26)	37 (30.08)	0.003*
Affect limb muscles, n (%)	16 (22.54)	26 (21.14)	0.820
Antibody status (missed 3)			0.220
AChRab +, n (%)	50 (72.46)	87 (71.31)	
MuSKab +, n (%)	3 (4.35)	13 (10.66)	
Seronegative, n (%)	13 (18.84)	19 (15.57)	
Abnormal thymus (missed 1), n (%)	27 (38.57)	42 (34.15)	0.380
RNS + (missed 13), n (%)	30 (44.78)	58 (50.88)	0.428
MG treatment			
Pyridostigmine, n (%)	65 (91.55)	122 (99.19)	0.019*
Prednisolone, n (%)	47 (66.20)	89 (72.36)	0.367
Immunosuppressants, n (%)	9 (12.68)	38 (30.89)	0.004*
AZA, n (%)	1 (1.41)	5 (4.07)	0.549
MMF, n (%)	2 (2.82)	8 (6.50)	0.434
Tacrolimus, n (%)	6 (8.45)	25 (20.33)	0.030*
Baseline MG-ADL, median (IQR)	3 (3, 3)	5 (3, 6)	< 0.001*

Note: **P*-value < 0.05 is significant. Seronegative MG indicates that all five antibodies are negative

Abbreviations: *MG* myasthenia gravis, *COVID-19* Coronavirus disease 2019, *IQR* Interquartile range, *SD* Standard Deviation, *BMI* Body mass index, *MGFA* Myasthenia Gravis Foundation of America, *AChRab* + Anti-acetylcholine receptor antibody positive, *MuSKab* + Anti-muscle-specific tyrosine kinase positive, *RNS* + Repetitive nerve stimulation positive, *AZA* Azathioprine, *MMF* Mycophenolate mofetil, *MG-ADL* MG activities of daily living profile, *QMGS* Quantitative MG Score

Table 4 Multivariable logistic regression analysis of predictors for clinical improvement in new-onset MG patients after COVID-19 outbreak

Variables	β Coefficient	OR (95% CI)	*P* value
Age at the onset	− 0.036	0.964 (0.947, 0.982)	< 0.001*
Baseline MG-ADL	0.477	1.611 (1.279, 2.208)	< 0.001*
Lack of Tacrolimus in MG treatment	− 0.744	0.475 (0.150, 1.501)	0.205
Lack of Pyridostigmine in MG treatment	− 2.485	0.083 (0.008, 0.903)	0.041*
MGFA < III	0.038	1.039 (0.317, 3.407)	0.950
OMG	− 0.914	0.401 (0.167, 0.962)	0.041*

Note: **P*-value < 0.05 is significant. *n* = 194 (123 for clinical improvement, 71 for without clinical improvement)

Abbreviations: *MG* Myasthenia gravis, *MG-ADL* MG activities of daily living profile, *MGFA* Myasthenia Gravis Foundation of America, *OMG* Ocular MG

Table 5 Features of new-onset OMG and GMG patients following COVID-19 outbreak

Variables	OMG ($n = 107$)	GMG ($n = 87$)	*P* value
Gender, female, n (%)	51 (47.66)	54 (62.07)	0.045*
Vaccination, ≥ 1, n (%)	94 (87.85)	77 (88.51)	0.888
Infection rate, n (%)	99 (92.52)	86 (98.85)	0.082
MG duration (w), median (IQR)	14 (5, 27)	16 (7, 36)	0.065
Age at onset (y), median (IQR)	37 (18, 54)	43 (35, 55)	0.013*
Abnormal thymus (missed 1), n (%)	36 (33.96)	33 (37.93)	0.535
Thymic pathology (13 = OMG and 14 = GMG), n (%)			0.016*
Thymic hyperplasia	5 (38.46)	0 (0)	
Thymoma	8 (61.54)	14 (100.00)	
RNS + (missed 13), n (%)	40 (39.60)	48 (60.00)	0.013*
Antibody status (missed 3)			< 0.00*1
AChRab +, n (%)	78 (74.28)	59 (68.60)	0.386
MuSKab +, n (%)	0 (0)	16 (18.60)	< 0.001*
LRP4ab + or RyR ab + or Titin ab +, n (%)	3 (2.86)	1 (1.16)	0.760
Seronegative, n (%)	24 (22.86)	10 (11.63)	0.044*
MG treatment			
Pyridostigmine, n (%)	104 (97.20)	83 (95.40)	0.505
Prednisolone, n (%)	60 (56.07)	76 (87.36)	< 0.001*
Immunosuppressants, n (%)	11 (10.28)	36 (41.38)	< 0.001*
Tacrolimus, n (%)	8 (7.48)	23 (26.44)	< 0.001*
MMF, n (%)	2 (1.87)	8 (9.20)	0.022*
AZA, n (%)	1 (0.93)	5 (5.75)	0.131
Baseline MG-ADL, median (IQR)	3 (3, 6)	5 (3, 6)	0.027*
Baseline QMGS, median (IQR)	5 (4, 7)	9 (6, 14)	< 0.001*

Note: **P*-value < 0.05 is significant. Seronegative MG indicates that all five antibodies are negative

Abbreviations: *MG* myasthenia gravis, *COVID-19* coronavirus disease 2019, *OMG* Ocular MG, *GMG* Generalized MG, *IQR* Interquartile range, *AChRab* + Anti-acetylcholine receptor antibody positive, *RNS* + Repetitive nerve stimulation positive, *MuSKab* + Anti-muscle-specific tyrosine kinase positive, *LRP4ab* + Anti-low-density lipoprotein receptor-related protein 4 positive, *RyRab* + Anti- ryanodine receptor positive, *Titin ab* + Anti-Titin antibody positive, *AZA* azathioprine, *MMF* Mycophenolate mofetil, *MG-ADL* MG activities of daily living profile, *QMGS* Quantitative MG Score

Table 6 Logistic regression analysis of predictors for clinical improvement in OMG and GMG patients

Clinical phenotype	Variables	Univariate analysis		Multivariate analysis	
		OR (95% CI)	*P* value	OR (95% CI)	*P* value
OMG ($n = 107$)	Baseline MG-ADL	1.843 (1.335, 2.543)	< 0.001*	2.318 (1.486, 3.616)	< 0.001*
	Age at the onset	0.963 (0.944, 0.983)	< 0.001*	0.948 (0.920, 0.977)	< 0.001*
	Onset in March	12.800 (1.208, 135.579)	0.034*	7.282 (0.524, 101.183)	0.139
	Vaccination	0.198 (0.042, 0.942)	0.042*	0.399 (0.049, 3.240)	0.399
GMG ($n = 87$)	Affect Limb muscles	0.351 (0.131, 0.942)	0.038*	0.705 (0.232, 2.143)	0.537
	Prednisolone	3.867 (1.055, 14.178)	0.041*	2.012 (0.478, 8.462)	0.340
	Baseline MG-ADL	1.495 (1.154, 1.935)	0.002*	1.374 (1.040, 1.814)	0.025*

Note: **P*-value < 0.05 is significant. $n = 107$ (60 for OMG patients with clinical improvement, 47 for OMG patients without clinical improvement). $n = 87$ (63 for GMG patients with clinical improvement, 24 for GMG patients without clinical improvement)

Abbreviations: *MG* myasthenia gravis, *OMG* Ocular MG, *GMG* Generalized MG, *MG-ADL* MG activities of daily living profile

visits decreased from 706 (before COVID-19 outbreak) to 571 (after COVID-19 outbreak), with the most significant drop occurring in December 2022 and January 2023. This decline was likely related to the COVID-19 outbreak, which peaked 1–2 months after the relaxation of prevention policies. Since hospitals were high-risk locations for infection, many patients opted to purchase medications online and reduced the frequency of their

hospital visits due to concerns about contracting or re-contracting the virus. This might explain why patients with new-onset MG after the COVID-19 outbreak took longer time to hospital treatment after the onset of symptoms, compared to those before the outbreak. In this retrospective study, the number of new-onset MG patients after the COVID-19 outbreak increased. Infection with the virus triggers an immune response in humans. Previous studies found a correlation between the occurrence of MG and infection with some virus [15–18], such as the Epstein-Barr virus, hepatitis E virus, West Nile virus, and human parvovirus B19. Several studies have reported that some people became ill with MG after infection with SARS-CoV-2 [6–8]. Some possible reasons for the increase in reports of new-onset MG during the COVID-19 pandemic are the similarity of MG-related receptors to SARS-CoV-2 receptors, or the activation and triggering of inflammatory responses and cytokine storms in the body after infection with SARS-CoV-2 [13]. Furthermore, people may have a higher chance of developing depression or anxiety during the COVID-19 pandemic, which could be associated with the occurrence and development of MG [19, 20]. This study also found that most people received the vaccine in 2021 or 2022, and the vaccination rate in patients with new-onset MG after the outbreak of COVID-19 was higher (88.14%). Some studies have reported the onset of MG after COVID-19 vaccination [9, 21]. Other studies have also reported that MG occurs after other vaccinations [22–24]. An autoimmune response occurs in the body after vaccination, activating T cells to participate in the autoimmune process. In addition, vaccines contain dsRNA or other analogs that could cause thymus-associated MG [25]. Therefore, we might speculate that vaccination maybe related to the occurrence of MG. However, the direct link between vaccines and the development of MG remains unclear currently, primarily due to the lack of comprehensive vaccination data for certain patients. The pre-existing diagnosis or immunotherapy might partially explain the lower vaccination rates in the before group. Besides, some people might have refused to be vaccinated in the early stages for fear that the vaccine would exacerbate or induce the disease. As time went on, most people realized COVID-19 was so easily infected and infection with COVID-19 could be fatal, so more and more people were vaccinated. Currently, there is no standardized peak season for MG worldwide. Seasonal peaks in MG have rarely been routinely counted in previous studies. That said, infectious diseases, especially viral infections, typically exhibit seasonal prevalence patterns. New-onset MG patients after the COVID-19 outbreak may show seasonal distribution trends, especially considering the occurrence of sporadic infection spikes. The onset time of new-onset MG patients in the after group was mainly in winter or spring in our study, that is, six months after the adjustment of prevention strategies in China, especially in the first three months. The number of new-onset MG patients in the three months after the COVID-19 outbreak was nearly double than that of other seasons. Features of the time of onset in the after group are inconsistent with a previous study conducted in 2014, which found that the incidence of MG patients peaked in late winter or late summer [26]. This is inconsistent with our findings. We speculate that the different onset times of MG patients may not only be related to the season but also to the large-scale outbreak of COVID-19 following the adjustments. Thus, the onset of MG may be related to SARS-CoV-2 infection, the psychosocial environment during the COVID-19 pandemic, COVID-19 vaccination, and the outbreak of COVID-19 in China.

The proportion of GMG (44.85%) in the after group was lower, with less involvement of the bulbar or respiratory muscles. However, in a 2020 real-world survey covering several countries in Europe during the global COVID-19 pandemic, 65.3% of the patients had GMG [27], indicating a higher proportion than that in our study. The use of prednisolone and tacrolimus was higher in patients with new-onset MG after the COVID-19 outbreak compared to the before group, potentially due to prednisolone and tacrolimus can significantly enhance therapeutic efficacy in MG management [28], coupled with the safety and tolerability of prednisolone combined with immunosuppressants in patients with moderate to severe systemic MG [29]. Additionally, we speculated that patients might be more concerned about their illnesses, and comprehensive understanding of disease-related information and awareness of the pandemic's impact may have contributed to improved treatment adherence among patients after experiencing COVID-19 [30]. Among the 194 new-onset MG patients in the study following the COVID-19 outbreak, a higher proportion of patients (15.98%) in the after group used tacrolimus. This trend might reflect an increased recognition by both physicians and patients of the effectiveness of immunosuppressive drugs for MG management during the pandemic. Additionally, a 2022 study suggested that existing immunosuppressive agents, such as tacrolimus, may be safe for use in MG patients with COVID-19 and should not be discontinued [31]. Tacrolimus can effectively improve symptoms in MG patients without COVID-19 [32], but taking immunosuppressant drugs has no significant relationship with the infection of SARS-CoV-2 [33]. Moreover, a study in China reported that immunosuppressant did not worsen or hospitalize MG with COVID-19 [13]. However, increased mortality after COVID-19 infection in patients with immune diseases is associated with the higher use

of immunosuppressant [34, 35]. Therefore, a personalized immunotherapy regimen should be adopted for MG patients.

The European study showed that 20.8% of MG patients received thymectomy during COVID-19 pandemic [27]. Thymectomy can continuously improve the symptoms of MG patients [36]. The study by Jiang et al. supported the need for thymectomy in the early stage of MG disease [37]. But the rate of thymectomy in new-onset MG patients after the COVID-19 outbreak was lower (13.92%), probably because the role of the thymus in developing MG during the high prevalence of SARS-CoV-2 is unclear. Although previous studies have shown that some cases of MG development are thymus-related, the virus may be involved in MG pathogenesis. A previous study showed that B2 or B3 thymoma was an independent risk factor for conversion to GMG [38], and the proportion of new-onset MG patients with a B-type thymus was lower in the after group. Higher MG-ADL and QMGS scores correlate with more severe disease. This is consistent with our findings that the baseline MG-ADL and QMGS scores in the after group were lower, thus the after group had a milder presentation of MG. In correlation, patients in the after group may delay going to the hospital because of their milder symptoms, and the MG duration was longer for them. Moreover, the clinical improvement rate (63.40%) of MG for the after group was lower. This could be linked to the higher proportion of OMG patients and their older age of OMG patients in the after group. Age at onset was a risk factor associated with OMG transition [39], and younger OMG patients were more likely to achieve complete remission of symptoms [38]. Early treatment with medication or surgery is crucial for improving MG symptoms. More CT scans showed lung inflammation in inpatients with new-onset MG after the COVID-19 outbreak (40.28%) compared with inpatients before the COVID-19 outbreak (20.00%). One reason for this may be the increase in disease-causing microbial infections. Social isolation measures and strict personal protection could reduce the occurrence of some diseases or infectious diseases, especially respiratory diseases [40, 41]. Following the adjustment of epidemic prevention policies in December 2022, adherence to personal protection measures decreased, leading to an observed rise in respiratory infections. In addition, inflammatory changes were observed in the lungs of patients infected with COVID-19 [42]. Surprisingly, the proportion of medical treatment with pyridostigmine (97.54%) was significantly higher than that of outpatients in the before group. This may be due to increased patient compliance. The serum antibody negative rate (15.83%) of MG outpatients in the after group was higher than that in the before group, which is consistent with previous studies that reported a small percentage of MG patients with serum antibody negativity (10% – 15%) [43].

In addition, the rate of clinical improvement in the after group was lower than that in the before group. Further logistic regression analysis revealed that MG-ADL was the only independent factor in the before group. Conversely, in the after group, there were four independent factors, of which MG-ADL was an independent positive predictor, whereas age at onset and OMG were independent negative predictors. Our data also indicated that the absence of pyridostigmine use was an independent predictor of clinical improvement in new-onset patients after the COVID-19 outbreak. We hypothesize that this might be due to pyridostigmine's better short-term therapeutic effect in assessing clinical improvement. However, since pyridostigmine is not a disease-modifying drug, its use leading to better outcomes lacks biological plausibility. As a result, this factor was excluded from our analysis. MG-ADL was an independent positive predictor in both groups, but it was lower in the after group than in the before group. Therefore, we conducted a more detailed analysis of the factors influencing clinical improvement of MG in the after group. Among patients with new-onset MG after the COVID-19 outbreak, those with improvement were more frequently found to have GMG. Further multivariate logistic regression analysis showed that OMG was an independent negative predictor of clinical improvement. We hypothesize that this might be due to the older onset age of OMG patients in the after group. However, we also found that the assertion that OMG has a poor clinical improvement may not align with existing literature. As a result, this factor was excluded from the prediction model. Our team will continue to investigate this issue in our subsequent studies. Our study found that patients with GMG after the COVID-19 outbreak were more likely to be taking tacrolimus and had higher baseline MG-ADL scores compared to those with OMG. Previous research has reported that the early use of tacrolimus in patients with GMG could result in long-term benefits in achieving better clinical outcomes [44], which is consistent with our findings. A multicenter study conducted in Germany in 2022 revealed that older age is a prognostic risk factor for MG patients [45], which is consistent with our finding that younger patients with MG are more likely to achieve clinical improvement. Our study found that age at onset and lack of pyridostigmine use were independent negative predictors of clinical improvement in patients with MG after the outbreak of COVID-19. The younger the age of onset, the better the patient's response to treatment. Mortality related to MG was significantly higher among the elderly in China [46]. Older MG patients are less tolerant to drugs, have more

comorbidities, and are more likely to be misdiagnosed, making diagnosis and treatment more difficult.

In the following step, we analyzed patients with new-onset MG after the COVID-19 outbreak. Further analysis revealed that the positive rate of MG-related antibodies was higher in GMG patients compared to patients with OMG, especially anti-Musk antibody (18.60%), which is in accordance with previous studies [27, 47]. Positive RNS findings and thymoma occurrence were more prevalent in GMG patients, consistent with prior reports [48, 49]. Moreover, patients with GMG had a longer MG duration, higher baseline MG-ADL and QMGS scores, and more complex diagnosis and treatment. In this study, the onset age of patients with GMG was older and most of them were female.

It is important to note that our study has some limitations. First, the data were collected from a single-center study, which is methodologically limited and not appropriate for generalizing disease incidence. Second, there were very few cases of new-onset MG after infection with SARS-CoV-2 in China before 2023; therefore, this study could not compare the characteristics of different variants of SARS-CoV-2.

Conclusions

In this single-center cross-sectional study, new-onset MG cases following the COVID-19 outbreak showed altered seasonal onset patterns, milder disease severity, and higher OMG onset age. Age at onset is an independent negative predictor of clinical improvement in new-onset MG patients after the COVID-19 outbreak, while baseline MG-ADL is an independent predictor of positive correlation. The study provides some valuable insights for the management of new-onset MG patients following the COVID-19 pandemic. Furthermore, our team will carry out multi-center research work in multiple hospitals in Guangxi in the future.

Abbreviations

MG	Myasthenia gravis
COVID-19	Coronavirus disease 2019
MGFA	Myasthenia Gravis Foundation of America
AChRab +	Anti-acetylcholine receptor antibody positive
MuSKab +	Anti-muscle-specific tyrosine kinase positive
LRP4ab +	Anti-low-density lipoprotein receptor-related protein 4 positive
RyRab +	Anti-Ryanodine receptor positive
Titin ab +	Anti-titin antibody positive
RNS +	Repetitive nerve stimulation positive
AZA	Azathioprine
MMF	Mycophenolate mofetil
MG-ADL	MG activities of daily living profile
QMGS	Quantitative MG Score
OMG	Ocular MG
GMG	Generalized MG
OR	Odds ratio
CI	Confidence interval
IQR	Interquartile range
SD	Standard deviation
BMI	Body mass index

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Authors' contributions

YH, YW AND SZ analyzed and interpreted the data. YH, YW, SZ, XQ, AJ, DS, TL, YC, ZL, CL, YW, SZ and WH were actively involved in the conception, data collection and completion of the study. YH drafted the manuscript with substantive revision by WH. All authors read and approved the final manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the First Affiliated Hospital of Guangxi Medical University (2024-E420-01), and written informed consent was obtained from all patients before starting the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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