Neurol Ther
https://doi.org/10.1007/s40120-024-00619-4

ORIGINAL RESEARCH

Epidemiology, Patient Characteristics, and Treatment Patterns of Myasthenia Gravis in Taiwan: A Population-Based Study

Nai-Wen Tsai · Li-Nien Chien · Connie Hung · Amanda Kuo · Yu-Ting Chiu · Hung-Wei Lin · Li-Shan Jian · Kai-Pei Chou · Jiann-Horng Yeh

Received: February 1, 2024 / Accepted: April 5, 2024

ABSTRACT

Introduction: Myasthenia gravis (MG) is a chronic neuromuscular disease leading to significant disease burden. This study aimed to investigate the epidemiology of MG in Taiwan.

Methods: A retrospective study was conducted using the Taiwan National Health Insurance Research Database. Prevalent patients with MG diagnosis (either ocular or generalized MG) from 2013 to 2019 were identified, and 2813 patients with initial MG diagnosis from 2014 to 2019 were further defined as the incident cohort. Patient characteristics, treatment patterns, and the occurrence of MG-related events were analyzed.

Results: The number of prevalent patients with MG increased from 4476 in 2013 to 5752 in 2019, with the prevalence rate increasing from 19 to 24 per 100,000 population. The incidence rate also slightly increased from 1.9 to 2.3 per 100,000 population during the study period. Almost all incident patients (99%, $n=2791$) received MG-related treatment during the follow-up period. Among 1876 patients who received monotherapy as their initial treatment in the outpatient setting, the mean time from the index date to initial treatment was 48.8 (standard deviation 164.3) days, and most patients received acetylcholinesterase inhibitors (88.5%, $n=1661$) as their initial treatment.

Nai-Wen Tsai and Li-Nien Chien contributed equally to the study.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40120-024-00619-4.

N.-W. Tsai
Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan

N.-W. Tsai
College of Medicine, Chang Gung University, Taoyuan, Taiwan

N.-W. Tsai
School of Medicine, College of Medicine, National Sun Yat-sen University, Kaohsiung, Taiwan

L.-N. Chien · Y.-T. Chiu
Institute of Health and Welfare Policy, College of Medicine, National Yang Ming Chiao Tung University, Taipei, Taiwan

C. Hung · A. Kuo
UCB Pharma, Taipei, Taiwan

H.-W. Lin · L.-S. Jian · K.-P. Chou
Real World Solutions, IQVIA Solutions Taiwan Ltd., Taipei, Taiwan

J.-H. Yeh (✉)
Department of Neurology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan
e-mail: M001074@ms.skh.org.tw

J.-H. Yeh
School of Medicine, College of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan

Published online: 27 April 2024

During the first year after the index date, 133 (4.7%) incident patients experienced their first myasthenic crisis, and 96.2% of these events occurred within 3 months.

Conclusion: The prevalence of MG increased steadily in Taiwan, and the treatment of patients with MG was consistent with guidelines. Despite a high treatment rate, patients still experienced MG-related events, highlighting the limitation of current treatments and emphasizing the need for early intervention and novel treatment approaches.

Keywords: Myasthenia gravis (MG); Epidemiology; Treatment pattern; Myasthenic crisis; Disease burden

Key Summary Points

Why carry out this study?

Myasthenia gravis (MG) is a chronic disease leading to muscle weakness that affects patients' daily activities as well as ocular and respiratory function. However, there is limited epidemiology data on MG in Taiwan.

The aim of the study was to understand the epidemiology and characteristics of patients with MG (including ocular and generalized MG) in Taiwan by utilizing the nationwide claims database. The treatment patterns and the occurrence of MG-related events (e.g., myasthenic crisis and use of plasma exchange) were also investigated.

What was learned from this study?

This study provides a detailed overview of MG in Taiwan. The prevalence of MG increased steadily in Taiwan and the treatment patterns were consistent with clinical guidelines.

Despite a high treatment rate, patients still experienced MG-related events, highlighting the limitation of current treatments and emphasizing the need for increased disease awareness, early intervention, and novel treatment approaches.

INTRODUCTION

Myasthenia gravis (MG) is a chronic disease mediated by autoantibodies to important proteins, such as acetylcholine receptors and muscle-specific tyrosine kinase in the postsynaptic region of the neuromuscular junction, leading to ocular, bulbar, and limb skeletal muscle weakness that affect patients' daily activities, sight, and respiratory function [1–3]. Studies have reported that MG is associated with a significant disease burden, including increased healthcare expenses, decreased productivity, and poor quality of life due to the consequences of muscle weakness and side effects of medications [4–7].

Epidemiology studies in several countries have found that the prevalence and incidence rates of MG have increased over recent decades [8–11]. Studies in Asia have also shown there is a large variation in the incidence rate among Asian countries (China, Japan, and South Korea), from 0.015 to 2.4 per 100,000 person-years [12–14]. However, there is limited epidemiology data on MG in Taiwan. A nationwide population-based study of Taiwanese patients with MG was published in 2010 [15], while a recent study only focused on generalized MG (gMG), a subgroup of MG [10].

In addition, data are also lacking on the characteristics, treatment patterns, and disease burden of MG in Taiwan. The treatment targets of MG are to avoid the unexpected deterioration and fluctuation of neurological and muscular symptoms, as well as the occurrence of myasthenic crisis (MG crisis) [16]. MG crisis is an acute and life-threatening manifestation of MG, which is associated with an increased risk of death and high burden of disease for patients with MG [17]. Studies and clinical guidelines have indicated that an individualized treatment

approach based on disease status, such as initial severity, may decrease the risk of MG crisis [18–20]. To gain a better understanding of the disease burden among patients with MG and to obtain clear insights into current treatment practices in Taiwan, a comprehensive and up-to-date epidemiology study of patients with MG in Taiwan was required.

This study aimed to investigate the epidemiology and characteristics of patients with MG in Taiwan by utilizing the Taiwan National Health Insurance Research Database (NHIRD). There were two main objectives: firstly, to understand the epidemiology, patient characteristics, and treatment patterns among prevalent patient with MG in Taiwan (*objective 1*); and secondly, to investigate the characteristics, treatment sequencing, and disease progression of incident patients with MG (*objective 2*).

METHODS

Data Sources

This study used data from the NHIRD, provided by the Health and Welfare Data Science Center, the Ministry of Health and Welfare. NHIRD is a claims-based database that contains healthcare data of beneficiaries who enrolled in National Health Insurance (NHI) in Taiwan [21]. The database contains inpatient visits, outpatient visits, emergency room visits, and pharmacy records [21, 22]. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM, before 2015) and the tenth version (i.e., ICD-10-CM, after 2016) were used in the NHIRD to record the diagnosis of patients. The data period for this study was from 1 January 2013 to 31 December 2020.

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Taipei Medical University (Approval number N202203018). Informed consent was waived because of the study's descriptive and non-interventional nature, and the analysis was de-identified. This study was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments.

Study Population

Patients who met the following criteria were defined as having MG: (1) at least one inpatient or outpatient MG diagnosis (ICD-9-CM 287.3 and ICD-10-CM G70.00–G70.01), and (2) a Catastrophic Illness Certificate (CIC) for MG [15]. The CIC record was used to increase the accuracy of the diagnosis since the CIC is only issued to patients with MG after their medical records have been reviewed by clinical experts of the NHI Administration [21]. The first date of MG diagnosis was defined as the index date.

For objective 1, patients with MG were included in the analysis after the index date, and patients who were alive at the end of each year (i.e., 31 December) between 2013 and 2019 were identified as prevalent patients with MG. Incident MG cases were further identified for objective 2. Patients with an MG diagnosis in 2013 were excluded from the incident cohort, as a 1-year washout period for identifying the newly diagnosed MG cases. Patients were followed up until death, withdrawal from NHI, or the end of the study period (31 December 2020), whichever came first.

Demographics and Comorbidities

Demographics (sex and age) of patients with MG were assessed in both the prevalent and incident cohorts. Patients in the incident cohort were defined as having comorbidities if they had at least two outpatient records or one inpatient diagnosis code 1 year before and after the index date. The comorbidities were categorized into thyroid disorders (autoimmune thyroiditis and other thyroid disorders), autoimmune disorders (rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes, ankylosis spondylitis, psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis), mental health disorders (anxiety, depression), metabolic diseases (dyslipidemia, osteoporosis, and type 2 diabetes), cardiovascular disorders (hypertension, cardiac arrhythmia), and thymus disorders (thymoma, hyperplasia of

thymus). The diagnostic codes used for the comorbidities are summarized in Table S1.

MG-Related Treatments and Outcomes

MG-related treatments were extracted using the Anatomical Therapeutic Chemical (ATC) classification and were categorized into three groups: acetylcholinesterase (AChE) inhibitors, including pyridostigmine and neostigmine, steroids (oral corticosteroids and parental steroids), and non-steroidal immunosuppressants (NSIST; azathioprine, methotrexate, rituximab, and cyclophosphamide). Treatment patterns in the prevalent cohort were evaluated if the patient was prescribed any drug in the category during the year. If patients received medications in different categories during the year, each treatment category was counted once; therefore, the sum of the proportions of each treatment category could exceed 100%. The treatment patterns of initial and subsequent treatments were investigated in the incident cohort. Patients were defined as receiving combination treatment if they received treatment from more than one category within the same prescription. Initial treatment was defined as the first MG-related treatment after the index date, and the first date of MG-related treatment after the index date was defined as the treatment initiation date. The prescription setting (inpatient or outpatient) was also identified. Patients who received monotherapy as initial treatment in the outpatient setting and had at least 1 year of follow-up after the treatment initiation date were used to investigate treatment sequencing. Patients were considered as having a second regimen if they received another treatment or were switched to a drug in a different category during the follow-up period.

The use of acute rescue treatment (ART), plasmapheresis or plasma exchange (PP/PE), indicates deterioration of MG. Episodes of rescue treatment in each year were measured in the prevalent cohort. Patients who received PP/PE regimens (NHI reimbursement code 58016C double filtration plasmapheresis or 58008C plasma exchange) within one hospitalization event were defined as having "one episode of ART," regardless of the number of regimens received. Intravenous immunoglobulin (IVIG) is also a rescue treatment recommended by clinical guidelines; however, it was not reimbursed for MG treatment in Taiwan during the study period and was not recorded in the NHIRD.

Two MG-related events, the initial use of PP/PE and the first MG crisis, were investigated among incident cohort patients. MG crisis was defined as patients who were hospitalized for MG and met one of the following criteria: (1) diagnosis of acute respiratory failure (ICD-9-CM 518.81/ICD-10-CM J96.00); (2) regulated mechanical ventilation during hospitalization (mechanical ventilation included endotracheal intubation, continuous positive airway pressure (CPAP), bilevel positive airway pressure (BiPAP), or non-invasive mechanical ventilation); (3) received PP/PE or IVIG during hospitalization; or (4) with intensive care unit (ICU) admission.

Statistical Analysis

Numbers of prevalent and incident patients with MG were reported. The prevalence and incidence rates of MG during the study period were calculated using the total population in Taiwan reported by the National Development Council (https://pop-proj.ndc.gov.tw/index.aspx) as the denominator.

The demographics of patients with MG (e.g., gender, age, and comorbidities) and treatment patterns were reported using descriptive analyses. Means (standard deviations [SD]) and medians (interquartile ranges) were reported for continuous variables, whereas frequencies and proportions were reported for categorical variables. A Sankey diagram was used to present the sequence of treatments in the incident cohort.

The first PP/PE and MG crisis events at or after the index date were identified to measure MG-related events. The number of events within 1 year was reported and grouped by the time from diagnosis to the event (at diagnosis, 0–3 months, and 3–12 months). MG-related event-free survival analysis was further performed using the Kaplan–Meier method, and the cumulative incidence rates over time were reported. Patients who had the event at the index date (t=0) were excluded from the survival

analysis since the patient was not in the risk set for any length of time.

All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), STATA 15 (Stata Corp., LP, College Station, TX, USA), and Microsoft Excel. The Sankey diagram was developed using the online Sankey MATIC (https://sankeymatic.com/).

RESULTS

Epidemiology of MG in Taiwan

The number of prevalent patients with MG increased from 4476 in 2013 to 5752 in 2019, with the prevalence rate increasing from 19 to 24 per 100,000 population (Fig. 1a). There were 440 to 540 newly diagnosed patients with MG annually, and the incidence rate slightly increased from 1.9 per 100,000 population in 2014 to 2.3 per 100,000 population in 2019 (Fig. 1b), resulting in a total of 2813 patients in the incident cohort for objective 2.

Characteristics and Treatment Patterns of Prevalent MG Cohort

The characteristics of prevalent patients with MG are presented in Table S2. Across all years studied, around 40% of patients were male, and more than half of patients were in the age groups of ≥ 50 years. The highest proportion of patients were in the age group of 50–59 years from 2013 to 2017 and 60–69 years thereafter.

Treatment patterns for prevalent patients with MG are reported in Fig. S1. During the study period, about 89.1% of prevalent patients with MG received at least one treatment from 2013 to 2019. AChE inhibitors and oral corticosteroids were the most commonly used MG treatments (from 2013 to 2019, 81.1% to 94.4% for AChE inhibitors and 56.6% to 60.7% for oral corticosteroids); while only 11.8% to 14.9% received NSIST during each year.

In addition, about 3–4% of prevalent patients with MG received at least one PP/PE each year, which remained constant over the study period. Among these patients, around 80% had only one episode of PP/PE during each year, with an average of 1.2–1.3 episodes annually (Fig. 1a and Table S3).

Characteristics of Incident Patients with MG

Among the incident cohort, 46.7% ($n = 1313$) were male, and most patients were aged either 60–69 years (23.5%) or 55–59 years (21.0%) at initial MG diagnosis (Table 1). The age of onset of MG was different in male and female patients. In the incident cohort, the peak age of onset was 50–69 years in male patients ($n = 306$ [23.1%] for 50–59 years; $n = 383$ [29.1%] for 60–69 years), whereas the age of onset was younger in female patients, with a plateau for the groups between 30 and 69 years (Fig. S2).

The most common comorbidities of MG were hypertension (35.7%, $n = 1005$), dyslipidemia (24.8%, $n = 699$), and type 2 diabetes (17.0%, $n = 479$). In the incident cohort, thymus and thyroid disorders were also common comorbidities (16.5%, $n = 463$ and 16.2%, $n = 455$, respectively; Table 1).

Treatment Patterns of Incident Patients with MG

Almost all incident patients (99%, $n = 2791$) received MG-related treatment during the follow-up period. Among incident patients with MG, 78.7% ($n = 2214$) received their initial MG treatment in the outpatient setting versus 20.5% ($n = 577$) in the inpatient setting (Table 2). Only 22 (0.8%) patients did not receive treatment during the follow-up period. In the outpatient setting, 85.2% ($n = 1887$) of patients received monotherapy as their initial MG treatment, and most of these patients ($n = 1666$; 88.3% out of 1887 monotherapy users) received AChE inhibitors. The most commonly used combination regimen was AChE inhibitors and oral corticosteroids ($n = 305$; 93.3%, out of 327 combination users) (Table 2).

A higher proportion of patients who received initial treatment in the inpatient setting received combination therapy (42.1%, $n = 243$ vs. 14.8%, $n = 327$) compared to patients who received initial treatment in the outpatient

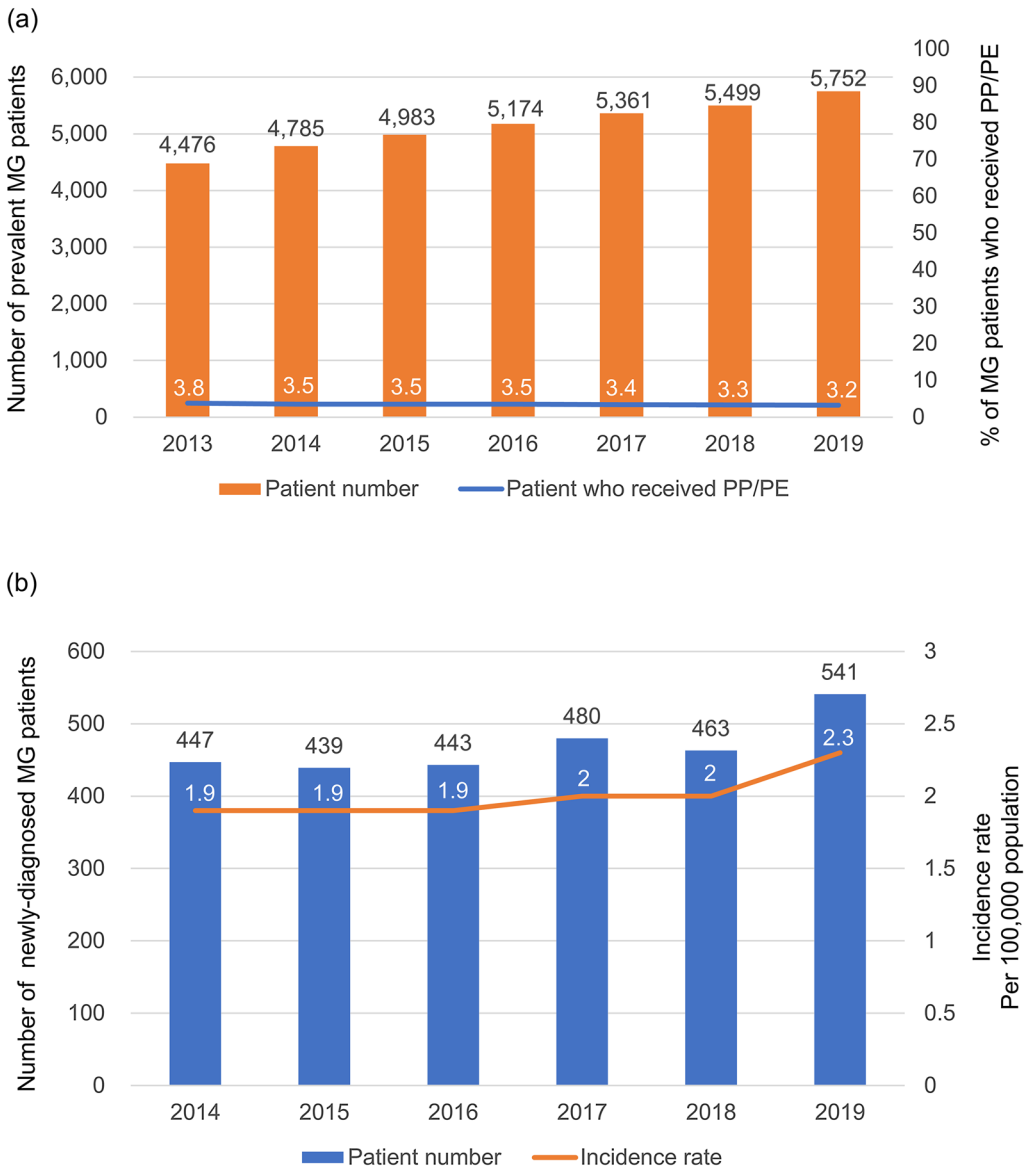

Fig. 1 **a** Prevalent patients with MG in Taiwan increased steadily from 2013 to 2019 and the percentage of patients receiving PP/PE remained consistent over the study period. **b** Incident patients with MG and the incidence rate of MG in Taiwan from 2014 to 2019. There were 440 to 540 newly diagnosed patients with MG annually. *MG* myasthenia gravis, *PP/PE* plasmapheresis or plasma exchange

setting. In the inpatient setting, AChE inhibitors ($n=260$; 77.8% out of 334 monotherapy users) and the AChE inhibitors + oral corticosteroids combination ($n=209$; 86.0% out of 243 combination users) were the most commonly used treatments in patients receiving monotherapy and combination therapy, respectively (Table 2).

We further identified 1876 incident patients who received monotherapy as their initial treatment in the outpatient setting before 31 December 2019 to follow up for treatment sequencing, as shown in Fig. 2. The mean number of days from the index date to initial treatment was 48.8 (SD 164.3) days, and the median was 0 days. During the follow-up period, 1528 (81.6%) patients had

Table 1 Baseline characteristics of incident patients with MG ($N = 2813$)

	Number	Percentage
Gender		
Male	1313	46.7
Age at the index date (years)		
≤ 18	112	4.0
19–29	206	7.3
30–39	368	13.1
40–49	469	16.7
50–59	590	21.0
60–69	662	23.5
70–79	311	11.1
≥ 80	95	3.4
Comorbidities		
Thyroid disorders		
Autoimmune thyroiditis	36	1.3
Other thyroid disorders	419	14.9
Autoimmune disorders		
Rheumatoid arthritis	24	0.9
Systemic lupus erythematosus	29	1.0
Type 1 diabetes	8	0.3
Ankylosis spondylitis	13	0.5
Psoriasis ± psoriatic arthritis	10	0.4
Crohn's disease	NR[a]	–
Ulcerative colitis	NR[a]	–
Sicca syndrome (Sjogren's syndrome)	90	1.7
Mental health disorders		
Anxiety	301	10.7
Depression	92	3.3
Metabolic diseases		
Dyslipidemia	699	24.8
Osteoporosis	78	2.8
Type 2 diabetes	479	17.0
Cardiovascular disorders		
Hypertension	1005	35.7
Cardiac arrhythmia	134	4.8
Thymus disorders		
Thymoma	366	13.0
Hyperplasia of thymus	97	3.5

MG myasthenia gravis, *NR* not reported

[a]Crohn's disease and ulcerative colitis were not reported because of count < 3, in accordance with the masking rule of the NHIRD

their treatment regimen changed. The mean and median times from initial treatment to regimen change were 219.7 days and 58 days, respectively. Most patients received AChE inhibitors (88.5%, $n = 1661$) as their initial treatment. Oral corticosteroid, as monotherapy or in combination with AChE inhibitors and/or NSIST, was the most common second treatment regimen ($n = 1320$; 79.5% of patients who had an AChE inhibitor as initial treatment). For patients who received oral corticosteroids as the initial treatment ($n = 211$), 75.4% ($n = 159$) had a second treatment, and most of them added on or switched to an AChE inhibitor ($n = 154$; 73.0% of patients who had initial treatment with oral steroids).

NSIST was the least commonly used treatment in both initial and second regimens. Only 0.2% ($n = 4$) of patients received NSIST as their initial treatment, and 4.3% (among 1872 patients with AChE inhibitor or oral corticosteroids as initial treatment; $n = 80$) received NSIST, as monotherapy or in combination with AChE inhibitors and/or oral corticosteroids when their regimen was changed.

MG-Related Events Among Incident Patients with MG

Among 2813 newly diagnosed patients with MG, 61 (2.2%) patients received their first PP/

Table 2 Treatment patterns of incident patients with MG

	Number	Percentage
Initial treatment in outpatient setting ($n = 2214$; 78.7%)		
Treatment pattern		
Monotherapy	1887	85.2[a]
AChE inhibitors	1666	
Other treatments[b]	221	
Combination therapy	327	14.8[a]
AChE inhibitors + steroids	305	
AChE inhibitors + NSIST	8	
NSIST + steroids	10	
AChE inhibitors + steroids + NSIST	4	
Initial treatment in inpatient setting ($n = 577$; 20.5%)		
Treatment pattern		
Monotherapy	334	57.9[c]
AChE inhibitors	260	
Other treatments[b]	74	
Combination therapy	243	42.1[c]
AChE inhibitors + steroids	209	
AChE inhibitors + NSIST	4	
NSIST + steroids	30	
AChE inhibitors + steroids + NSIST	0	
No MG-related treatment during the follow-up period ($n = 22$; 0.7%)		

AChE acetylcholinesterases, *MG* myasthenia gravis, *NSIST* non-steroidal immunosuppressant

[a]Total number of cases who received first-line regimen in an outpatient setting ($n = 2214$) as denominator

[b]Other treatments include NSIST and/or steroids. Data cannot be reported because of the masking rule of the NHIRD

[c]Total number of cases who received first-line regimen in an inpatient setting ($n = 577$) as denominator

PE treatment during the first year after the index date, and 78.7% ($n = 48$) of these received PP/PE at the index date. Similar results were found for MG crisis events; 133 (4.7%) patients experienced their first MG crisis during the first year after the index date, and 96.2% ($n = 128$) of these crisis events occurred within 3 months (Fig. 3).

Patients with events at index date were excluded from the MG-related event-free survival analysis ($n = 48$ for PP/PE and $n = 95$ for MG crisis, respectively). With the longest follow-up of 96 months in the survival analysis, the median time to the first PP/PE was 3.4 months, and the median time to the first MG crisis was 3.7 months. The cumulative event rate of PP/PE was 0.10 and 0.18 in the 12th month and 96th month, and the cumulative event rate of MG crisis was 0.25 and 0.43 in the 12th month and 96th month, respectively (Fig. 4).

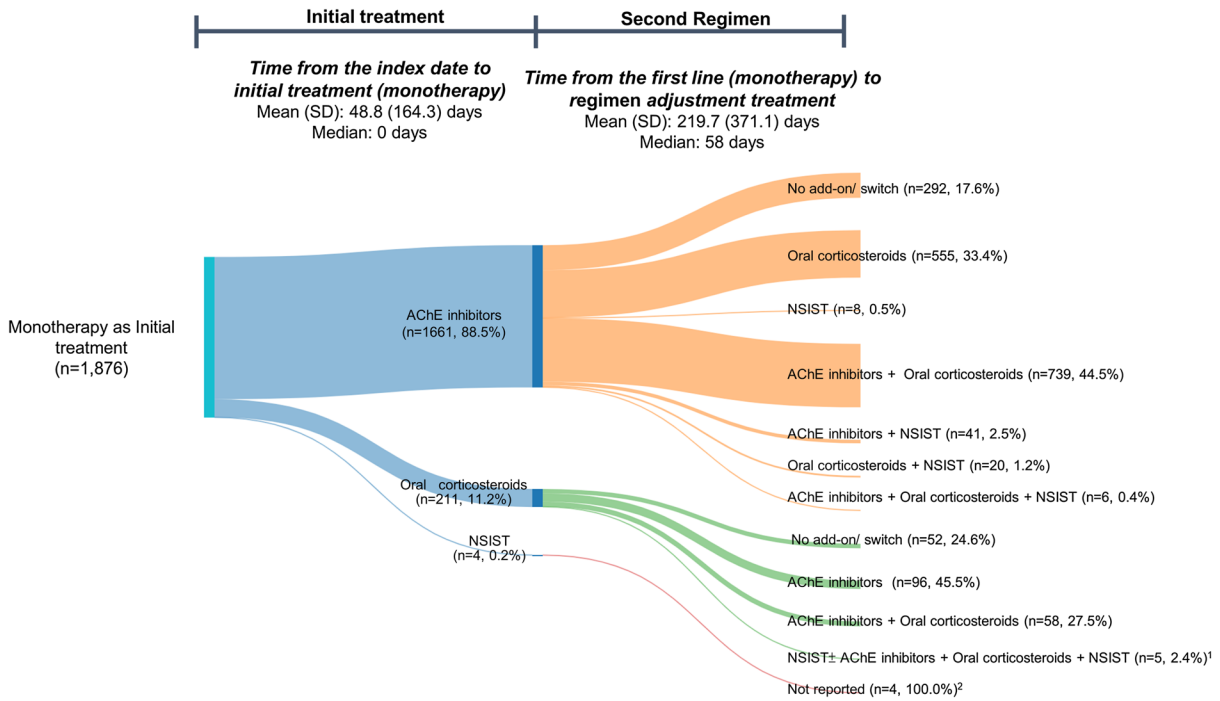

Fig. 2 Treatment patterns among incident patients with MG who received initial treatment in an outpatient setting. Most patients received AChE inhibitors as their initial treatment and 81.6% patients had their treatment changed during the follow-up period. The median time from initial treatment to regimen change was 58 days. [1]Data of IST + AChE inhibitors + oral corticosteroids and IST were combined in accordance with the masking rule of the NHIRD. [2]Second regimen was not reported in accordance with the masking rule of the NHIRD. *AChE* acetylcholinesterase, *NSIST* non-steroidal immunosuppressants, *NR* not reported, *SD* standard deviation

DISCUSSION

By utilizing the NHIRD, this study provides a detailed overview of MG in Taiwan, with comprehensive information on epidemiology, treatment patterns, and MG-related events among patients with MG in a real-world setting.

Epidemiology and Demographics of MG in Taiwan

Compared with studies reported in other Asian countries, the incidence of MG in Taiwan (1.9–2.3 per 100,000 person-years) was similar to Korea (2.4 per 100,000 person-years) but higher than in China (0.015–0.036 per 100,000 patient-years) and Japan (0.45–0.69 per 100,000 patient-years) [12–14]. In the present study, the incidence of MG in Taiwan remained constant at around 2 per 100,000 population during 2014–2019, and this led to a steady increase in the prevalence rate (19–24 per 100,000 population). The previous NHIRD study by Lai and Tseng reported that the prevalence rate increased from 8.4 in 2001 to 14.0 in 2007 per 100,000 population [15]. Using the same data source, the current study can be considered an extension of the study by Lai and Tseng, and overall we observed an increase in the MG population over the past two decades. By leveraging the current study and the study by Herr et al. published in 2023 [10], we can estimate that 47% of patients with MG in Taiwan have gMG. The distribution of ocular MG and gMG in Taiwan was comparable to data from other countries (49% gMG in the USA) [23]. However, this result should be interpreted

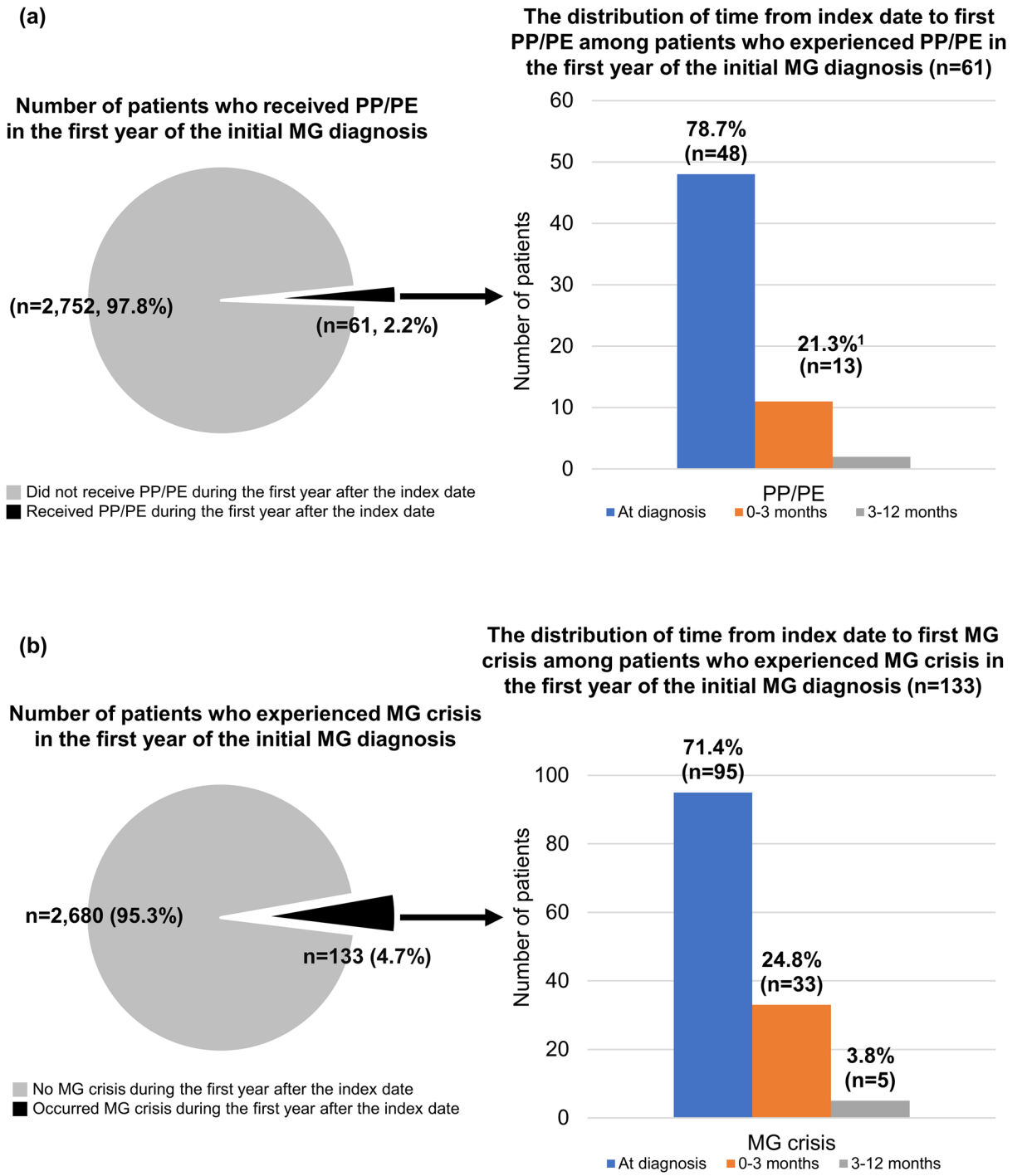

Fig. 3 Occurrence of **a** PP/PE and **b** MG crisis in the first year after the initial MG diagnosis and the distribution of time from the index date to the first **a** PP/PE or **b** MG crisis. Of the patients who experienced PP/PE or MG crisis in the first year of the initial MG diagnosis, more than two-thirds of them experienced these events at the time of diagnosis. [1]Data of PP/PE between 0–3 months and 3–12 months were combined in accordance with the masking rule of the NHIRD. *MG* myasthenia gravis, *PP/PE* plasmapheresis or plasma exchange

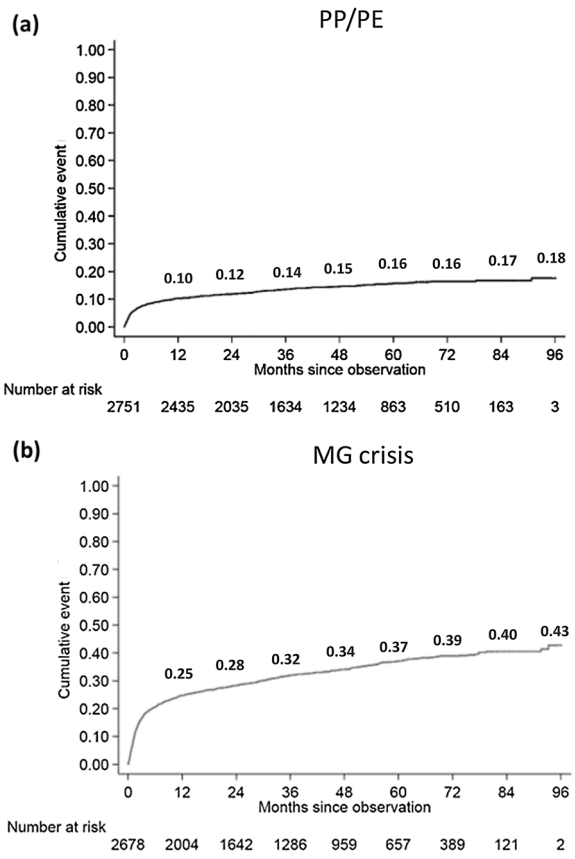

Fig. 4 Cumulative event of **a** PP/PE and **b** MG crisis among incident patients with MG without the event at the index date. With the longest follow-up of 96 months, the median time to the first PP/PE was 3.4 months, and for MG crisis it was 3.7 months. *MG* myasthenia gravis, *PP/PE* plasmapheresis or plasma exchange

cautiously since the operational definitions of MG and gMG differed between studies.

MG is considered "a disease of young women and old men" [8, 24, 25], which indicates that age and gender are two major epidemiological risk factors for the incidence of MG. The age of MG onset is an important predictor of disease prognosis and mortality [26]. Patients who develop MG after the age of 50 years (i.e., late-onset MG) or 70 years (i.e., very late-onset MG) are likely to have more severe disease. Furthermore, the increased risk of adverse effects of medications and comorbidities in the elderly requires careful monitoring [26, 27]. The prevalence rate of late-onset MG has increased in both Western and Asian countries [9, 12]. In our study cohort, more than half (59.0%) of incident patients were late-onset MG, whereas only approximately 42% were late-onset MG in the cohort of 2001–2007 reported by Lai and Tseng [15]. The results indicate that the prevalence of late-onset MG in Taiwan may increase the need for healthcare resources and intensive care. In an analysis by gender, we found a late-onset peak for male patients compared with more early-onset MG in female patients. Hormones during the fertile period or pregnancy might be the mediator of sex differences in autoimmunity and may lead to early-onset MG in female patients [24]. MG management for female patients with early-onset MG is a challenge since it affects women during childbearing age and may have a negative impact on quality of life, which implies that a safe and effective treatment is needed for this patient population [28–30].

Thyroid and thymus disorders are two major comorbidities of MG. Most of the thyroid and thymus disorders were diagnosed after the MG diagnosis in the current study. Thirty-seven patients with thymus disorder were diagnosed in the baseline period, while 426 were diagnosed during the 1-year follow-up period. A similar trend was found for thyroid disorders: 282 out of 419 (67.3%) thyroid disorders were diagnosed during the 1-year follow-up period (data not shown). Since MG shares similar clinical features as well as similar pathophysiological and histological mechanisms with these conditions [31, 32], these potential comorbidities should be closely monitored after the diagnosis of MG.

Treatment Patterns of MG in Taiwan and Unmet Needs of MG Treatment

Regarding MG treatment patterns in prevalent patients, in agreement with previous studies, AChE inhibitors were the most commonly used MG treatment [10, 11]. The percentage of NSIST use (e.g., azathioprine, the only NSIST reimbursed for MG in Taiwan) in prevalent patients with gMG (44–56%) previously reported by Herr et al. [10] was higher than the percentage in our study cohort (11.8–14.9%), indicating that gMG is a more severe disease than ocular MG with

muscles affected throughout the body, necessitating treatment with NSISTs.

The sequence of treatments for MG after diagnosis in Taiwan was investigated in the incident cohort. In line with clinical guidelines and results from Western countries [19, 20, 33, 34], AChE inhibitors were the most commonly prescribed initial treatment for MG. Almost all incident patients with MG (99.2%) received MG-related treatment in this study, which is consistent with the data reported in a US study (95%) [33].

In addition, the results from the current study suggest that patients who received their initial treatment in an inpatient setting (about 20% of incident cases) might have more severe disease and need more intensive clinical care. Our data showed that more patients were prescribed combination therapy when they received initial treatment during hospitalization compared to patients who received initial treatment in an outpatient setting (42.1% vs. 14.8%).

The treatment targets for MG are to avoid the unexpected deterioration and fluctuation of neurological symptoms, as well as the occurrence of MG crisis [16], and the quality of life of patients improves with better disease control [35]. Despite the high treatment rate of patients with MG in Taiwan (89–92% of prevalent patients with MG received at least one MG-related treatment in each calendar year during the study period) compared to data from a German study (68.5%) [11], there were still 3.2–3.8% of patients receiving at least one PP/PE annually, which might be due to inadequate disease control. PP/PE can be considered as the proxy for the occurrence of MG crisis in prevalent patients as it is only reimbursed for MG crisis, not for chronic use in Taiwan [36, 37]. The true incidence of MG crisis could be even higher than found in our study, since some treatments that are not reimbursed (e.g., IVIG) were not captured in the NHIRD.

The unmet needs of MG treatment may also be highlighted by the results of time to a second regimen in the incident cohort, which may indicate that these patients did not achieve satisfactory disease control with their initial treatment. We found that 82% of patients who received monotherapy as initial treatment had a change in their treatment regimen (added-on or switched to another category) during the follow-up period, with a median time to the second regimen of only 2 months. Similar results were found in the study of patients with gMG by Herr et al., with the median duration of first-line treatment ranging from 0.8 to 6.2 months [10]. Both findings highlight that patients with MG may need to change their regimen to obtain better disease control, especially in the initial stage of treatment.

The most common treatment category for patients who changed their regimen was steroids, which were prescribed to 79.5% of patients who received an AChE inhibitor as initial treatment. However, previous studies have shown that chronic steroid use is associated with several side effects such as hypertension, osteoporosis, and diabetes and may lead to increased disease and economic burden [1, 38, 39].

Taken together, these findings suggest that treatment outcomes for patients with MG in Taiwan should be further investigated, and effective and safe treatments are needed to avoid disease fluctuations and occurrence of MG crisis [40]. According to recent evidence, patients with MG, particularly those with refractory disease, could be benefit from novel targeted treatments, including neonatal Fc receptor antagonists, complement inhibitors, B cell depletors, chimeric antigen receptor T cell immunotherapy, etc. These novel agents showed advantages over conventional immunosuppressive treatments, with faster onset of action and favorable safety profile [41].

Occurrence of MG-Related Events and Need for Increasing Disease Awareness and Early Intervention in MG

The importance of increasing disease awareness and early treatment intervention should also be highlighted for patients with MG in Taiwan. In line with other studies [33, 40], we found that the first MG crisis event generally occurred in the first year after MG diagnosis, implying the need for early intervention with individualized treatment based on disease characteristics to better control MG symptoms. Moreover, 78.7% of

first MG crisis events and 71.4% of first PP/PE regimens were observed at the time of receiving the first MG diagnosis, which indicates that a proportion of patients were experiencing severe symptoms when they were diagnosed with MG.

Recent studies found that early intervention is beneficial for both ocular MG and gMG and could provide long-term benefits and, for patients with ocular MG, may delay or prevent the development of generalized disease [42–45]. Although most patients in the current study received MG-related treatment at the index date (the median time from the index date to initial treatment was 0 days in the outpatient setting), there was still a large variation in treatment initiation timing (the average number of days from index to treatment initiation was 54.1 [SD 166.4] days), indicating that some patients in Taiwan did not receive early intervention.

As a result of the fluctuating nature of MG symptoms and the overlap of symptoms with other neurological diseases, a delay in the diagnosis of MG has been commonly reported in previous studies [46, 47]. Increased disease awareness and early referral to specialists may ensure the early initiation of effective treatment which may lead to better clinical outcomes [21, 48].

Study Strengths and Limitations

To the best of our knowledge, the current study is the most up-to-date analysis of the MG patient landscape in Taiwan. Our study not only provides detailed data on the epidemiology, patient characteristics, and treatment patterns of MG in Taiwan but also highlights the unmet needs of patients with MG. With better knowledge of patients with MG in Taiwan, the clinical practitioner can provide individualized care for patients with MG to achieve favorable treatment outcomes, and the best use of healthcare resources. There are some limitations from the data source we used. Firstly, the NHIRD does not capture records of self-paid treatment or clinical data. For example, the use of NSIST might be underestimated since only azathioprine is reimbursed by the NHI. In addition, the incidence of MG crisis might be underestimated since one of the main ARTs, IVIG, is not reimbursed by the NHI, and we used proxies such as a diagnosis code of respiratory failure or healthcare utilization (e.g., ICU or ventilator) because of the lack of clinical information in the NHIRD. Secondly, as a result of the retrospective nature of the NHIRD, we cannot identify the subgroup of MG (ocular or generalized) through the diagnosis codes, and miscoding of diseases may have occurred. Thirdly, although the current study provides an overview of the sequence of treatments for patients with MG in Taiwan, the second regimen might be miscategorized since the add-on or switch could not be identified accurately in the NHIRD if there was an overlap or a gap period between two prescriptions. Finally, this study was based on the population in Taiwan and might not be generalizable to other countries.

CONCLUSIONS

The prevalence of MG increased steadily in Taiwan, and the treatment of patients with MG in the real-world setting was consistent with clinical guidelines. However, patients continue to experience exacerbations and crises despite a high rate of treatment, highlighting the limitations of current treatments and emphasizing the need for early intervention and new treatment approaches.

ACKNOWLEDGEMENTS

Medical Writing and Editorial Assistance. The authors thank Veronica Porkess, Ph.D., of UCB Pharma, for publication and editorial support. UCB Pharma funded the medical writing and editorial assistance.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. Study concept and design: all authors; Data acquisition and analysis: Li-Nien Chien and Yu-Ting Chiu; Data interpretation: Nai-Wen Tsai, Jiann-Horng Yeh, Li-Nien Chien, Connie Hung and Amanda Kuo; Writing – original draft preparation: Hung-Wei Lin and Li-Shan Jian; Writing – review and editing: Nai-Wen Tsai, Li-Nien Chien, Jiann-Horng Yeh, Connie Hung, Amanda Kuo and Kai-Pei Chou; Administrative support: Li-Nien Chien, Yu-Ting Chiu and Kai-Pei Chou.

Funding. The Research was funded by UCB Pharma, Taipei, Taiwan. UCB Pharma, Taipei, Taiwan funded medical writing and editorial support from IQVIA Solutions Taiwan Ltd, Taipei, Taiwan, and funded the journal's Rapid Service Fee.

Data Availability. The datasets generated during and/or analyzed during the current study are not publicly available due to UCB's data sharing policy and NHIRD regulations.

Declarations

Conflict of Interest. Connie Hung and Amanda Kuo are employees of UCB Pharma. Hung-Wei Lin, and Kai-Pei Chou are employees of IQVIA Solutions Taiwan Ltd. Li-Shan Jian is a former employee of IQVIA Solutions Taiwan Ltd., and the work was done while affiliated with IQVIA Solutions Taiwan Ltd.

Ethical Approval. The study protocol was reviewed and approved by the Institutional Review Board (IRB) of Taipei Medical University (Approval number N202203018). Informed consent was waived because of the study's descriptive and non-interventional nature, and the analysis was de-identified. This study was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments.

REFERENCES

1. Salari N, Fatahi B, Bartina Y, et al. Global prevalence of myasthenia gravis and the effectiveness of common drugs in its treatment: a systematic review and meta-analysis. J Transl Med. 2021;19(1):516.
2. Wang L, Zhang S, Xi J, et al. Efficacy and safety of tacrolimus for myasthenia gravis: a systematic review and meta-analysis. J Neurol. 2017;264(11):2191–200.
3. Phillips WD, Vincent A. Pathogenesis of myasthenia gravis: update on disease types, models, and mechanisms. F1000Res. 2016;5:1513.
4. Guptill JT, Sharma BK, Marano A, Soucy A, Krueger A, Sanders DB. Estimated cost of treating myasthenia gravis in an insured U.S. population. Muscle Nerve. 2012;45(3):363–6.
5. Schneider-Gold C, Hagenacker T, Melzer N, Ruck T. Understanding the burden of refractory myasthenia gravis. Ther Adv Neurol Disord. 2019;12:1756286419832242.
6. Lehnerer S, Jacobi J, Schilling R, et al. Burden of disease in myasthenia gravis: taking the patient's perspective. J Neurol. 2022;269(6):3050–63.
7. Basta IZ, Pekmezović TD, Perić SZ, et al. Assessment of health-related quality of life in patients with myasthenia gravis in Belgrade (Serbia). Neurol Sci. 2012;33(6):1375–81.
8. Pallaver F, Riviera AP, Piffer S, et al. Change in myasthenia gravis epidemiology in Trento, Italy, after twenty years. Neuroepidemiology. 2011;36(4):282–7.

9. Murai H, Yamashita N, Watanabe M, et al. Characteristics of myasthenia gravis according to onset-age: Japanese nationwide survey. J Neurol Sci. 2011;305(1–2):97–102.

10. Herr KJ, Shen SP, Liu Y, Yang CC, Tang CH. The growing burden of generalized myasthenia gravis: a population-based retrospective cohort study in Taiwan. Front Neurol. 2023;14:1203679.

11. Mevius A, Jöres L, Biskup J, et al. Epidemiology and treatment of myasthenia gravis: a retrospective study using a large insurance claims dataset in Germany. Neuromuscul Disord. 2023;33(4):324–33.

12. McGrogan A, Sneddon S, de Vries CS. The incidence of myasthenia gravis: a systematic literature review. Neuroepidemiology. 2010;34(3):171–83.

13. Park SY, Lee JY, Lim NG, Hong YH. Incidence and prevalence of myasthenia gravis in Korea: a population-based study using the national health insurance claims database. J Clin Neurol. 2016;12(3):340–4.

14. Fang W, Li Y, Mo R, et al. Hospital and healthcare insurance system record-based epidemiological study of myasthenia gravis in southern and northern China. Neurol Sci. 2020;41(5):1211–23.

15. Lai CH, Tseng HF. Nationwide population-based epidemiological study of myasthenia gravis in Taiwan. Neuroepidemiology. 2010;35(1):66–71.

16. Jackson K, Parthan A, Lauher-Charest M, Broderick L, Law N, Barnett C. Understanding the symptom burden and impact of myasthenia gravis from the patient's perspective: a qualitative study. Neurol Ther. 2023;12(1):107–28.

17. Claytor B, Cho SM, Li Y. Myasthenic crisis. Muscle Nerve. 2023;68(1):8–19.

18. Nelke C, Stascheit F, Eckert C, et al. Independent risk factors for myasthenic crisis and disease exacerbation in a retrospective cohort of myasthenia gravis patients. J Neuroinflammation. 2022;19(1):89.

19. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis: executive summary. Neurology. 2016;87(4):419–25.

20. Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. Myasthenia gravis: association of british neurologists' management guidelines. Pract Neurol. 2015;15(3):199–206.

21. Hsieh CY, Su CC, Shao SC, et al. Taiwan's National Health Insurance Research Database: past and future. Clin Epidemiol. 2019;11:349–58.

22. Hung GY, Lee CY, Yen HJ, Lin LY, Horng JL. Incidence of immune thrombocytopenia in Taiwan: a nationwide population-based study. Transfusion. 2018;58(11):2712–9.

23. Hendricks TM, Bhatti MT, Hodge DO, Chen JJ. Incidence, epidemiology, and transformation of ocular myasthenia gravis: a population-based study. Am J Ophthalmol. 2019;205:99–105.

24. Bubuioc AM, Kudebayeva A, Turuspekova S, Lisnic V, Leone MA. The epidemiology of myasthenia gravis. J Med Life. 2021;14(1):7–16.

25. Poulas K, Tzartos SJ. The gender gap in autoimmune disease. Lancet. 2001;357(9251):234.

26. Tang YL, Ruan Z, Su Y, et al. Clinical characteristics and prognosis of very late-onset myasthenia gravis in China. Neuromuscul Disord. 2023;33(4):358–66.

27. Aarli JA. Late-onset myasthenia gravis: a changing scene. Arch Neurol. 1999;56(1):25–7.

28. Bansal R, Goyal MK, Modi M. Management of myasthenia gravis during pregnancy. Indian J Pharmacol. 2018;50(6):302–8.

29. Dong D, Chong MK, Wu Y, et al. Gender differences in quality of life among patients with myasthenia gravis in China. Health Qual Life Outcomes. 2020;18(1):296.

30. Wilcke H, Glaubitz S, Kück F, et al. Female sex and overweight are associated with a lower quality of life in patients with myasthenia gravis: a single center cohort study. BMC Neurol. 2023;23(1):366.

31. Amin S, Aung M, Gandhi FR, Pena Escobar JA, Gulraiz A, Malik BH. Myasthenia gravis and its association with thyroid diseases. Cureus. 2020;12(9):e10248.

32. Romi F. Thymoma in myasthenia gravis: from diagnosis to treatment. Autoimmune Dis. 2011;2011:474512.

33. Mahic M, Bozorg A, Rudnik J, Zaremba P, Scowcroft A. Treatment patterns in myasthenia gravis: a United States health claims analysis. Muscle Nerve. 2023;67(4):297–305.

34. Narayanaswami P, Sanders DB, Wolfe G, et al. international consensus guidance for management of myasthenia gravis: 2020 update. Neurology. 2021;96(3):114–22.

35. Alanazy MH, Binabbad RS, Alromaih NI, et al. Severity and depression can impact quality of life in patients with myasthenia gravis. Muscle Nerve. 2020;61(1):69–73.

36. Bril V, Barnett-Tapia C, Barth D, Katzberg HD. IVIG and PLEX in the treatment of myasthenia gravis. Ann N Y Acad Sci. 2012;1275:1–6.

37. Sanders DB, Wolfe GI, Benatar M, et al. International consensus guidance for management of myasthenia gravis. Exec Summ. 2016;87(4):419–25.

38. Mantegazza R, Bonanno S, Camera G, Antozzi C. Current and emerging therapies for the treatment of myasthenia gravis. Neuropsychiatr Dis Treat. 2011;7:151–60.

39. Yeh JH, Chen HJ, Lin CC, Chen YK, Chiu HC, Kao CH. Risk of diabetes mellitus among patients with myasthenia gravis. Acta Neurol Scand. 2015;132(2):132–8.

40. Wendell LC, Levine JM. Myasthenic crisis. Neurohospitalist. 2011;1(1):16–22.

41. DeHart-McCoyle M, Patel S, Du X. New and emerging treatments for myasthenia gravis. BMJ Med. 2023;2(1):e000241.

42. Farrugia ME, Goodfellow JA. A practical approach to managing patients with myasthenia gravis-opinions and a review of the literature. Front Neurol. 2020;11:604.

43. Uzawa A, Suzuki S, Kuwabara S, et al. Effectiveness of early cycles of fast-acting treatment in generalised myasthenia gravis. J Neurol Neurosurg Psychiatry. 2023;94(6):467–73.

44. Kupersmith MJ. Ocular myasthenia gravis: treatment successes and failures in patients with long-term follow-up. J Neurol. 2009;256(8):1314–20.

45. Vitturi BK, Pellegrinelli A, Valerio BCO. Medication adherence in patients with myasthenia gravis in Brazil: a cross-sectional study. Acta Neurol Belg. 2020;120(1):83–9.

46. Sobierajski T, Lasek-Bal A, Krzystanek M, Gilhus NE. Diagnosis and therapy of myasthenia gravis-the patients' perspective: a cross-sectional study. Front Neurol. 2023;14:1214041.

47. Spillane J, Higham E, Kullmann DM. Myasthenia gravis. BMJ. 2012;345: e8497.

48. Scherer K, Bedlack RS, Simel DL. Does this patient have myasthenia gravis? JAMA. 2005;293(15):1906–14.