Risk of subsequent atrial fibrillation in patients with myasthenia gravis
A population-based cohort study

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Abstract
The purpose of this study was to explore the association between myasthenia gravis (MG) and the risk of atrial fibrillation (AF) in an Asian population. The risk was analyzed in a cohort of 5528 patients with history of MG and 5528 individuals without MG using a hospitalization claim dataset. Both groups were matched by age, sex, index year and baseline comorbidities as an original analysis. A Cox proportional hazard model was used to estimate the hazard ratio and 95% confidence interval of AF after adjusting for demographic and relevant clinical covariates. The adjusted hazard ratio of the MG group compared with that of the non-MG group was 1.03 (95% confidence interval, 0.76–1.38) for AF. A stratified analysis showed that compared with the propensity score matched non-MG group, there was no increased risk of developing AF based on age categories, gender, or comorbidities. Different time follow-up periods results showed no increased risk of AF compared with the non-MG group. Overall, in the Taiwanese cohort, MG is not associated with an increased risk of AF.

Abbreviations: AChR = acetylcholine receptor, AF = atrial fibrillation, aHR = adjusted hazard ratio, CI = confidence interval, ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification, MG = myasthenia gravis, NHIRD = National Health Insurance Research Database.

Keywords: atrial fibrillation, cohort, myasthenia gravis

1. Introduction
Myasthenia gravis (MG) is an autoimmune disease that mainly affects the neuromuscular junction. Patients are grouped according to the serological conditions, symptoms, age at onset, and thymic involvement.\textsuperscript{[1]} Coexisting conditions such as secondary autoimmune disease,\textsuperscript{[2]} thymoma, cardiac disease, and therapy-induced disorders represent a major challenge in the treatment of MG patients. In treating MG, medications such as pyridostigmine, corticosteroids, and other immunosuppressants are given. In addition, a thymectomy is conducted if concurrent thymoma, early onset MG without thymoma, or generalized MG with acetylcholine receptor antibodies in late onset group is present.\textsuperscript{[3]} When myasthenic crisis occurs, immune globulin or plasma exchange plays a pivotal role in intensive care. Atrial fibrillation (AF) is one of the most clinically significant cardiac arrhythmias that poses a threat to the cardiovascular system. A 5-fold increased risk for stroke, a 2-fold increased risk for all-cause mortality, and subsequent cardiomyopathy have been reported.\textsuperscript{[4]} The interplay between MG and the cardiac arrhythmia is postulated by different mechanisms. Autonomic dysfunction may play a role in inducing arrhythmia. In MG patient, parasympathetic cardiac impairment was found, and the associated baroreflex sensitivity was decreased. Dysfunction in the baroreflex mechanism may lead to dizziness, syncope, atrioventricular block, and even lethal atrial fibrillation.\textsuperscript{[5]} Critical arrhythmias such as ventricular and supraventricular arrhythmias as well as QTc prolongation, have also been reported.\textsuperscript{[6]} In another recent study, myocardial inflammation was suggested to facilitate AF. Cardiomyositis is a rare but fatal
complication reported in thymoma MG and late-onset MG in patients who present with anti kv-1.4 muscle antibodies,[7] while one older population study stated that MG is associated with a lower incidence of cardiac-related deaths.[8] A dog model aimed at studying AF found that cholinergic stimulation is the main factor in the development of spontaneous AF. The acetylcholinesterase inhibitor, which is commonly used to treat MG inhibits the breakdown of acetylcholine, thereby increasing both the level and duration of the acetylcholine effect in the autonomic ganglia and the neuromuscular junction.[9] However, augmentation of vagal tone causes a nodal conduction block and atrial arrhythmias.[10,11] One case series found that new-onset AF can occur during myasthenic crisis. However, to the best of our knowledge, there is no epidemiologic evidence to support this result. Thus, we performed a nationwide population-based cohort study to analyze the subsequent risk of AF in people with a history of MG.

2. Methods

2.1. Data source

This study used the data from the inpatient datasets of the National Health Insurance Research Database (NHIRD). The NHIRD was established by the National Health Insurance (NHI) program of Taiwan, which was launched in 1995. Encryption and anonymity were performed to protect the privacy of beneficiaries. The claims data contained the information regarding basic demographics, coding of disease diagnoses based on the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM), details of inpatient orders, and inpatient admission and discharge dates. The study was approved by the Research Ethics Committee at China Medical University and Hospital (CMUH104-REC2-115(AR-4)). Because the study applied de-identified the secondary dataset, released for research purposes, the need for informed consent was waived.

2.2. Study population

The date of initial diagnosis of myasthenia gravis (MG) (ICD-9-CM: 385.0) was defined as the index date, and the end of follow-up was the date of onset of atrial fibrillation (ICD-9-CM: 427.31), the date of withdrawal or death, or December 31, 2013. Exclusion criteria were as follows: the index date could not be between the enrollment and the withdrawal date; the index year could not be between 2000 and 2012; atrial fibrillation could not be diagnosed before the index date; and patients could not be younger than 18 years of age. Subjects with MG were included in the MG cohort. Subjects without MG were included in the non-MG cohort and were randomly matched with the MG cohort in a 1:1 ratio by propensity scores based on age, gender, index year, and baseline comorbidities. Figure 1 displays the flowchart of the method used for population selection.

2.3. Comorbidities and procedures

The baseline comorbidities included hypertension (ICD-9-CM: 401-405), diabetes (ICD-9-CM: 250), hyperlipidemia (ICD-9-CM: 272), coronary heart disease (ICD-9-CM: 410-414), heart failure (ICD-9-CM: 428), chronic kidney disease (ICD-9-CM: 585), chronic obstructive pulmonary disease (ICD-9-CM: 490-496), sleep disorders (ICD-9-CM: 307.4 and 780.5), hyperthyroidism (ICD-9-CM: 242), gout (ICD-9-CM: 274), and peripheral arterial occlusive disease (PAOD) (ICD-9-CM: 440.0, 440.2, 440.3, 440.8, 440.9, 443, 444.0, 444.22, 444.8, 447.8, 447.9). Procedures included thymectomy (ICD-9-CM Procedure Code: 07.8) and plasmapheresis (ICD-9-CM Procedure Code: 99.71).

2.4. Statistical analysis

Descriptive statistics included numbers and percentages for categorical variables and means and standard deviations (SDs) for continuous variables. Standardized mean differences (SMDs) were performed to test whether there were differences in characteristics between cohorts. The incidence rate was calculated by dividing the number of events by the number of person-years in
the follow-up period. The cumulative incidence was estimated using the Kaplan–Meier approach. The log-rank test was conducted to assess the differences in cumulative incidence curves between cohorts. To assess the risk of developing subsequent AF, we performed Cox regression analysis to obtain crude and adjusted hazard ratios. The criterion for determining the significance was a p-value of <0.05. Data analyses and plotting were completed using SAS 9.4 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Characteristics of the study population

Figure 1 shows the cohort assembling process. There were 5528 subjects with MG and 5528 subjects without MG (propensity score-matched cohort) in this study, with similar distributions of age, sex, and clinical covariates. In the MG group, the mean age at diagnosis was 50.1 (16.7) years. Most were diagnosed in the younger age group (<50 years, 47.02%) and there was a higher proportion of females (56.82%). The average follow-up time for the non-MG cohort (6.45 years) was negligibly different from that of the MG cohort (6.09 years) (SMD = 0.0951). The baseline characteristics and comorbidities were well balanced between the groups after matching. (Table 1)

3.2. Risk factors of atrial fibrillation and subgroup analysis

Table 2 gives the results of the Cox regression analysis of each variable associated with atrial fibrillation. Among the mentioned variables, being older than 50 years and having some comorbidities were associated with a higher risk of developing AF. Patients who had a history of MG had no significant risk of developing AF (adjusted hazard ratio [aHR] = 1.03, 95% CI 0.76–1.38), after adjusting for full covariates listed in Table 2. Compared with the reference patient group (aged <50), those aged older than 50 years had a higher risk of developing AF (aHR = 2.38). Males had no higher risk of developing AF compared to females (aHR = 1.03, 95% CI 0.93–1.70). A higher risk of developing AF was shown in patients with hypertension (aHR = 1.48, 95% CI 1.02–2.13), hyperlipidemia (aHR = 1.66, 95% CI 1.05–2.64), heart failure (aHR = 1.85, 95% CI 1.11–3.10), chronic kidney disease (aHR = 2.08, 95% CI 1.07–4.03), and chronic obstructive pulmonary disease (aHR = 1.56, 95% CI 1.03–2.38).

Figure 2 displays the cumulative incidence of AF in subjects with and without MG using the Kaplan–Meier method. The result of the log rank test was P = .5330. There was no difference in cumulative incidence curves between the non-MG and the MG cohorts.

Table 3 represents the association between MG and the risk of developing AF in terms of age subgroups, gender subgroups, and comorbidity subgroups. In the age subgroups analysis, no statistically significant adjusted HR was found. In the gender subgroup analysis, although males had a higher incidence rate of developing AF compared with females in both the MG and non-MG group (3.38 vs. 1.77; 3.43 vs 2.1, respectively), there was no gender difference in risk of AF after adjusting for age, and comorbidities (male aHR = 1.19, 95% CI 0.80–1.79 vs. female aHR = 1.05, 95% CI 0.76–1.46).
aHR = 0.88, 95% CI 0.56–1.38). In the comorbidity subgroup analysis, gout subjects with MG were less likely to develop AF compared to those without MG (aHR = 0.19, 95% CI 0.04–0.90).

Table 4 shows comparisons of incidence of AF in subjects with or without MG and with or without accordant procedures. Subjects with MG and receiving thymectomy or plasmapheresis had a decreased risk of getting AF, but not statistically significant no matter when compared to subjects without MG (aHR = 0.55, 95% CI 0.25–1.19) or subjects with MG but not receiving any procedures (aHR = 0.49, 95% CI 0.22–1.08).

Table 5 shows comparisons of the incidence of AF between subjects with and without MG in the different follow-up periods. For subjects with less than 5 years of follow up, subjects with MG did not have a higher risk of developing AF compared to subjects without MG (aHR = 0.98, 95% CI 0.68–1.41). Similarly, for subjects with more than 5 years of follow up, subjects with MG did not have higher risk of developing AF compared to subjects without MG (aHR = 1.21, 95% CI 0.70–2.07).

4. Discussion

This is the first nationwide study aimed at investigating the risk of developing atrial fibrillation (AF) among Asian patients with a history of MG. Comorbidities that frequently accompany AF were identified in a previous study. We compared the MG cohort with a matched non-MG cohort using propensity score matching to analyze the risk of developing AF. The results showed MG patients had no higher risk of developing AF than the non-MG cohort.

A recent case series reported eight patients with myasthenic crisis and concurrent AF during hospitalization. The majority of these patients were males with an average age above 50, seropositive for the acetylcholine receptor (AChR) antibody, and diagnosed with late-onset MG. AF status subsided once myasthenic crisis or MG activity stabilized. The authors speculated that autoantibodies targeted at cardiac muscle or autonomic instability were possible mechanisms. Anti-Kv1.4 antibodies were found to be associated with myocarditis in MG patients. Suzuki et al found that 10% of 650 MG patients were...
seropositive for anti-Kv1.4 antibodies, and eight patients who were clinically diagnosed with myocarditis were all anti-Kv1.4 antibody positive. Cardiac abnormalities including ventricular tachycardia, complete atrioventricular block, atrial fibrillation, and even sudden death were found.\[14\] MG patients with thymoma, those who were AChR antibody positive without thymoma, and those who were MuSK antibody positive were prone to developing autonomic dysfunction and subsequent cardiac arrhythmia.\[15\] AChR antibodies are classified into two groups (muscular or neuronal) based on their targets. Up to 90% of MG patients were found to be seropositive for muscle AChR antibodies that were highly targeted to the neuromuscular synaptic junction (muscle AChR α1 subunit). Ganglionic AChR antibodies were targeted mainly to the α3 subunit of neuronal AChR and were responsible for pathogenesis in autoimmune autonomic ganglionopathy, a disease that presents with dysautonomia due to impaired cholinergic transmission at the ganglionic synaptic junction.\[16\] Although AChR antibodies in MG were thought to be highly specific to muscular AChR, dysautonomia still occurred in MG patients. One study reported that 3% of MG patients were seropositive for both muscle and ganglionic AChR antibodies.\[17\] Further, 8% of cases with MG with thymoma were seropositive for both AChR antibodies.\[18\] Muscular AChR antibodies might be cross reactive with neuronal AChR to some extent.\[19\] Based on the aforementioned theories, acetylcholinesterase inhibitor used for routine MG treatment seems to be a potential therapy for autonomic disorders as well.\[16\] However, Sharifov et al, who conducted test using dog models, postulated that cholinergic stimulation is the pivotal factor in spontaneous AF initiation, while adrenergic stimulation

| Table 3 | Comparisons of incidence of atrial fibrillation between subjects with and without MG in the different stratifications. |
|----------|----------------------------------------------------------------------------------------------------------------------|
| Variable | Event n=95 | IR 1,000 person-years | Event n=82 | IR 1,000 person-years | Crude HR (95% CI) P-value | Adjusted HR (95% CI) P-value |
| All | 95 | 35,645 | 2.67 | 82 | 33,654 | 2.44 | 0.91 (0.68, 1.22) 0.5339 | 1.03 (0.76, 1.38) 0.8608 |
| Age (yr) | | | | | | | |
| <50 | 4 | 18,850 | 0.21 | 4 | 18,447 | 0.22 | 1.01 (0.25, 4.06) 0.9838 | 1.01 (0.24, 4.21) 0.9843 |
| 50-59 | 15 | 6,818 | 2.20 | 9 | 6,368 | 1.41 | 0.65 (0.28, 1.48) 0.3007 | 0.66 (0.28, 1.54) 0.3334 |
| 60-69 | 16 | 4,893 | 3.27 | 18 | 4,470 | 4.03 | 1.25 (0.64, 2.45) 0.5201 | 1.26 (0.64, 2.48) 0.598 |
| 70-79 | 39 | 4,096 | 9.52 | 36 | 3,548 | 10.15 | 1.06 (0.68, 1.67) 0.7908 | 1.08 (0.68, 1.71) 0.7459 |
| ≥80 | 21 | 988 | 21.26 | 15 | 821 | 18.27 | 0.85 (0.44, 1.65) 0.6296 | 1.03 (0.52, 2.06) 0.9237 |
| Gender | | | | | | | |
| Female | 43 | 20,504 | 2.10 | 35 | 19,769 | 1.77 | 0.84 (0.54, 1.31) 0.4419 | 0.88 (0.56, 1.38) 0.5844 |
| Male | 52 | 15,141 | 3.43 | 47 | 13,885 | 3.38 | 0.98 (0.66, 1.46) 0.9292 | 1.19 (0.80, 1.79) 0.3918 |
| Comorbidities | | | | | | | |
| Hypertension | 42 | 3,768 | 11.15 | 31 | 3,638 | 8.52 | 0.76 (0.48, 1.21) 0.5344 | 0.85 (0.53, 1.36) 0.4848 |
| Diabetes | 20 | 2,301 | 8.69 | 18 | 2,028 | 8.88 | 1.03 (0.54, 1.94) 0.9357 | 1.06 (0.55, 2.05) 0.8627 |
| Hyperlipidemia | 18 | 1,315 | 13.69 | 10 | 1,101 | 9.08 | 0.66 (0.31, 1.44) 0.3008 | 0.76 (0.33, 1.73) 0.5152 |
| Coronary heart disease | 24 | 1,804 | 13.30 | 16 | 1,648 | 9.71 | 0.73 (0.39, 1.38) 0.3362 | 0.95 (0.49, 1.84) 0.8780 |
| Heart failure | 14 | 784 | 17.85 | 7 | 492 | 14.22 | 0.76 (0.31, 1.89) 0.5610 | 0.85 (0.33, 2.21) 0.7391 |
| Chronic kidney disease | 10 | 342 | 29.23 | 1 | 135 | 7.40 | 0.27 (0.03, 2.08) 0.2067 | 0.22 (0.02, 2.05) 0.1850 |
| COPD | 19 | 1,562 | 12.16 | 12 | 1,237 | 9.70 | 0.79 (0.38, 1.73) 0.5277 | 0.81 (0.38, 1.70) 0.5702 |
| Sleep disorders | 3 | 573 | 5.24 | 0 | 471 | 0.00 | NA | NA |
| Hypothyroidism | 2 | 352 | 5.68 | 2 | 495 | 4.04 | 0.77 (0.11, 5.45) 0.7894 | NA |
| Gout | 12 | 652 | 18.40 | 2 | 410 | 4.88 | 0.28 (0.06, 1.18) 0.0813 | 0.19 (0.04, 0.90) 0.0362 |
| PAOD | 2 | 248 | 8.06 | 0 | 132 | 0.00 | NA | NA |

COPD, chronic obstructive pulmonary disease; CI, confidence interval; HR, hazard ratio; IR, incidence rate; MG, myasthenia gravis; NA, not available; PAOD, peripheral arterial occlusive disease.
* Adjusted for age, sex, and baseline comorbidities.

| Table 4 | Comparisons of incidence of atrial fibrillation in subjects with or without MG and with or without procedures. |
|----------|----------------------------------------------------------------------------------------------------------------------|
| Variable | Event n=177 | IR 1,000 person-years | Crude HR (95% CI) P-value | Adjusted HR (95% CI) P-value |
| Subgroup | | | | |
| Non-MG | 95 | 35,645 | 2.67 | 1 (Reference) | 1 (Reference) |
| MG without PP and OP | 75 | 24,537 | 3.06 | 1.14 (0.84, 1.54) .4118 | 1 (Reference) |
| MG with PP or OP | 7 | 9,118 | 0.77 | 0.29 (0.14, 0.63) .0017 | 0.55 (0.25, 1.19) .1287 |

CI, confidence interval; HR, hazard ratio; IR, incidence rate; MG, myasthenia gravis; OP, operation; PP, plasmapheresis.
* Adjusted for age, sex, and comorbidities.
has both initiation and maintenance roles.\textsuperscript{[20]} One randomized study studied the effect of botulinum injection on epicardial fat, and found that it inhibited acetylcholine release and decreased the AF burden.\textsuperscript{[21]} Aside from autonomic dysfunction, interleukin-6 (IL-6) may cause interplay between MG and AF. Anti-AChR antibodies were found to increase IL-6 production in a muscle biopsy study.\textsuperscript{[22]} Pyridostigmine stimulated rather than suppressed pro-inflammatory cytokines including IL-6.\textsuperscript{[23]} Post-thymectomy induced myasthenic crisis was observed with concurrent overproduction of IL-6.\textsuperscript{[24]} Dai et al demonstrated positive correlations between serum IL-6 and TNF-α levels with AF inducibility and duration using rat models.\textsuperscript{[25]} Another study have determined that the chronic inflammatory process that occurs via the upregulation of IL-6 is an important mediator in the pathophysiology of AF.\textsuperscript{[26]} Whether or not the overproduction of IL-6 in MG will actually lead to the induction of AF is unknown. Further study is needed to clarify the detailed mechanism responsible for this. However, from an epidemiology aspect, in our cohort, we observed that individuals with MG did not have and increased AF risk (aHR = 1.03). There was no increased risk, even after different follow-up periods (<5 years, aHR = 0.98, 95% CI 0.68–1.41; ≥5 years, aHR = 1.21, 95% CI 0.70–2.07).

One study analyzed non-cardiac thoracic surgery and found that undergoing a lobectomy, esophagectomy, or thymectomy may increase the risk of developing AF.\textsuperscript{[27]} The use of plasma exchange is indicated in diseases such as Guillain-Barré syndrome, thrombotic thrombocytopenic purpura, rheumatoid arthritis (RA), systemic lupus erythematosus, and MG.\textsuperscript{[28]} In a Swedish study, 1% of patients who underwent plasma exchange developed complications, such as hypotension or arrhythmias, that needed medication or interrupted of the treatment.\textsuperscript{[29]} In our cohort, however, we observed that there was no increased risk of AF in MG subgroups with or without procedures comparing to non MG subgroup.

Paroxysmal AF is often asymptomatic, but its prevalence in general population has been reported to be up to 12.4%.\textsuperscript{[30]} Patients may not seek medical help due to being asymptomatic. Diagnosis of AF is time and resource consuming, as it requires a 24-hr Holter scan, serial electrocardiography, loop recorders, in-hospital monitoring, and use of an insertable cardiac monitor.\textsuperscript{[31]} Although the results for our cohort did not detect a higher risk of developing AF in MG patients, it is still possible that occult AF exists among MG patients without diagnosis. Furthermore, whether paroxysmal AF occurs, especially in patients with hemodynamically unstable MG status, is unknown. Thus, further study is needed.

There were some limitations in our study. First, the diagnoses of MG and AF were dependent on ICD-9 codes. The disease status of MG patients upon diagnosis and subgroup classification were unknown. Also, the NHIRD does not provide detailed patient information, such as body mass index, tobacco consumption, dietary habits, and lifestyle factors. Secondly, the hospitalization claim dataset does not include laboratory reports, indication of treatment (thymectomy and plasma exchange), or drug information. Third, according to one cohort study, autoimmune disease is associated with 40% increase in risk of atrial fibrillation.\textsuperscript{[32]} Chang et al reported that patients with MG had higher overall incidence rate of autoimmune diseases.\textsuperscript{[25]} However, we did not analyze the risk of developing AF in patient subgroup of MG with concurrent second autoimmune diseases due to our study design. Further study should focus on exploring the risk of MG with second autoimmune disease and subsequent AF. Unknown confounders may also have existed due to our retrospective cohort study design, and we attempted to eliminate the potential biases by using multivariable models. Finally, the majority of patients included in NHIRD are Taiwanese, thus the result of our study may have population bias and it would not be generalizable to population of other ethnics. Further clinical studies should focus on exploring the risk of MG with second autoimmune diseases due to our study design. Further study should focus on exploring the risk of MG with second autoimmune disease and subsequent AF. Unknown confounders may also have existed due to our retrospective cohort study design, and we attempted to eliminate the potential biases by using multivariable models. Finally, the majority of patients included in NHIRD are Taiwanese, thus the result of our study may have population bias and it would not be generalizable to population of other ethnics. Further clinical studies should include patients with diverse nationalities to extrapolate the observed results.

5. Conclusion

Our population-based cohort showed that individuals with MG had no higher risk of subsequent development of AF than the general population in Taiwan. However, we still need to be aware of occult AF, especially when hemodynamical instability or cardiac involvement occurs in MG patients.

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