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## PROGNOSIS OF MYASTHENIA GRAVIS: A COMPREHENSIVE SYSTEMATIC REVIEW

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### ABSTRACT

**Background:** The complex disease progression and treatment challenges affect the overall prognosis in myasthenia gravis (MG) patients. Recent advancements in managing MG have brought about significant progress in attaining complete stable remission as the treatment objective. This study aims to systematically review the prognosis of MG in literatures of the last 10 years.

**Methods:** This systematic review complied with the PRISMA 2020 standards and focused on full-text English literature published between 2014 and 2024. Articles such as editorials and review papers from the same journal, as well as submissions lacking a DOI, were excluded from consideration. Literature was sourced from online platforms like PubMed and SagePub.

**Result:** We found 627 articles on PubMed and 810 articles on SagePub. Restricting our search to the past decade (2014-2024), PubMed presented 425 articles, whereas SagePub presented 309 articles. From these, we selected 5 papers meeting our criteria, with 2 from PubMed and 3 from SagePub.

**Conclusion:** Significant progress has been achieved in treating MG over the past decade. While some patients experience spontaneous remission, the majority require treatment with steroids or similar drugs. Other treatment modalities such as monoclonal antibody treatment, pulmonary function testing, and thymectomy can be employed to improve the prognosis of MG.

**Keyword:** Myasthenia gravis, prognosis

## INTRODUCTION

Myasthenia gravis (MG) is an autoimmune disorder affecting the neuromuscular junction. The current definition of MG is a heterogeneous group of autoimmune diseases with a postsynaptic defect of neuromuscular transmission. It is characterized by autoantibodies attacking components of this junction. Prior to the introduction of acetylcholinesterase inhibitors in 1934, individuals diagnosed with MG faced a bleak outlook, often experiencing respiratory failure and pneumonia within a short period of 1–2 years.<sup>1</sup>

The defining feature of MG is fluctuating and marked weakness primarily affecting voluntary muscles, with exertion often worsening this weakness. Initially presenting as focal weakness, MG commonly begins with eye muscle involvement, leading to double vision and drooping eyelids. When confined to ocular muscles, it is termed 'ocular myasthenia'. Weakness in the muscles involved in speech, chewing, and swallowing may occur due to oropharyngeal weakness. In generalized MG, weakness in the limb girdle is typically more pronounced proximally than distally. Myasthenic crisis, a life-threatening exacerbation of MG, results from respiratory muscle weakness and swallowing difficulties.<sup>2</sup>

Studies conducted in Canada, Italy, and Japan have shown a notable increase in the prevalence of MG among the elderly in recent years. For instance, in British Columbia, the annual incidence of initial cases of MG positive for anti-acetylcholine receptor (AChR) has risen from 21.4 per million per year during 1984–88 to 52.9 during 2004–08 among individuals aged 65 and above. This global trend may be attributed to a heightened awareness among medical professionals, resulting in a more frequent consideration of MG as a potential diagnosis in older patients.<sup>2</sup>

Recent advancements in managing MG have led to significant strides in achieving complete stable remission (CSR) as the treatment goal. However, there is increasing recognition of diversity in disease progression and treatment response based on the patient's antibody profile. Patients with antibodies to muscle-specific tyrosine kinase (anti-MuSK positive) exhibit reduced responsiveness to standard therapies compared to those with antibodies to the acetylcholine receptor (anti-AChR positive) or individuals lacking both anti-MuSK and anti-AChR antibodies.<sup>3</sup>

Managing MG poses challenges, especially for patients who don't respond to standard treatments and experience recurrent hospitalizations for MG crises, necessitating ongoing intravenous immunoglobulin (IVIG) or plasmapheresis (PLEX). In severe cases, aggressive approaches such as "rebooting" the immune system with high-dose cyclophosphamide or autologous bone marrow transplantation are considered. However, chronic use of steroids or other immunosuppressants, commonly employed to manage MG, may lead to significant side effects that can impact lifespan or quality of life.<sup>1</sup>

This complex disease progression and treatment challenges affect the overall prognosis in MG patients. This study aims to systematically review the prognosis of MG in literatures of the last 10 years.

## METHODS

### Protocol

The author meticulously followed the guidelines set forth in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 to ensure that the study fully complied with its requirements. This methodological approach was specifically chosen with the aim of guaranteeing the precision and reliability of the conclusions derived from the investigation.

### Criteria for Eligibility

This systematic review examined evidence concerning the prognosis of myasthenia gravis over the past decade, carefully compiling and analyzing data to offer insights and improve patient treatment strategies. The main aim of this paper is to underscore the significance of the identified key points collectively.

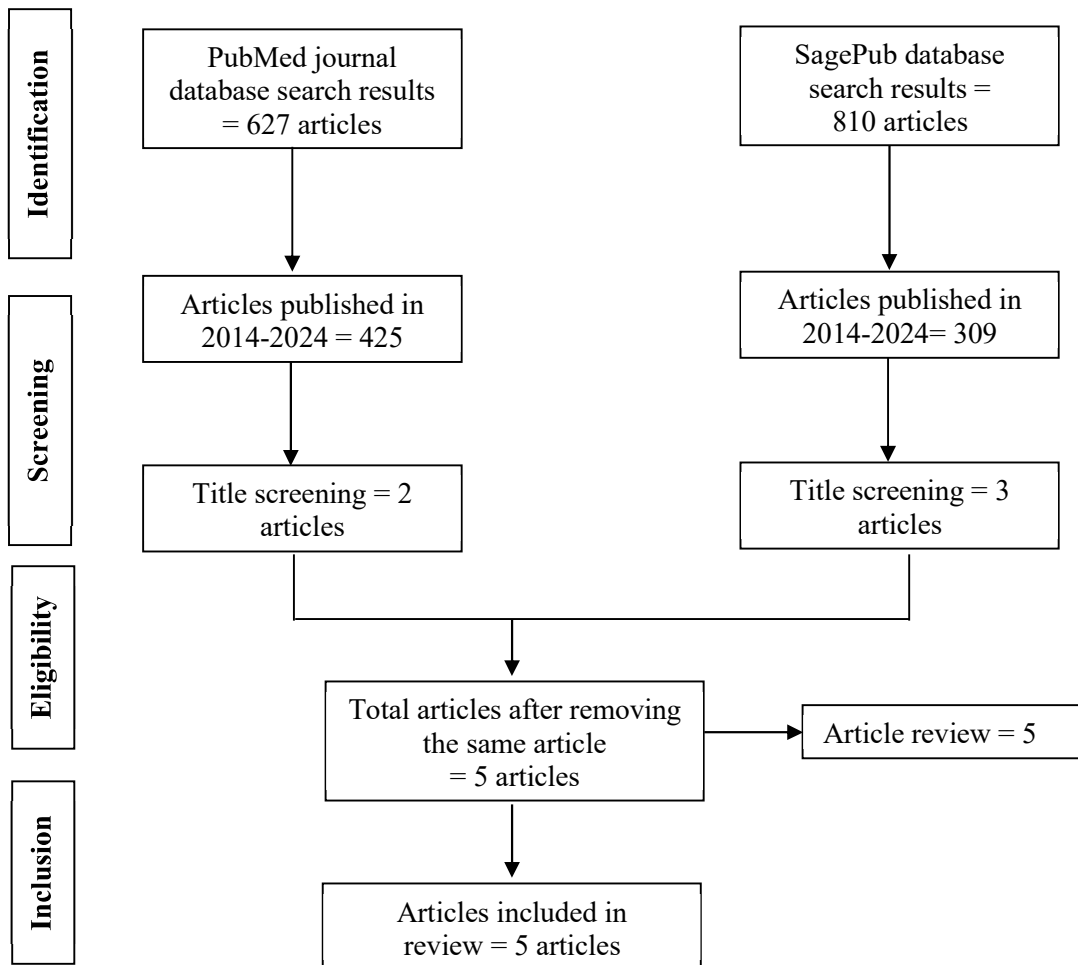
The inclusion criteria for this study are: 1) Papers must be in English, and 2) Papers must be published between 2014 and 2024. The exclusion criteria are: 1) Editorials; 2) Submissions lacking a DOI; 3) Previously published review articles; and 4) Duplicate entries in journals.

### Search Strategy

We used "myasthenia gravis" and "prognosis" as keywords. The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words (("myasthenia gravis"[MeSH Terms] OR ("myasthenia"[All Fields] AND "gravis"[All Fields]) OR "myasthenia gravis"[All Fields]) AND ("prognosis"[MeSH Terms] OR "prognosis"[All Fields] OR "prognoses"[All Fields])) AND ((y\_10[Filter]) AND (ffft[Filter]) AND (fft[Filter])).

**Data retrieval**

The authors evaluated studies by examining their abstracts and titles to determine their eligibility. Relevant studies were chosen based on their adherence to the inclusion criteria, aligning with the objectives of the article. A consistent trend observed across multiple studies led to a definitive conclusion. The selected submissions had to meet the eligibility criteria of being in English and previously unpublished.



**Figure 1. Article search flowchart**

This systematic review exclusively incorporated literature that conformed to all predefined inclusion criteria and directly pertained to the topic under investigation. Studies failing to meet these criteria were systematically excluded, and their respective findings were omitted from consideration. The subsequent analysis explored various details revealed during the research process, encompassing elements such as titles, authors, publication dates, locations, study methodologies, and parameters.

**Quality Assessment and Data Synthesis**

Each author independently assessed the research outlined in the publication's title and abstract to determine which publications warranted further exploration. The subsequent stage entails assessing all articles that fulfill the predefined criteria for inclusion in the review. Decisions regarding the inclusion of articles in the review will be based on the findings uncovered during this evaluation process. This criteria serves to streamline the paper selection process for further assessment, providing a comprehensive discussion of previous investigations and the factors that render them suitable for inclusion in the review.

**RESULT**

We identified 627 articles from the PubMed database and 810 from SagePub. After applying a ten-year filter (2014-2024), PubMed yielded 425 articles, and SagePub produced 309 articles. Ultimately, five papers meeting the criteria were chosen for the study, with two from PubMed and three from SagePub. Table 1 presents the selected literature included in this analysis.

**Table 1. The literature included in this study**

Author	Origin	Method	Sample	Result
Li, et al. <sup>4</sup> (2022)	Changsha, China	Retrospective cohort study	388 diagnosed MG patients	Between July 2015 and July 2019, a study at Xiangya Hospital involved 388 patients diagnosed with myasthenia gravis (MG). Detailed examination of their medical records was conducted to identify cases achieving minimal manifestation status (MMS). Out of these patients, 124 (50.2%) attained MMS, with a median time of 26 months. The study found that several factors were linked to MMS induction, including positivity for muscle-specific tyrosine-protein kinase receptor (MuSK) antibodies, having isolated ocular involvement, and having a low baseline quantitative myasthenia gravis score (QMG score). These factors were subsequently validated in a separate test cohort, confirming the significance of isolated ocular

				involvement and low baseline QMG scores in predicting MMS induction.
<b>Van Gaal, et al.<sup>5</sup> (2019)</b>	Ottawa, Canada	Retrospective cohort study	39 patients	This study analyzed a group of consecutive patients treated for exacerbations of myasthenia gravis at a single medical center, recording their demographic data, pulmonary function tests (PFTs), and any respiratory events necessitating intubation or urgent respiratory therapy during each encounter. The correlation between PFTs and age was examined both continuously and categorically (with a cutoff age of 70 years). Results indicated a negative association between age and slow vital capacity (SVC), with a correlation coefficient of 0.46 and a significant p-value of .002. Furthermore, elderly patients exhibited significantly lower maximum inspiratory pressure (MIP) and SVC compared to nonelderly patients (MIP: 20.0 vs. 30.0 cm H <sub>2</sub> O, p-value .004; SVC: 16.5 vs. 23.4 mL/kg, p-value .013). However, there was no statistically significant difference in the occurrence of respiratory events between elderly and nonelderly patients (p-value .08).
<b>Narita, et al.<sup>6</sup> (2023)</b>	Nagasaki, Japan	Retrospective cross sectional study	135 patients with ocular MG	The study gathered clinical data from 135 ocular myasthenia gravis (OMG) patients, encompassing factors like demographics, symptoms, treatment history, complications, and outcomes. Treatment for OMG

				<p>proved complex, involving diverse immunotherapeutic approaches. Eight patients experienced spontaneous remission without immunotherapy, while 117 showed improvement with treatment, and 10 exhibited refractory responses. Although overall outcomes were positive, 60.7% of patients still had symptoms after treatment. Among those receiving immunotherapy (90 patients), only two were refractory, contrasting with eight refractory cases among the 45 patients without immunotherapy. This indicates a significantly lower refractory rate in the immunotherapy group (p=0.001). Moreover, medical centers with frequent immunotherapy use for OMG had a lower proportion of generalized MG cases among all MG cases.</p>
<p><b>Muppidi, et al.<sup>7</sup> (2019)</b></p>	<p>Multicenter, USA</p>	<p>Randomized controlled trial</p>	<p>117 patients</p>	<p>In a study involving 117 patients, eculizumab was administered every 2 weeks for an average of 22.7 months. The safety profile of eculizumab remained consistent with previous findings, and no meningococcal infections were reported during the analysis period. The exacerbation rate of myasthenia gravis decreased by 75% compared to the year prior to treatment with eculizumab. Patients experienced sustained improvements in daily activities, muscle strength, functional ability, and quality of</p>

				life over three years, with 56% achieving minimal manifestations or pharmacological remission. Patients initially on placebo and later switched to eculizumab showed rapid and sustained improvements.
<b>Wolfe, et al.<sup>8</sup> (2016)</b>	Multicenter	Randomized controlled trial	126 patients	The study compared extended transsternal thymectomy plus alternate-day prednisone with alternate-day prednisone alone in patients aged 18 to 65 with generalized nonthymomatous myasthenia gravis. Thymectomy patients showed lower disease severity scores, reduced prednisone requirements, and fewer hospitalizations for exacerbations compared to the prednisone-only group. Thymectomy also decreased the need for additional immunosuppression. Treatment-associated complications were similar between groups, but thymectomy patients experienced fewer symptoms and lower distress levels related to medication.

Li, et al.<sup>4</sup> (2022) examined factors influencing minimal manifestation status (MMS) induction in diagnosed MG patients and discovered that isolated ocular involvement and having a low baseline QMG score were indicators of MMS induction. These results could assist in personalizing treatment approaches and prognosis.

Van Gaal, et al.<sup>5</sup> (2019) showed that elderly patients treated for MG exacerbation exhibit significantly reduced pulmonary function compared to nonelderly patients. Despite this, most elderly patients do not require intubation, although they necessitate intensive monitoring for potential severe respiratory complications.

Narita, et al.<sup>6</sup> (2023) found that the overall prognosis for patients diagnosed with ocular myasthenia gravis (OMG) who undergo immunotherapy was positive. However, the outcomes for certain patients, particularly those who did not undergo immunotherapy, were less favorable. Immunotherapy seems to offer benefits for individuals with OMG.

Muppidi, et al.<sup>7</sup> (2019) confirmed eculizumab's rapid and enduring effectiveness and safety in patients with refractory generalized myasthenia gravis (gMG) who previously had persistent symptoms despite conventional therapy. Eculizumab not only maintains improvements in daily activities and quality of life over three years but also reduces disease exacerbations.

Wolfe, et al.<sup>8</sup> (2016) demonstrated the benefits of thymectomy in patients with myasthenia gravis over a three-year period. It showed improvements in clinical outcomes, reduced reliance on prednisone and azathioprine therapy, fewer symptoms and less distress related to immunosuppressive agents, and decreased hospitalizations for disease exacerbations.

## DISCUSSION

Myasthenia gravis (MG) is an autoimmune disorder affecting the neuromuscular junction, driven by T-cells and antibodies. Pathogenic antibodies disrupt postsynaptic structures through complement activation, resulting in anti-acetylcholine receptor (AChR) internalization, AChR blockage, or interference with the agrin/LRP4/MuSK/Dok7/rapsyn pathway. These processes impair neuromuscular junction transmission, leading to fluctuating muscle weakness and fatigability.<sup>4</sup>

The majority of MG patients initially presented with ocular symptoms, peaking within one to three years before stabilizing. Progression to generalized MG symptoms often occurred within the first year, with weakness reaching its peak within six months to two years. Mortality rates were significant, with around one-third of patients diagnosed with generalized MG between 1940 and 1960 succumbing to the condition. In a 1981 study, a notable percentage of MG-related deaths occurred within the first five years of onset.<sup>3</sup>

Although ocular myasthenia gravis (OMG) is typically non-life-threatening and considered mild, the symptoms of diplopia and ptosis often create significant challenges in daily activities and overall quality of life. The European Federation of Neurological Society/European Neurological Society (EFNS/ENS) guidelines recommend initiating treatment with pyridostigmine. According to the updated formal consensus guidance from international MG experts, patients with ophthalmoparesis or ptosis in OMG that does not respond to anticholinesterase agents should consider immunosuppressive treatment if symptoms significantly impact functionality or cause distress. The overall prognosis for patients diagnosed with OMG who undergo immunotherapy was positive. However, the outcomes for certain patients, particularly those who did not undergo immunotherapy, were less favorable. Immunotherapy seems to offer benefits for individuals with OMG.<sup>6</sup>

Advancements in intensive care and immunotherapy have notably reduced MG mortality, enabling many patients to achieve minimal manifestation status (MMS) or better. The concept of MMS in MG was introduced in 2000 and is widely used in clinical studies. It is recommended as a treatment goal in MG management, involving two phases: induction and maintenance. Achieving MMS early can reduce reliance on high-dose steroids and improve quality of life. Intensive treatment strategies have shown result in earlier attainment of MMS, hence improving the prognosis of the disease.<sup>4</sup>

Approximately 10% to 15% of MG patients do not respond adequately to long-term corticosteroid treatment or multiple steroid-sparing immunosuppressive therapies (IST). They may experience intolerable side effects or require ongoing intravenous immunoglobulin (IVIg) or plasma exchange. This persistence of myasthenic symptoms can significantly impact daily activities such as breathing, speaking, swallowing, walking, and muscle strength, as well as overall quality of life. These patients also face increased risks of myasthenic exacerbations and crises, necessitating more frequent hospitalizations, intensive care unit admissions, and emergency room visits.<sup>7</sup>

Respiratory failure is a severe complication of MG, often requiring hospitalization for careful monitoring to prevent emergency intubation. Spirometry is used to assess respiratory function, but previous studies have shown that measurements like vital capacity (VC) and maximal inspiratory pressure (MIP) are not reliable indicators of the need for mechanical intervention. The combination of age and MG has an additional impact on respiratory function, which physicians must consider when contemplating intubation for patients. Elderly patients with MG face increased risks during intubation, including prolonged intubation periods and associated complications such as atelectasis, infection, anemia, and congestive heart failure. Prolonged intubation also correlates with poorer functional outcomes following myasthenic crises. Pulmonary function testing can aid in the prevention of needless intubation and its potential risks.<sup>5</sup>

Eculizumab is a humanized monoclonal antibody that targets human terminal complement protein C5. By inhibiting the cleavage of C5 to C5a and C5b, it prevents C5a-induced chemotaxis of proinflammatory cells and formation of the C5b-induced membrane attack complex. In the 6-month randomized, double-blind, placebo-controlled REGAIN study, eculizumab demonstrated efficacy and was well tolerated in patients with antiacetylcholine receptor antibody-positive (AChR+) refractory generalized MG (gMG). It led to clinically significant improvements in daily activities, muscle strength, functional ability, and quality of life. Eculizumab is approved for the treatment of adults with AChR+ gMG, as well as paroxysmal nocturnal hemoglobinuria (PNH).<sup>7</sup>

Thymectomy is considered for the treatment of myasthenia gravis (MG) based on multiple lines of evidence indicating the thymus plays a central role in the disease's pathogenesis. Thymomas, present in 10% of MG patients, often necessitate thymectomy to prevent further complications. Additionally, up to 70% of remaining MG patients exhibit hyperplastic



thymic changes not observed in healthy individuals. However, the success of immunotherapy has led to questions about the necessity of thymectomy. A randomized controlled trial demonstrated the benefits of thymectomy in MG patients over a 3-year period, including improved clinical outcomes, reduced need for prednisone and azathioprine therapy, fewer symptoms and distress related to immunosuppressive agents, and decreased hospitalizations for disease exacerbations.<sup>8</sup>

## CONCLUSION

Significant progress has been achieved in treating MG over the past decade. While some patients experience spontaneous remission, the majority require treatment with steroids or similar drugs. Other treatment modalities such as monoclonal antibody treatment, pulmonary function testing, and thymectomy can be employed to improve the prognosis of MG.

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