

Review Paper

Myasthenia Gravis and COVID-19: A Systematic Review and Meta-analysis



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ABSTRACT

Introduction: Patients with myasthenia gravis (MG), an autoimmune disease affecting the neuromuscular junction, exhibits varying rates of COVID-19 infection across different studies. This systematic review and meta-analysis aim to estimate the pooled prevalence of COVID-19 infection in individuals with MG.

Methods: We systematically searched PubMed, Scopus, EMBASE, Web of Science, Google Scholar, and gray literature, including references to the research published before October 2021. The total number of participants, the first author, the publication year, the country of origin, the number of MG patients, their symptoms, hospitalization rates, and deaths were all extracted as study data.

Results: Our literature search yielded 253 articles, of which 75 remained after removing duplicates. Finally, 18 articles were included in the meta-analysis. The pooled prevalence of COVID-19 infection in MG cases was found to be 2% (95% CI, 1%, 3%; I²=85%, P<0.001). Additionally, the pooled prevalence of hospitalization among those with COVID-19 infection was 43% (95% CI, 26%, 60%; I²=97.6%; P<0.001), and the pooled prevalence of MG exacerbation was 33% (95% CI, 20%, 46%; I²=92.6%; P<0.001).

Conclusion: In summary, this systematic review and meta-analysis reveal that the pooled prevalence of COVID-19 infection in individuals with MG is 2%.

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Highlights

- The pooled prevalence of COVID-19 infection in myasthenia gravis (MG) cases was 2%.
- The pooled prevalence of hospitalization among individuals with COVID-19 infection was 43%.
- The pooled prevalence of MG exacerbation among individuals with COVID-19 infection was 33%.
- The pooled prevalence of mortality in infected cases was 9%.

Plain Language Summary

Patients with myasthenia gravis (MG), an autoimmune disease affecting the neuromuscular junction, exhibits varying rates of COVID-19 infection across different studies. This systematic review and meta-analysis aim to estimate the pooled prevalence of COVID-19 infection in individuals with MG. The pooled prevalence of COVID-19 infection in MG cases was found to be 2%. Additionally, the pooled prevalence of hospitalization among those with COVID-19 infection was 43%, and the pooled prevalence of MG exacerbation was 33%. In summary, this systematic review and meta-analysis reveal that the pooled prevalence of COVID-19 infection in individuals with MG is 2%.

1. Introduction

In December 2019, a new coronavirus emerged in China and rapidly spread worldwide, leading to a pandemic (Moghadasi, 2021). Fever, cough, and malaise are the most frequent clinical symptoms, while different factors such as the presence of underlying diseases, advanced age, and used medications play crucial roles in the prognosis of the COVID-19 infection (Li et al., 2021). Myasthenia gravis (MG) is an autoimmune disorder that affects the neuromuscular junction, and patients should use immune suppressors as the treatment (Hübers et al., 2020). Administration of immune suppressors predisposes these cases to severe form of the disease, and anti-virus treatments such as hydroxyl-chloroquine exacerbate MG (Anand et al., 2020; Gilhus et al., 2018).

Various studies have reported different rates of COVID-19 infection in patients with MG. Consequently, this systematic review and meta-analysis were designed to estimate the pooled prevalence of COVID-19 infection in patients with MG.

2. Materials and Methods

We systematically searched PubMed, Scopus, EMBASE, Web of Science, Google Scholar, and gray literature, including references to the included studies published before October 2021.

The search strategy was as follows:

((“Myasthenia gravis” AND “ocular”) OR “ocular myasthenia gravis” OR (“myasthenia gravis” AND “generalized”) OR (generalized myasthenia gravis) OR (“muscle-specific receptor tyrosine kinase myasthenia gravis”) OR (“muscle specific receptor tyrosine kinase myasthenia gravis”) OR (“muscle-specific tyrosine kinase antibody positive myasthenia gravis”) OR (“muscle specific tyrosine kinase antibody positive myasthenia gravis”) OR (“MuSK MG”) OR (“MuSK myasthenia gravis”) OR (“myasthenia gravis” AND “MuSK”) OR (“anti-MuSK myasthenia gravis”) OR (“anti MuSK myasthenia gravis”) OR (“myasthenia gravis” AND “anti-MuSK”)) AND (“COVID 19” OR “COVID-19 virus disease” OR “COVID 19 virus disease*” OR “COVID-19 virus disease*” OR (disease AND “COVID-19 Virus”) OR (“virus disease” AND COVID-19) OR “COVID-19 virus infection*” OR “COVID 19 virus infection” OR (infection AND “COVID-19 virus”) OR (“virus infection” AND COVID-19) OR “2019-nCoV infection” OR “2019 nCoV infection*” OR (infection AND 2019-nCoV) OR “coronavirus disease-19” OR “coronavirus disease 19” OR “2019 novel coronavirus disease” OR “2019 novel coronavirus infection” OR “2019-nCoV disease” OR “2019 nCoV disease” OR “2019-nCoV diseases” OR (disease AND 2019-nCoV) OR “COVID19” OR “coronavirus disease 2019” OR (“disease 2019” AND coronavirus) OR “SARS coronavirus 2 infection” OR “SARS-CoV-2 infection” OR (infection AND SARS-CoV-2) OR “SARS CoV 2 infec-

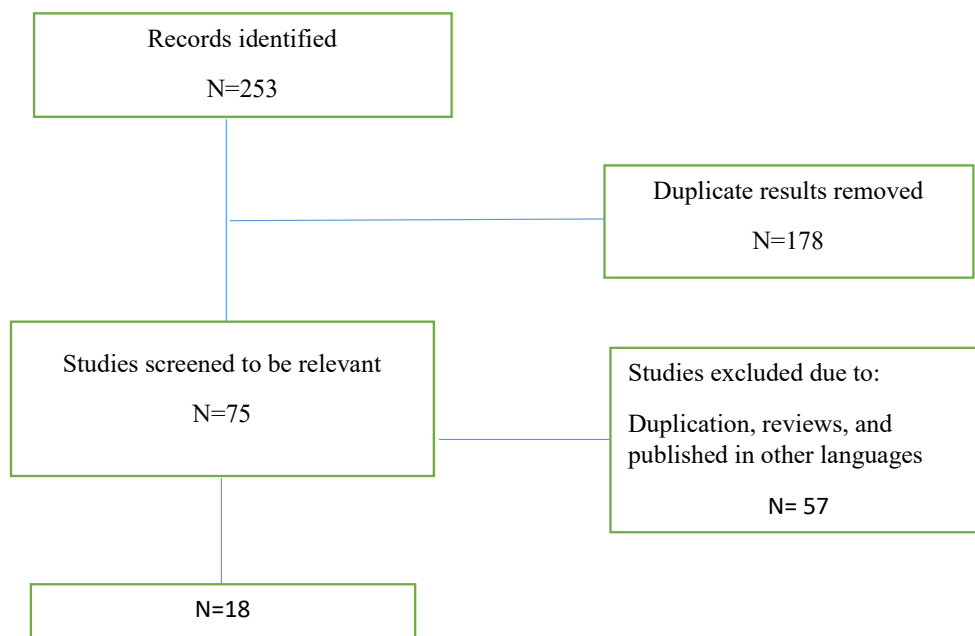


Figure 1. Flowchart outlining the determination of eligible research

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tion*” OR “COVID-19 pandemic*” OR “COVID 19 pandemic” OR (pandemic AND COVID-19))

Inclusion criteria

We included cross-sectional studies or case series reporting the incidence of COVID-19 infection, hospitalization, or mortality in individuals with MG.

Exclusion criteria

We excluded letters to the editor, case-control studies, and case reports. Data were extracted regarding the total number of participants, first author, publication year, country of origin, individuals with myasthenia gravis, symptoms, hospitalization, and death.

Risk of bias assessment

We assessed the risk of bias using the Newcastle-Ottawa scale (NOS) for cross-sectional studies (Modesti et al., 2016).

Statistical analysis

All statistical analyses were performed using STATA software, Version 14.0 (Stata Corp LP, College Station, TX, USA), employing random-effects models. We calculated inconsistency (I^2) to determine heterogeneity.

3. Results

We found 253 articles utilizing a literature search; after excluding duplicates, 75 remained. Finally, 18 articles were selected for meta-analysis (Figure 1).

A total of 18 articles were included in the analysis, and their basic characteristics are presented in Table 1.

Figure 2 displays the pooled prevalence of COVID-19 infection in MG cases, which was 2% (95% CI, 1%-3%; $I^2=85%$; $P<0.001$).

Figure 3 provides information on the pooled prevalence of hospitalization among individuals with COVID-19 infection, which was calculated to be 43% (95% CI, 26%, 60%; $I^2=97.6%$; $P<0.001$).

Figure 4 shows the pooled prevalence of MG exacerbation among those with COVID-19 infection, which was 33% (95% CI, 20%, 46%; $I^2=92.6%$; $P<0.001$).

According to Figure 5, the pooled prevalence of mortality in infected cases was 9% (95% CI, 5%, 12%; $I^2:85.3%$; $P<0.001$).

4. Discussion

To our understanding, this systematic review and meta-analysis is the first to evaluate the prevalence of COVID-19 infection in MG cases. The findings indicate that

Table 1. Basic characteristics of the studies included in the analysis

Author	Year	Country	Study Type	Total. MG	Number. COVID-19 ¹	Number Confirmed by PCR ²	Age Case 3	Age:SD_Case	Female Case	Male Case	Disease. Duration. SD Case	Disease. Duration Case	Fever	Cough	Dyspnea	MG Exacerbation for COVID-19	Myalgia. Arthralgia	Hospitalized	Death	NOS Quality Assessment
Sarmiento-Monroy et al., 2021	2021	Spain	Cohort	75	5	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	4	NR	6/9
Županić et al., 2021	2021	Republic of Croatia	Case series	8	8	8	62	NR	2	6	NR	5.5	2	2	3	4	NR	NR	1	NR
Muppidi et al., 2020	2020	US	Abstract (cross-sectional)	36	36	36	58	NR	19	17	NR	NR	NR	NR	NR	17	NR	NR	10	NR
Kopanidis et al., 2021	2021	UK	Abstract (cohort)	487	12	NR	63.8	NR	NR	NR	NR	NR	NR	NR	NR	4	NR	6	1	6/9
Businaro et al., 2021	2021	Italy	Cohort	162	11	3	66	NR	6	5	NR	6	9	8	5	1	6	3	2	8/9
Anand et al., 2020	2020	US	Case series	5	5	5	63.4	NR	3	2	NR	6.6	1	4	1	1	NR	NR	1	NR
Rzepliński & Zawałka-Kunikowska, 2021	2021	Poland	Cohort	30	10	10	46.3	NR	9	1	NR	9.7	5	6	1	3	7	2	0	8/9
Muppidi et al., 2020	2020	US	Cohort	91	91	80	56.24	16.1	49	42	NR	NR	NR	NR	NR	36	NR	63	22	7/9
Roy et al., 2021	2021	USA	Cohort	40392	380	NR	63.2	16.4	185	195	NR	NR	NR	NR	NR	20	NR	102	26	6/9

Author	Year	Country	Study Type	Total. MG	Number. COVID-19 ¹	Number Confirmed by PCR ²	Age Case 3	Female Case	Male Case	Disease. Duration Case	Disease. Duration. SD Case	Fever	Cough	Dyspnea	Myalgia. Arthralgia MG Exacerbation for COVID-19	Hospitalized	Death	NOS Quality Assessment
Sole et al., 2021	2021	France	Cohort	3558	34	20	55	19	15	8.47	8.5	NR	NR	NR	NR	19	5	7/9
Martinez-Hernandez et al., 2021	2021	Barcelona	Cross-sectional	75	4	NR	61(M)	1	3	NR	NR	NR	NR	NR	NR	3	1	7/10
Saied et al., 2021	2021	Tunisia	Case series	5	5	5	49.6	4	1	8.2	NR	3	1	2	1	NR	1	NR
Camelo-Filho et al., 2020	2020	Brazil	Cohort	15	15	15	45.22	9	6	8.93	NR	13	10	14	7	NR	4	7/9
Etemadifar et al., 2021	2021	Iran	Cohort	150	14	14	48.28	10	4	9.28	9.1	9	NR	6	NR	4	2	7/9
Mitchala et al., 2021	2021	Czech Republic	Cohort	93	93	93	65.33(M)	46	47	6(M)	NR	NR	NR	NR	14	34	10	7/9
Suri et al., 2021	2021	US	Abstract (Case Series)	6	6	NR	NR	5	1	NR	NR	NR	NR	NR	1	NR	0	NR
Granger et al., 2021	2021	US	Abstract (Case Series)	7	7	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	5	2	NR
Neykova et al., 2021	2021	Bulgaria	Case Series	5	5	5	33.4	5	NR	7.4	NR	3	2	NR	1	0	NR	NR

Abbreviation: MG: Myasthenia gravis; NOS: Newcastle-Ottawa Scale; MG: Myasthenia Gravis; NR: Not reported; SD: Standard deviation. ¹ Number of MG patients affected by COVID-19, ²Number of MG patients whose status as a case of COVID-19 has been validated by PCR, ³Case refers to all MG patients who have been affected by COVID-19.

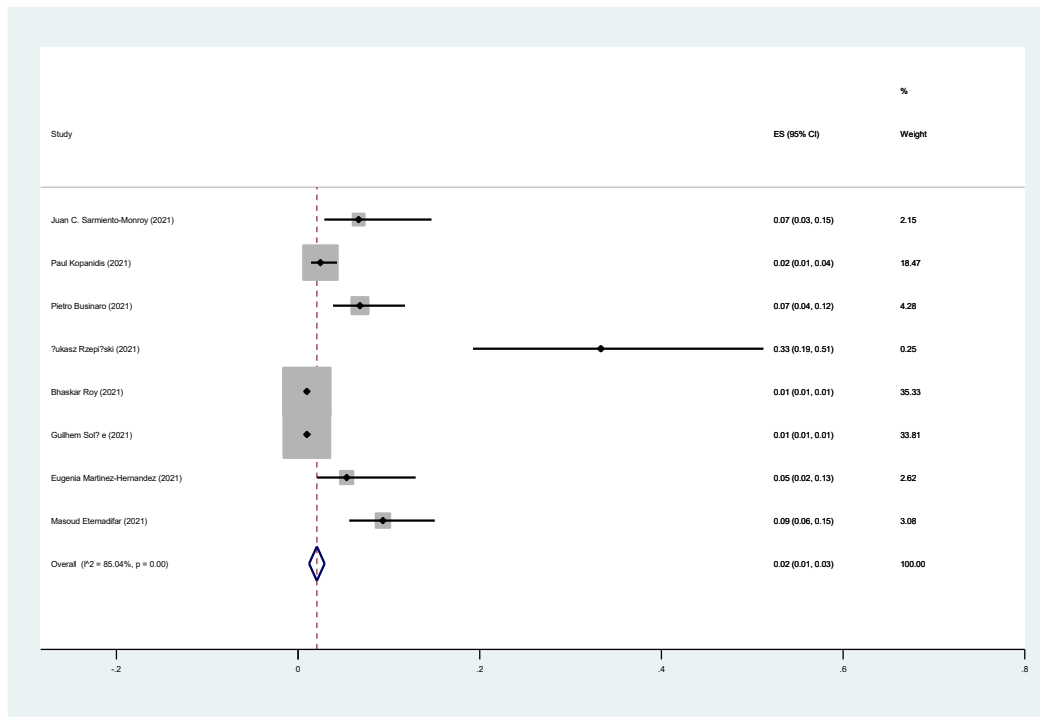


Figure 2. The pooled prevalence of COVID-19 infection in patients with MG

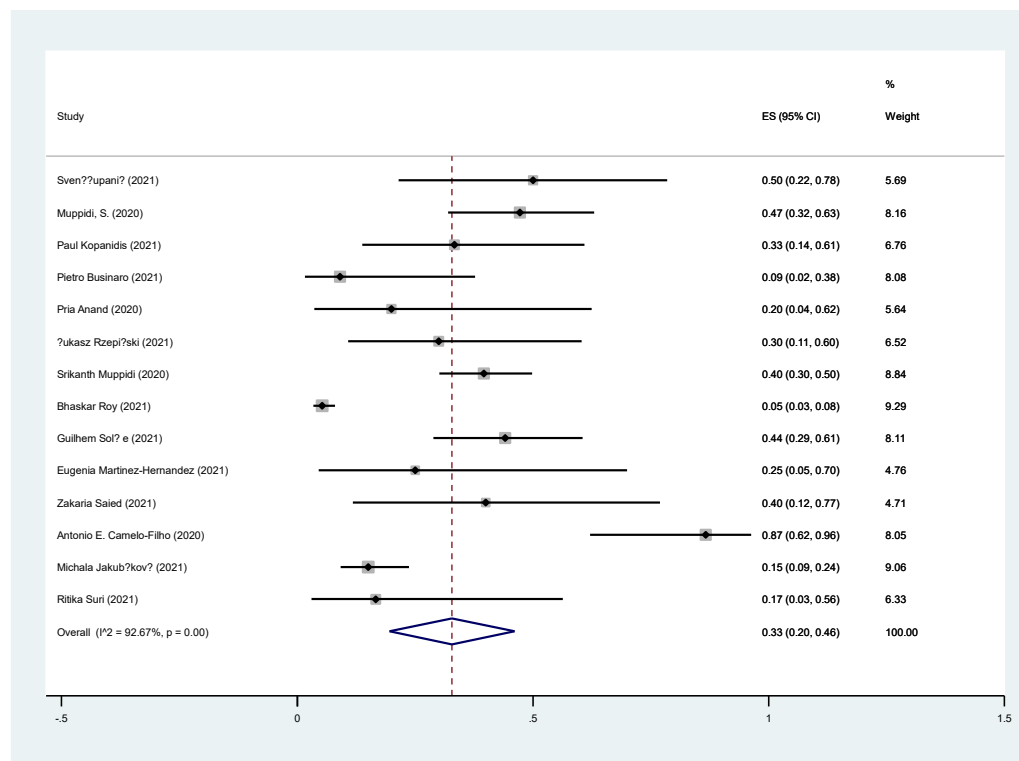


Figure 3. The pooled prevalence of hospitalization among infected cases

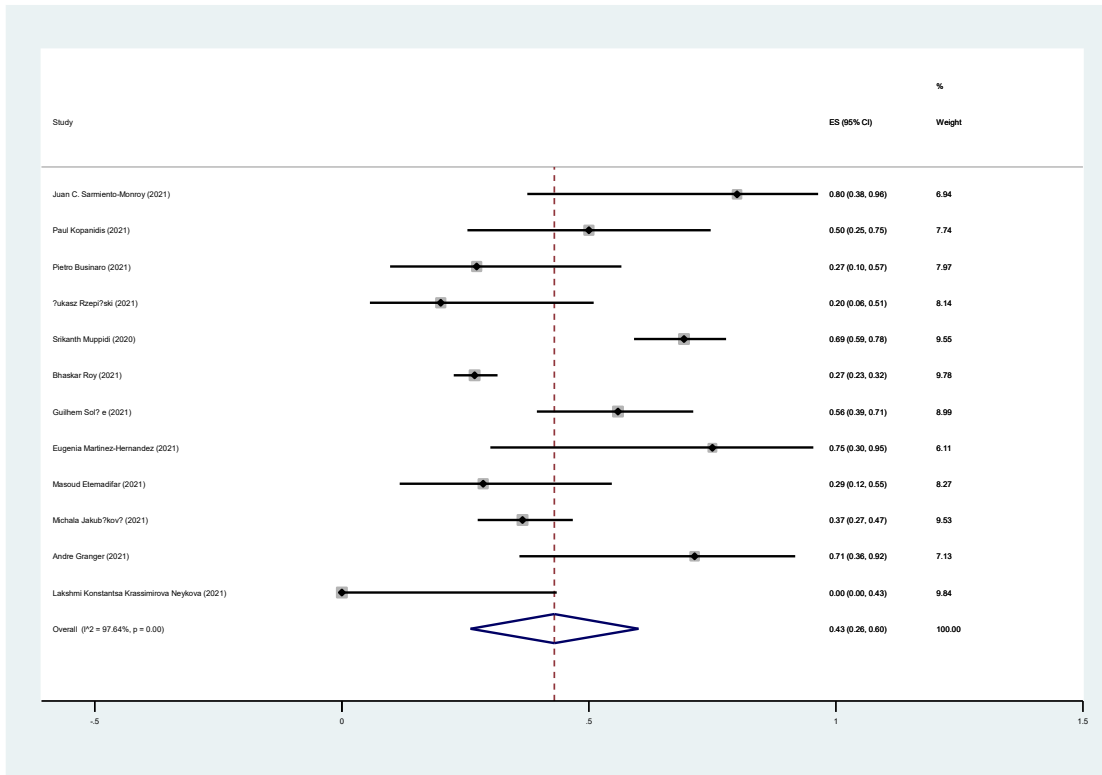


Figure 4. The pooled prevalence of MG exacerbation among infected cases

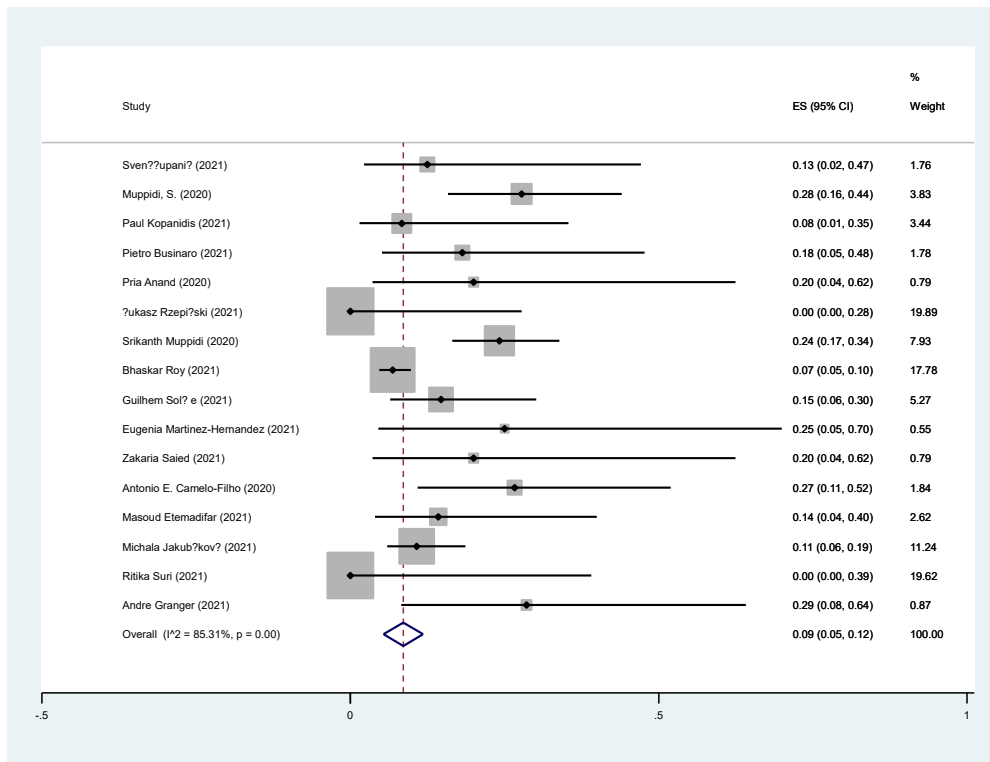


Figure 5. The pooled prevalence of mortality in COVID-19-infected cases

the pooled prevalence of COVID-19 infection in MG cases is 2%, the pooled hospitalization rate is 43%, disease exacerbation is 33%, and the pooled mortality rate is 9%.

Previous studies evaluating patients who received immunosuppressive agents demonstrated that using medications does not predispose patients to higher COVID-19 infection risk. A 2021 systematic review and meta-analysis reported that the pooled prevalence of COVID-19 in MS cases was 4%, and the pooled hospitalization rate was 10% (Moghadasi et al., 2021). Businaro et al. evaluated 162 MG patients and reported COVID-19 infection in 11. They found that the severity of MG was not related to the seriousness of COVID-19 infection (Businaro et al., 2021). Rein et al. reported three cases of COVID-19 infection and MG and reported favorable outcomes, and only one experience exacerbation of the disease (Rein et al., 2020).

Our results show that the pooled prevalence of disease exacerbation was 33%, which indicates that COVID-19 infection interferes with MG's nature.

It is suggested that early administration of intravenous immunoglobulins or steroids could prevent complications in MG cases (International MG/COVID-19 Working Group et al., 2020).

Rzepiński et al. evaluated 30 MG cases who had no vaccination against COVID-19 and found that exacerbation of MG was presented in 11, which needed hospitalization (Rzepiński & Zawadka-Kunikowska, 2021). Muppidi et al. evaluated 91 MG patients who had COVID-19 infection and reported hospitalization, disease exacerbation, and mortality in 69%, 40%, and 22%, respectively (Muppidi et al., 2020). By including 3558 MG cases, Sole et al. reported 34 cases of COVID-19 infection, of whom 5 died due to illness. They found that disease severity was not associated with infection severity (Solé et al., 2021). Anand et al. described COVID-19 infection in 5 MG cases who were hospitalized and were immunosuppressed. Four had favorable outcomes, and mycophenolate mofetil was held in two cases (Anand et al., 2020).

It should be considered that patients with COVID-19 infection experience a wide range of neurological complications. Farsalinos et al. suggested that SARS-CoV-2 may interact with the nicotinic AChR, potentially leading to dysregulation of the cholinergic anti-inflammatory pathway (Farsalinos et al., 2020).

The International MG/COVID-19 Working Group suggested continuing medications in MG cases and medication changes or stops after consultation with the health care provider (International MG/COVID-19 Working Group, et al., 2020).

This study holds several strengths. Firstly, it represents the pioneering systematic review and meta-analysis in this context. Secondly, we included all relevant research manuscripts in our analysis.

5. Conclusion

The findings derived from this systematic review and meta-analysis indicate that the pooled prevalence of COVID-19 infection in MG cases is 2%.

Ethical Considerations

Compliance with ethical guidelines

This article is a meta-analysis with no human or animal sample.

Funding

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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