Title: Myasthenia Gravis and COVID-19: A Systematic Review and Meta-Analysis

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Abstract:

Myasthenia gravis, 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 myasthenia gravis(MG). We conducted a systematic search of PubMed, Scopus, EMBASE, Web of Science, Google Scholar, and gray literature, which includes references to the included research that were published prior to 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 data. Our literature search yielded 253 articles, of which 75 remained after removing duplicates. Eighteen 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). In summary, this systematic review and meta-analysis reveal that the pooled prevalence of COVID-19 infection in individuals with MG is 2%.

Keywords: Myasthenia gravis, COVID-19, Prevalence

Introduction:

In December 2019, a new coronavirus emerged in China and rapidly spread worldwide, ultimately leading to a pandemic(1). Fever, cough, and malaise are the most frequent clinical symptoms while different factors such as presence of underlying diseases, advanced age, used medications play crucial roles in the prognosis of the COVID-19 infection(2).

Myasthenia gravis is an autoimmune disorder that affects neuromuscular junction which patients should administer immune suppressors as the treatment(3).

Administration of immune suppressors predispose thee cases to severe form of the disease while anti-virus treatments such as hydroxyl-chloroquine cause myasthenia gravis exacerbation (4, 5).

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

Methods:

We conducted a systematic search of PubMed, Scopus, EMBASE, Web of Science, google scholar and also gray literature including references of the included studies which were published before October 2021.

The search strategy was:

((“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 Infection*” 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 myasthenia gravis.

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 QUALITY ASSESSMENT SCALE adapted for cross-sectional studies(6).

Statistical analysis:

All statistical analyses were performed using STATA (Version 14.0; Stata Corp LP, College Station, TX, USA), employing random-effects models. We calculated Inconsistency (I2) to determine heterogeneity.

Results:

We found 253 articles by literature search, after excluding duplicates 75 remained. Eighteen articles were selected for meta-analysis (figure 1).

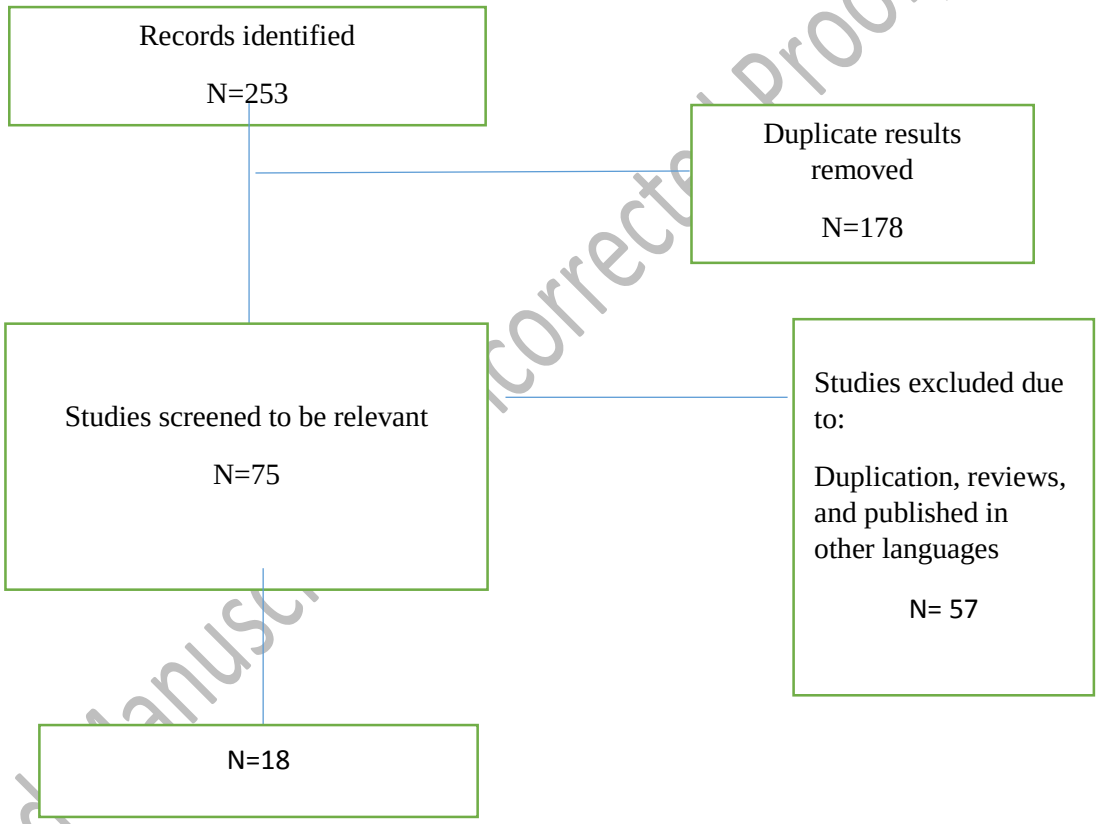

Figure 1: Flowchart outlining the determination of eligible researches

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

Table 1: Basic characteristics of the studies that were included in the analysis .

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

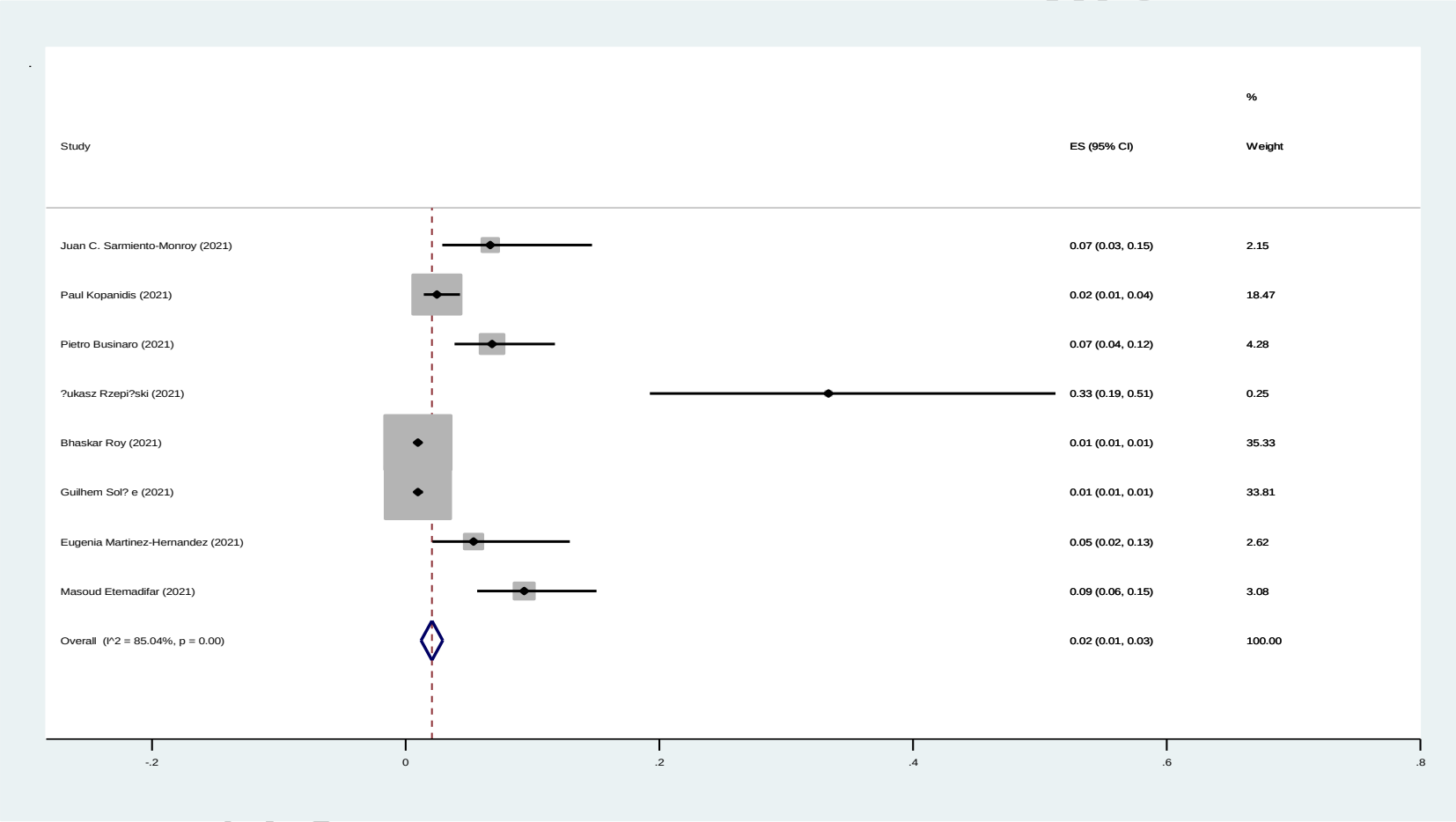

Figure 2: The pooled prevalence of COVID-19 infection in patients with MG.

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) .

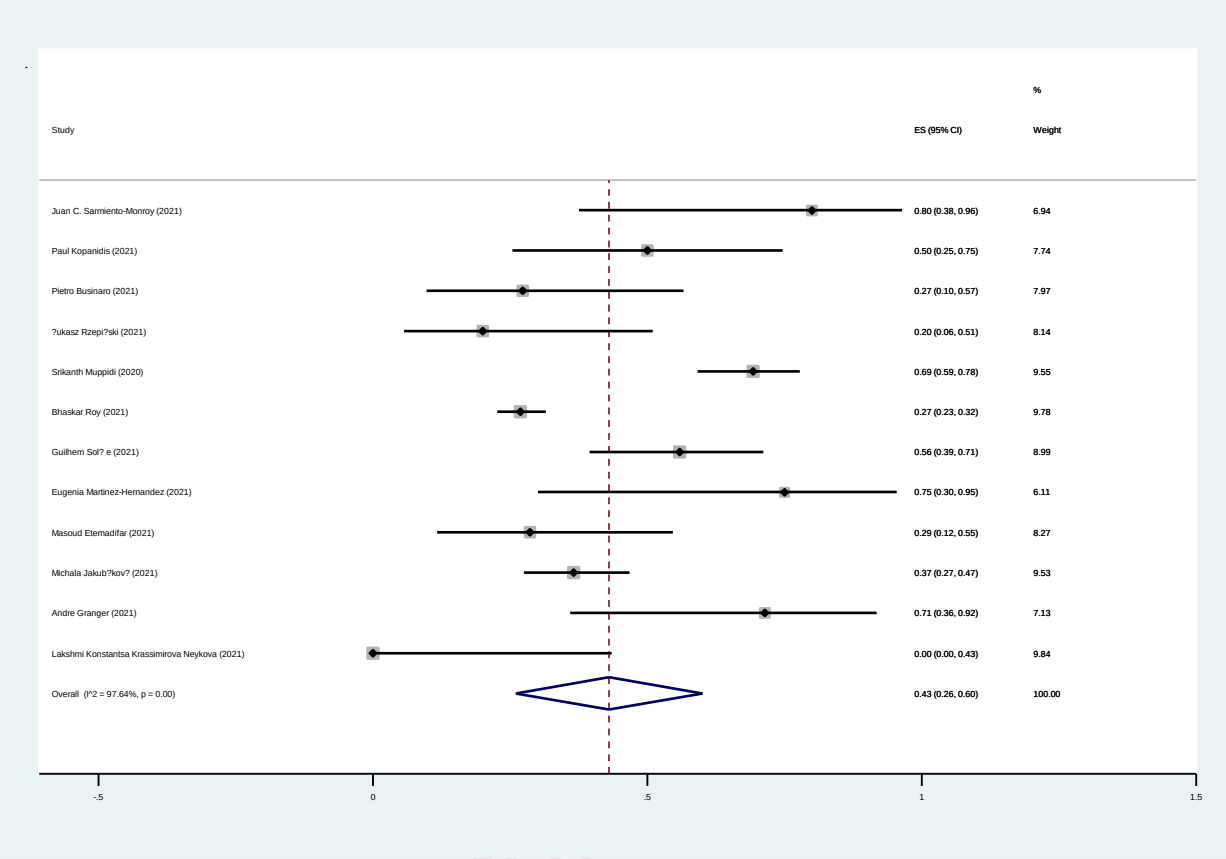

Figure 3: The pooled prevalence of hospitalization among infected cases.

Figure 4 shows the pooled prevalence of MG exacerbation among those with COVID-19 infection, which was 33% (95%CI: 20-46%) (I2=92.6%, P<0.001).

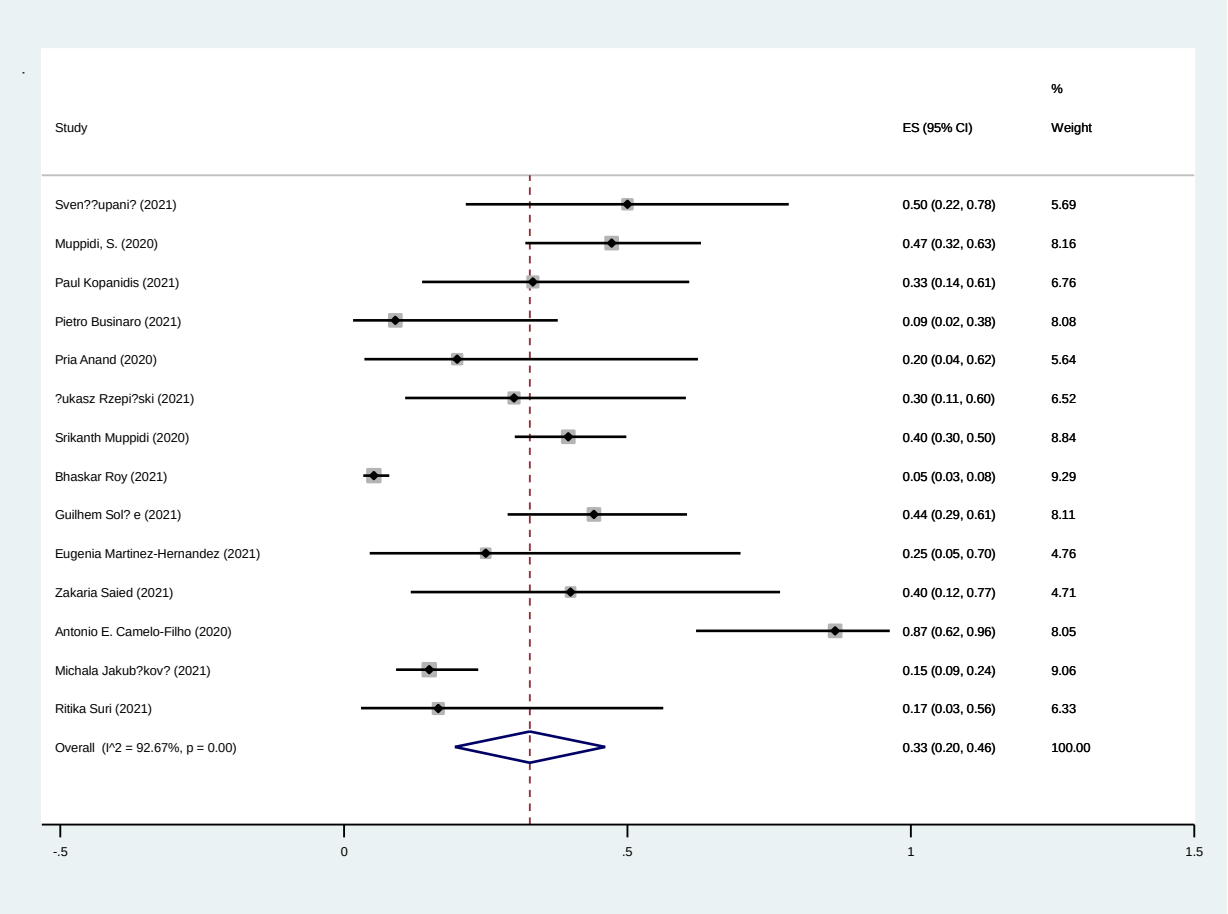

Figure 4: The pooled prevalence of MG exacerbation among infected cases.

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

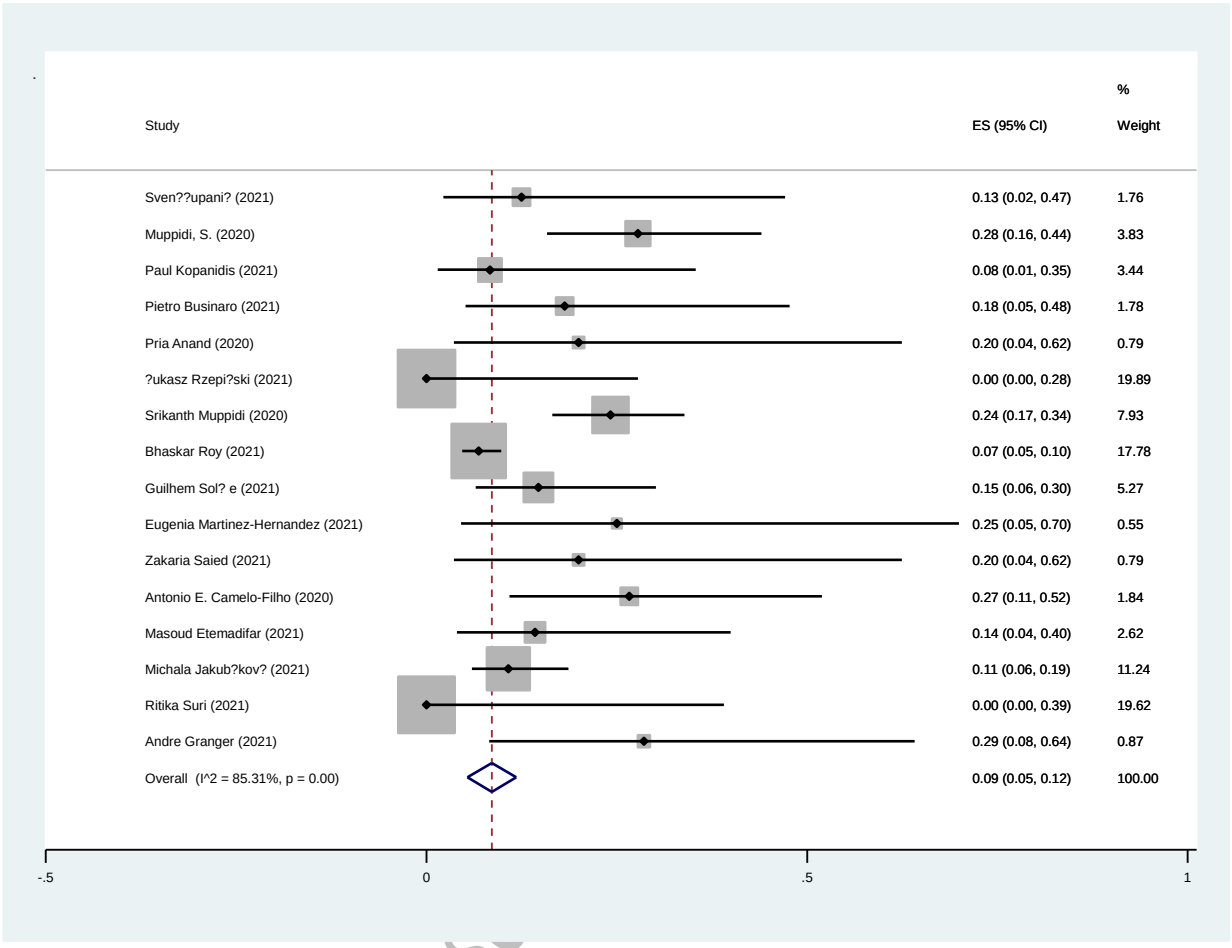

Figure 5: The pooled prevalence of mortality in COVID-19 infected cases.

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

Previous studies evaluating patients who received immunosuppressive agents demonstrated that the medication do not predispose patients to higher COVID-19 infection risk.

In a 2021 systematic review and meta-analysis, it was reported that the pooled prevalence of COVID-19 in MS cases was 4%, and the pooled hospitalization rate was 10% (7).

Businaro et al evaluated 162 MG patients and reported COVID-19 infection in 11. They found that severity of MG was not related with severity of COVID-19 infection(8).

Rein et al reported three cases of COVID-19 infection and MG and reported favorable outcome and only one experience exacerbation of the disease(9).

As our results show, pooled prevalence of disease exacerbation was 33% which shows COVID-19 infection interferes with MG nature.

It is suggested that early administration of intravenous immunoglobulins or steroids could prevent complications in MG cases(10).

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(11).

Muppidi et al evaluated 91 MG patients who had COVID-19 infection and reported hospitalization, disease exacerbation and mortality in 69%, 40% and 22%(12).

By including 3558 MG cases, Sole et al reported 34 cases with COVID-19 infection, of whom 5 died due to infection. They found that disease severity was not associated with infection severity(13).

Anand et al described COVID-19 infection in 5 MG cases who were hospitalized and were immunosuppressed. Four of them had favorable outcome and mycophenolate mofetil was hold in two included cases(5).

It should be considered that patients with COVID-19 infection experience a wide range of neurological complications. Farsalinos and colleagues suggested that SARS-CoV-2 may

interact with the nicotinic AChR, potentially leading to dysregulation of the cholinergic anti-inflammatory pathway (14).

The International MG/COVID-19 Working Group suggested continuation of medications in MG cases and medication change or stop after consultation with the health care provider(15).

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.

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%.

Conflict of interests: The authors declare no conflict of interest.

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