Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Clinical Neurology and Neurosurgery 213 (2022) 107140

Contents lists available at ScienceDirect

Clinical Neurology and Neurosurgery

journal homepage: www.elsevier.com/locate/clineuro

Characteristics, treatment, and outcomes of Myasthenia Gravis in COVID-19 patients: A systematic review

Alzhraa Salah Abbas [a], Nicole Hardy [b], Sherief Ghozy [c,d], Mahmoud Dibas [e], Geeta Paranjape [f], Kirk W. Evanson [f], Natalie L. Reierson [b], Kathryn Cowie [b], Shelby Kamrowski [b], Scarlett Schmidt [b], Yutao Tang [b], Amber R. Davis [f], Jillienne C. Touchette [f], Kevin M. Kallmes [b], Ameer E. Hassan [g], Ranita Tarchand [b], Mansi Mehta [h], John M. Pederson [b,f], Mohamed Abdelmegeed [f,*]

[a] *Minia University (Faculty of Medicine), Minia, Egypt*
[b] *Nested Knowledge, St. Paul, MN, United States*
[c] *Mansoura University (Neurosurgery Department), Mansoura, Egypt*
[d] *El Sheikh Zayed Specialized Hospital (Neurosurgery Department), Giza, Egypt*
[e] *Sulaiman Al Rajhi University (College of Medicine), Qassim, Saudi Arabia*
[f] *Superior Medical Experts, St. Paul, MN, United States*
[g] *Valley Baptist Medical Center (Department of Neuroradiology), Harlingen, TX, United States*
[h] *Kasturba Medical College, Manipal, Manipal Academy of Higher Education, Karnataka, India*

ARTICLE INFO

Keywords:
Myasthenia Gravis
Coronavirus disease 2019
Autoimmune Disorders
Neuromuscular Disorders
Diagnostic Testing
Systematic Review

ABSTRACT

Objective: Recent studies suggest that the clinical course and outcomes of patients with coronavirus disease 2019 (COVID-19) and myasthenia gravis (MG) are highly variable. We performed a systematic review of the relevant literature with a key aim to assess the outcomes of invasive ventilation, mortality, and hospital length of stay (HLoS) for patients presenting with MG and COVID-19.

Methods: We searched the PubMed, Scopus, Web of Science, and MedRxiv databases for original articles that reported patients with MG and COVID-19. We included all clinical studies that reported MG in patients with confirmed COVID-19 cases via RT-PCR tests. We collected data on patient background characteristics, symptoms, time between MG and COVID-19 diagnosis, MG and COVID-19 treatments, HLoS, and mortality at last available follow-up. We reported summary statistics as counts and percentages or mean±SD. When necessary, inverse variance weighting was used to aggregate patient-level data and summary statistics.

Results: Nineteen studies with 152 patients (mean age 54.4 ± 12.7 years; 79/152 [52.0%] female) were included. Hypertension (62/141, 44.0%) and diabetes (30/141, 21.3%) were the most common comorbidities. The mean time between the diagnosis of MG and COVID-19 was7.0 ± 6.3 years. Diagnosis of COVID-19 was confirmed in all patients via RT-PCR tests. Fever (40/59, 67.8%) and ptosis (9/55, 16.4%) were the most frequent COVID-19 and MG symptoms, respectively. Azithromycin and ceftriaxone were the most common COVID-19 treatments, while prednisone and intravenous immunoglobulin were the most common MG treatments. Invasive ventilation treatment was required for 25/59 (42.4%) of patients. The mean HLoS was 18.2 ± 9.9 days. The mortality rate was 18/152 (11.8%).

Conclusion: This report provides an overview of the characteristics, treatment, and outcomes of MG in COVID-19 patients. Although COVID-19 may exaggerate the neurological symptoms and worsens the outcome in MG patients, we did not find enough evidence to support this notion. Further studies with larger numbers of patients with MG and COVID-19 are needed to better assess the clinical outcomes in these patients.

* Correspondence to: Superior Medical Experts, 1430 Avon Street North, St. Paul, MN 55117, USA.
E-mail address: mohamed.abdelmegeed@supedit.com (M. Abdelmegeed).

https://doi.org/10.1016/j.clineuro.2022.107140
Received 6 July 2021; Received in revised form 19 January 2022; Accepted 20 January 2022
Available online 22 January 2022

1. Introduction

Patients with myasthenia gravis (MG) are prone to infection with severe coronavirus disease 2019 (COVID-19) because of many factors, such as reduced baseline respiratory efficiency and the immunocompromised state that results from immunosuppressive treatment [1]. MG patients with respiratory muscle weakness are more vulnerable to COVID-19 complications [2,3]. Further, some drugs that are used for treating COVID-19 can cause exacerbation of MG such as azithromycin [4] and hydroxychloroquine [5].

Recent investigations have reported that many neuromuscular disorders, including MG, were associated with COVID-19 infection [3,6–9]. However, the clinical outcomes of MG in patients with COVID-19 remain uncharacterized. We performed a systematic review of the relevant literature with key aims to assess the outcomes of invasive ventilation, mortality, and hospital length of stay (HLoS) for patients presenting with MG and COVID-19.

2. Methods

2.1. Search protocol

We conducted this systematic review in accordance with the recommendations of Preferred Reporting Items for Systematic Review and Meta-Analysis checklist (PRISMA) [10,11]. We screened the literature by performing a comprehensive search through PubMed, Scopus, Web of Science, and MedRxiv databases, reporting all available results on October 29, 2021. We used the standard search string "[(COVID-19 OR SARS-CoV-19 OR "novel coronavirus") AND "Myasthenia Gravis"]," and we adjusted this string according to each database. We also performed a manual search by checking the references of the included studies, and by screening the relevant papers in PubMed and Google Scholar. The protocol of this study was not preregistered with any prospectively maintained databases of systematic review protocols (e.g., PROSPERO).

2.2. Eligibility criteria and study selection

We included all original studies that reported MG in patients with confirmed COVID-19 cases via RT-PCR tests. We included all eligible patients without regard to patient demographics (e.g., age, sex, or race). We excluded studies from before November 2019 since the possibility that these studies report clinical evidence of COVID-19 is slim. We excluded any study that has any following criteria: 1) in vitro, in vivo, in silico, and animal studies; 2) studies with duplicated datasets; 3) abstract-only articles; 4) opinion article; 5) protocols, methods articles, and technical notes; 6) reviews and meta-analysis; 7) articles that were unavailable in English; and 8) articles without patients with both MG and COVID-19 diagnosis 9) MG in patients without confirmed COVID-19 cases via RT-PCR tests. Three independent authors (S.K., S.S., and Y.T.) initially screened the retrieved studies for the eligibility of their inclusion.

2.3. Data extraction and analysis

Three authors (S.K., S.S., and Y.T.) performed data extraction and another author (J.M.P.) further checked the extracted data for accuracy. The collected data included patient-level data as well as summary data, including age, sex, comorbidities, COVID-19 presenting symptoms, MG presenting symptoms, time between MG and COVID-19 diagnosis, reverse transcription polymerase chain reaction (RT-PCR) COVID-19 testing results, computed tomography (CT) or magnetic resonance imaging (MRI) abnormalities of the body and central nervous system, positivity for AChR or MuSK receptor autoantibodies, the Myasthenia Gravis Foundation of America (MGFA) [12] class, subtype and MGFA score, and treatments for both COVID-19 and MG. Additionally, the HLoS in days, complications, and the vital status (dead or alive) at discharge or last available follow-up were collected. The number of patients with recorded data were different for the evaluated variables based on data availability for the included studies, as shown in Tables 1–3. We reported pooled summary statistics as counts and percentages or mean±SD for all variables. Due to limited data, we neither performed inferential statistics nor created prediction models. However, in cases where summary data was presented (e.g., mean±SD for patient age), we used inverse variance weighting using the 'meta' package in R (4.0.3) in order to aggregate patient-level and summary data [13].

Table 1
Patient demographics and baseline characteristics.

Variable (Number of Patients (Nnew-a))	n/N (%) or mean ± SD
Sex (N = 152)	
Female	79/152 (52.0)
Male	73/152 (48.0)
Age (N = 59)	54.4 ± 12.7
Decade of life (N = 59)	0/59 (0.0)
10 – 19	15/59 (25.4)
20 – 39	20/59 (33.9)
40 – 59	24/59 (40.7)
≥ 60	
Comorbidities (N = Variable)	
None (healthy) (N = 141)	18/141 (12.8)
Hypertension (N = 141)	62/141 (44.0)
Diabetes (N = 141)	30/141 (21.3)
Obesity (N = 48)	5/48 (10.4)
Hepatitis (N = 48)	2/48 (4.2)
Hypothyroidism (N = 48)	3/48 (6.3)
Baseline MGFA (N = 49)	
MGFA 0	2/49 (4.1%)
MGFA I	13/49 (26.5)
MGFA IIa/IIb	20/49 (40.8)
MGFA IIIa/IIIb	9/49 (18.4)
MGFA IVa/IVb	2/49 (4.1)
MGFA V	3/49 (6.1)
MGFA Unknown	103 (67.8)
Time between MG and COVID-19 presentation in years (N = 151)	7.0 ± 6.3
COVID-19 Symptoms (N = Variable)	
Fever (N = 59)	40/59 (67.8)
Cough (N = 59)	35/59 (59.3)
Dyspnea (N = 59)	29/59 (49.2)
Chills/Shivering (N = 44)	6/44 (13.6)
Myalgia (N = 59)	17/59 (28.8)
Hyposmia (N = 44)	4/44 (9.1)
Fatigue (N = 44)	4/44 (9.1)
Ageusia/anosmia (N = 44)	4/44 (9.1)
Headache (N = 44)	7/44 (15.9)
Dysgeusia (N = 44)	0/44 (0.0)
Odynophagia (N = 44)	1/44 (2.3)
MG Symptoms present during infection (N = 55)	
Diplopia	5/55 (9.1)
Ptosis	9/55 (16.4)
Dysphagia	5/55 (9.1)
Lower limb weakness	8/55 (14.6)
Upper limb weakness	7/55 (12.7)
Facial weakness/paralysis	3/55 (5.5)
No symptoms	18/55 (32.7)
History of thymectomy (N = 142)	
Not performed	88/142 (62.0)
Performed	54/142 (38.0)
MG treatments Before COVID (N = 58)	
Prednisone/Corticosteroids	37/58 (63.8)
IVIG	8/58 (13.8)
PLEX	0/58 (0.0)
Mycophenolate Mofetil	9/58 (15.5)
Pyrazolones	0/58 (0.0)

COVID-19 =coronavirus disease 2019; MG=Myasthenia gravis; MGFA =Myasthenia Gravis Foundation of America; IVIG=Intravenous immunoglobulin;; PLEX=Plasma exchange

[a] N may vary for different variables based on recorded data.

Table 2
Diagnostic testing results.

Variable (Number of Patients (Nnew-a))	n (%)
Antibody AChR (N = 140)	
Positive	110/140 (78.6)
Negative	30/140 (21.4)
Antibody MuSK (N = 119)	
Positive	5/119 (4.2)
Negative	114/119 (95.8)
Body CT/MRI abnormality (N = 36)	
Abnormal	19/36 (52.8)
Normal	17/36 (47.2)

AChR=Acetylcholine receptor; CT=Computed Tomography; MRI=Magnetic resonance imaging; MuSK=Muscle specific kinase, RT-PCR=Reverse transcriptase-polymerase chain reaction

[a] N may vary for different variables based on recorded data.

Table 3
Treatment details and patient outcomes.

Variable (Number of Patients (Nnew-a))	n/N (%)
COVID-19 treatments (N = 59)	
Hydroxychloroquine	7/59 (11.9)
Lopinavir-Ritonavir	2/59 (3.4)
Oseltamivir	4/59 (6.8)
Tocilizumab	2/59 (3.4)
Tazobactam/piperacillin	5/59 (8.5)
Azithromycin	22/59 (37.3)
Ceftriaxone	19/59 (32.2)
Meropenem	5/59 (8.5)
Heparin	5/59 (8.5)
MG treatments After COVID (N = Variable)	
Prednisone/Corticosteroids (N = 59)	37/59 (62.7)
IVIG (N = 152)	29/152 (19.1)
PLEX (N = 59)	6/59 (10.2)
Mycophenolate Mofetil (N = 152)	19/152 (12.5)
Pyrazolones (N = 152)	0/152 (0.0)
Other Non-pharmacological treatments (N = 59)	
Invasive ventilation	25/59 (42.4)
Non-invasive ventilation	17/59 (28.8)
None	17/59 (28.8)
Hospital Length of Stay, days (N = 36)	18.2 ± 9.9
Mortality (N = 152)	
Survived	134/152 (88.2)
Died	18/152 (11.8)

COVID-19 =Coronavirus disease 2019; IVIG=Intravenous immunoglobulin; MG=Myasthenia gravis, PLEX=Plasma exchange
FIGURES CAPTIONS

[a] N may vary for different variables based on recorded data.

3. Results

3.1. Search results

We identified 107 potentially relevant studies from four databases and other sources, of which 88 articles were excluded. After examining the titles and abstracts of the remaining articles, 19 studies with 152 patients with confirmed MG diagnosis and COVID-19 were included in the qualitative systematic review (Fig. 1) [3,6,8,14–33]. Of these studies, 10 were case series, 8 were case reports, and one was a cohort study, as shown in Supplementary Tables 1 and 4.

3.2. Patient demographics and baseline characteristics

Table 2 and Supplementary Tables 1 and 4 provide a summary and detailed information, respectively, of the recorded demographics and characteristics of the patients. The mean age of the patients was 54.4 ± 12.7 years, with females and males constituting 52.0% and 48.0% of the patients, respectively. There was no recorded incidence of MG and COVID-19 in the 10–19 age group. For the remaining age groups 20–39, 40–59, and ≥ 60 years, the incidence was (15/59, 25.4%), (20/59, 33.9%), and (24/59, 40.7%), respectively (Table 1). Hypertension (62/141, 44.0%) and diabetes (30/141, 21.3%) were the most common comorbidities, while (18/141, 12.8%) of the patients were healthy (Table 1).

The mean duration between MG diagnosis and COVID 19 diagnosis was 7.0 ± 6.3 years (Table 1). MGFA IIa/IIb was the most common presenting class of MG (20/49, 40.8%). Fever was the most common presenting symptom of COVID-19 (40/59, 67.8%), followed by cough (35/59, 59.3%) and dyspnea (29/59, 49.2%). For MG, ptosis was the most common presenting symptom (9/55, 16.4%), followed by lower limb weakness (8/55, 14.6%), while (18/55, 32.7%) had no symptoms of MG present during infection (Table 1). Most patients had a history of thymomectomy (88/142, 62.0%). The most common MG treatment before COVID-19 diagnosis were prednisone/corticosteroids (37/58, 63.8%) and intravenous immunoglobulin (IVIG) (8/58, 13.8%).

3.3. Diagnostic testing

Table 2 and Supplementary Tables 1, 2**, and 4** provide a summary and detailed information, respectively, of the recorded diagnostic testing results of patients. The majority of patients were positive for AChR antibody test (110/140, 78.6%), while only (5/119, 4.2%) of patients were positive for MuSK antibody test (Table 2). Lung CT or MRI showed abnormal imaging results in (19/36, 52.8%) of patients.

3.4. Treatment details, complications, and outcomes

Table 3 and Supplementary Tables 2, 3**, and 5** provide a summary and detailed information, respectively, of the available treatments' information, complications, and outcomes of patients. The most common COVID-19 pharmacological treatments were azithromycin (22/59, 37.3%) and ceftriaxone (19/59, 32.2%). The most common MG treatment after COVID-19 diagnosis were prednisone/corticosteroids (37/59, 62.7%) and IVIG (29/152, 19.1%). Invasive ventilation treatment was required for 25/59 (42.4%) of patients, while 17/59 (28.8%) of patients required noninvasive ventilation. Of the patients included in our review (18/152, 11.8%) died (Table 3).

Survival data for patients with history of thymomectomy before COVID-19 diagnosis were available for 20 patients, while it was available for 29 patients who did not have thymomectomy. We found that 5.0% of patients with history of thymomectomy died, while 17.2% of those with no history of thymomectomy died (Supplementary Table 1**)**. Survival data for patients with history of treatment with prednisone/corticosteroids alone before COVID-19 diagnosis were available for only 5 patients. Of these, 60.0% died (Supplementary Table 3**)**. Survival data for patients with history of treatment with prednisone/corticosteroids combined with other pharmacological treatments before COVID-19 diagnosis were available for 35 patients. Of these, 5.7% patient died (Supplementary Table 3**)**. Survival data for patients with history of treatment with prednisone/corticosteroids alone during COVID-19 were available for 7 patients. Of these, 85.7% required invasive ventilation and 42.9% died (Supplementary Table 3**)**. Survival data for patients with history of treatment with prednisone/corticosteroids combined with other pharmacological treatments during COVID-19 diagnosis were available for 32 patients. Of these 34.4% required invasive ventilation and 6.3% died (Supplementary Table 3**)**. The mean HLoS was 18.2 ± 9.9 days (Table 3).

4. Discussion

Our systematic review of studies reporting characteristics and outcomes of patients with confirmed MG and COVID-19 diagnosis did not reveal any specific unusual incidences or outcomes that would not occur in patients diagnosed with either MG or COVID-19. Since respiratory distress and neurological symptoms can occur in MG and COVID-19, the

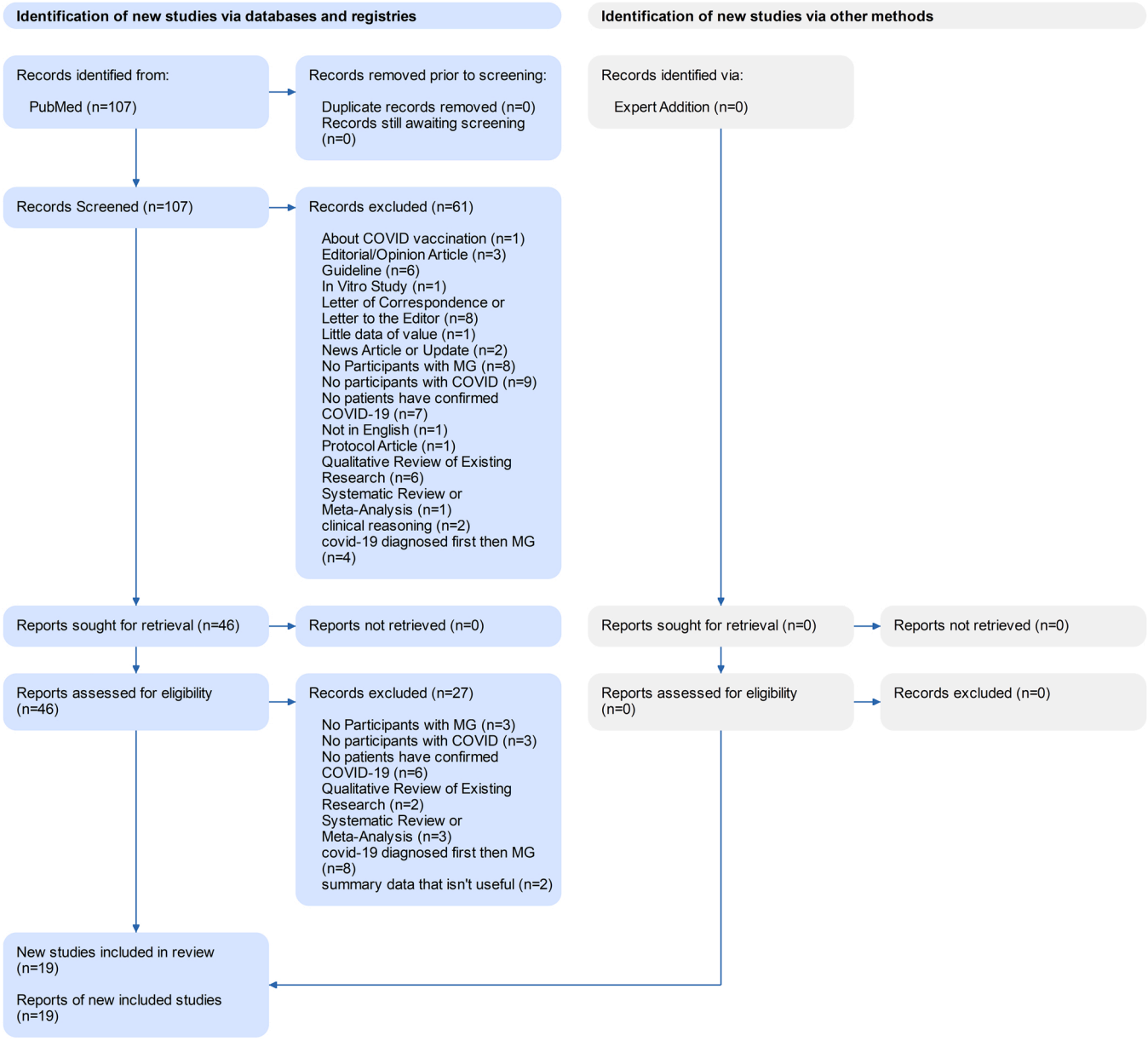

Fig. 1. PRISMA diagram of search records and included studies.

presence of COVID-19 infection in patients with MG may worsen the clinical outcomes. Although we assessed the outcomes of invasive ventilation, mortality, and HLoS for patients presenting with MG and COVID-19, our data are insufficient to establish any definitive conclusions about outcomes in these patients.

MG has higher incidence among patients over the age of 65 years, regardless of sex [34–37]. In our study, the mean age of the patients with MG and COVID-19 was 54.4 ± 12.7 years, with an age range of 20–90 years. We did not monitor a high incidence among any particular age group. The main presenting symptoms in patients with MG and COVID-19 patients in this study were like those reported in previous studies of patients with MG, with ptosis, upper and lower limb weakness, diplopia, and dysphagia being the most common [38,39]. However, respiratory muscle weakness was not reported in patients with MG and COVID-19 in this study, compared to a previous report that estimated 15% of MG patients with respiratory muscle weakness [39]. Our data revealed that fever and cough were the most common presenting symptoms similar to those reported in patients with COVID-19 [40,41].

Infection is also regarded as one of the risk factors that can cause a fulminant exacerbation of MG (myasthenic crisis) that is characterized by worsening of muscle weakness, resulting in respiratory failure that requires intubation and mechanical ventilation [42–46]. Currently there is no confirmed link between the development of MG and COVID-19 infection. Although all cases in our study have MG diagnosis prior to the diagnosis of COVID-19, other reports showed that MG can occur after COVID-19 infection [30,47,48]. Therefore, it is recommended to rule out the presence of COVID-19 in patients with myasthenic crisis/exacerbations, with new onset of generalized MG requiring hospital admission or with symptoms that may suggest COVID-19.

Since preneoplastic lesions in the thymus have been known to affect the development of MG [49–51], total thymectomy is recommended to treat generalized MG with AChR antibodies [52]. The suppression of immune response by thymectomy can minimize the loss of self-tolerance and autoimmune reactivity which consequently leads to reduction of MG symptoms. We found that the survival rate was higher in patients treated with thymectomy (95.0%) than those without the surgery (82.8%). The effect of immunosuppression, whether by immunosuppressive drugs, as discussed above, or thymectomy in patients with MG

and COVID-19 has not been established. These data underscore the complex role of immunosuppression in the regulation of MG and other autoimmune diseases. Infection frequency and severity in MG before and after total thymectomy has not been well-characterized and warrants further investigation to assess the role of the thymus gland in the treatment of patients with MG and COVID-19.

Patients with MG are susceptible to infection with COVID-19, due to the immunocompromised state resulting from immunosuppressive treatment and reduced baseline respiratory efficiency. For instance, immunosuppressive corticosteroids have been estimated to increase the risk of infection by 20–50% [53–55]. Previous long-term treatment particularly in higher dose was reported to be among the most important predictors of severe COVID-19 in MG patients [29]. However, some reports have suggested that suppression of the immune response may be protective against infection since immunosuppression can decrease the dramatic upregulation of inflammatory cytokines that can cause complications [56,57], while others suggested that the risk of COVID-19 in MG patients does not appear to be higher than that of the general population, regardless of immunosuppressive therapies [28]. We found that in our study, patients treated with prednisone/corticosteroids before the diagnosis of COVID-19 or during COVID-19 had a high rate of mortality when used alone. When prednisone/corticosteroids used with other treatments when used before the diagnosis of COVID-19 or during COVID-19, the mortality rate was lower vs prednisone/corticosteroids when used alone. This data suggests that other drugs such as intravenous immunoglobulin (IVIG) and plasma exchange (PLEX), among others when used with prednisone may have a protective effect against aggravating MG in COVID-19 patients. Indeed, a recent report showed that adjuvant treatment with IVIG before starting treatment with prednisone significantly improved a paradoxical symptom exacerbation (2.2%) in the first weeks of starting prednisone, relative to the rates reported in a historical series (42.0%) [58]. However, we still cannot conclude that prednisone/corticosteroids is the reason of the unfavorable clinical outcomes due to the low number of patients in this study. Therefore, the relationship between the immunosuppressive effects induced by prednisone and the outcomes of treated patients with MG and COVID-19 patients still need to be better characterized; better characterization of this relationship may lead to development of a better treatment strategy for patients with MG and COVID-19.

Although IVIG and PLEX are commonly used as treatments for MG, both have been considered.

potential treatments of COVID-19 since they induce favorable anti-inflammatory cytokines [59–61]. Overall, patients who received IVIG and PLEX treatment in this study had favorable outcomes. Treatment with drugs used to treat patients with COVID-19 such as such as hydroxychloroquine and azithromycin can cause myasthenic crisis [62]. However, in our patient cohort, we could not assess whether these treatments exacerbate MG.

The use of mechanical ventilation in this study (42.4%) is higher than the rate reported for.

COVID-19 patients that ranged from 2.3% [41] to 33.1% [63]. The death rate of this study (13.6%) is higher than the death rate reported for the general population with COVID-19 [64], while other studies report a higher intrahospital death rate (21–28%) for COVID-19 patients [65, 66]. This discrepancy may be related to differences in patient cohorts. For instance, the study cohorts may represent a mixture of patients with varying severity or maybe follow-up data was not collected, and only in-hospital outcomes were assessed. The mean HLoS in our study (18.2 ± 9.9 days) is higher than the death rate reported in a recent single-site, retrospective study that showed a median HLoS of 7.18 (IQR 3.86, 12.15) days among 687 COVID-19 patients in the US [67], and higher than a recent systematic review of 52 studies that showed a median HLoS of 14 (IQR 10–19) days for COVID-19 patients in China, and 5 (IQR 3–9) days outside of China [68]. Overall, this data suggest that COVID-19 may worsens the outcome in MG patients; however, the data from this study is insufficient to establish this notion.

This study has some limitations. Studies reporting patients with MG and COVID-19 are limited, resulting in a relatively small sample, and increasing the risk of bias. Since the majority of studies were either case reports or case series, we did not perform a formal risk of bias assessment; nonetheless, each study provided sufficient patient-level data to directly determine their applicability to the target patient population. Our ability to efficiently assess the impact of the association between MG and COVID-19 on the outcome in these patients was hampered by the heterogeneous reporting of patients' characteristics, methods of diagnosis, inconsistent data reporting and outcomes. Thus, our data is not conclusive with respect to the demographics or outcomes in this patient population. However, to our knowledge, our study evaluated the largest number of patients with MG and COVID-19 and shed light on the outcomes of invasive ventilation, mortality, and HLoS for patients presenting with MG and COVID-19.

5. Conclusion

This report provides an overview of the characteristics, treatment, and outcomes of MG in COVID-19 patients. Although COVID-19 may exaggerate the neurological symptoms and worsens the outcome in MG patients, we did not find enough evidence to support this notion. Further studies with larger numbers of patients with MG and COVID-19 are needed to better assess the clinical outcomes in these patients, relative to outcomes in patients with COVID-19 only.

Declarations

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest/Competing interests

N.L.R., S.K., S.S., R.T., and Y.T. work for Nested Knowledge. G.P., K. W.E., A.R.D., and J.C.T. are employed by Superior Medical Experts. M.A. is employed by and holds equity in Superior Medical Experts K.M.K. works for and holds equity in Nested Knowledge, Superior Medical Experts, and Marblehead Medical. J.M.P. is employed and holds equity in Nested Knowledge and Superior Medical Experts. N.H and K.C. work for and hold equity in Nested Knowledge. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Availability of data and material

All collected data from the systematic review are available in the supplementary information. Detailed results of our study search, screening, and data extraction process are hosted on the Nested Knowledge website (www.nested-knowledge.com).

Code availability

The R code (. R) that was used for aggregating summary statistics is available from the corresponding author.

Ethics approval

This manuscript does not require ethics approval.

Consent for publication

We confirm all authors have reviewed this manuscript and approved its submission for publication.

CRediT authorship contribution statement

Alzhraa Salah Abbas: Conceptualization, Writing – review & editing. **Nicole Hardy:** Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Sherief Ghozy:** Conceptualization, Writing – review & editing. **Mahmoud Dibas:** Conceptualization, Writing – review & editing. **Geeta Paranjape:** Writing – review & editing. **Kirk W. Evanson:** Writing – review & editing. **Natalie L. Reierson:** Writing – review & editing. **Kathryn Cowie:** Writing – review & editing. **Shelby Kamrowski:** Investigation, Writing – review & editing. **Scarlett Schmidt:** Investigation, Writing – review & editing. **Yutao Tang:** Investigation, Writing – review & editing. **Amber R. Davis:** Conceptualization, Writing – review & editing. **Jillienne C. Touchette:** Conceptualization, Writing – review & editing. **Kevin M. Kallmes:** Conceptualization, Investigation, Writing – review & editing. **Ameer E. Hassan:** Writing – review & editing. **Ranita Tarchand:** Investigation, Writing – review & editing. **Mansi Mehta:** Investigation, Writing – review & editing. **John M. Pederson:** Conceptualization, Investigation, Formal analysis, Writing – original draft, Writing – review & editing. **Mohamed Abdelmegeed:** Conceptualization, Investigation, Formal analysis, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

N.L.R., S.K., S.S., R.T., and Y.T. work for Nested Knowledge. G.P., K. W.E., A.R.D., and J.C.T. are employed by Superior Medical Experts. M.A. is employed by and holds equity in Superior Medical Experts K.M.K. works for and holds equity in Nested Knowledge, Superior Medical Experts, and Marblehead Medical. J.M.P. is employed and holds equity in Nested Knowledge and Superior Medical Experts. N.H and K.C. work for and hold equity in Nested Knowledge. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Acknowledgements

We acknowledge Karl Holub, Stephen Mead, and Darian Lehmann-Plantenberg for their design and support of the Nested Knowledge software which was used to conduct this systematic review.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.clineuro.2022.107140.

REFERENCES

[1] N.E. Gilhus, F. Romi, Y. Hong, G.O. Skeie, Myasthenia gravis and infectious disease, J. Neurol. 265 (6) (2018) 1251–1258.
[2] M.G.C.-W.G. International, S. Jacob, S. Muppidi, A. Guidon, J. Guptill, M. Hehir, J. F. Howard, I. Jr, R. Illa, H. Mantegazza, K. Murai, J. Utsugisawa, H. Vissing, R. J. Wiendl, Nowak, Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic, J. Neurol. Sci. 412 (2020), 116803.
[3] S. Singh, R. Govindarajan, COVID-19 and generalized Myasthenia Gravis exacerbation: A case report, Clin. Neurol. Neurosurg. 196 (2020), 106045.
[4] R. Cadisch, E. Streit, K. Hartmann, [Exacerbation of pseudoparalytic myasthenia gravis following azithromycin (Zithromax)], Schweiz Med Woche 126 (8) (1996) 308–310.
[5] O. Varan, H. Kucuk, A. Tufan, Myasthenia gravis due to hydroxychloroquine, Reumatismo 67 (3) (2015) 849.
[6] F. Delly, M.J. Syed, R.P. Lisak, D. Zutshi, Myasthenic crisis in COVID-19, J. Neurol. Sci. 414 (2020), 116888.
[7] L. Mao, H. Jin, M. Wang, Y. Hu, S. Chen, Q. He, J. Chang, C. Hong, Y. Zhou, D. Wang, X. Miao, Y. Li, B. Hu, Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China, JAMA Neurol. 77 (6) (2020) 683–690.
[8] S.B. Ramaswamy, R. Govindarajan, COVID-19 in Refractory Myasthenia Gravis- A Case Report of Successful Outcome, J. Neuromuscul. Dis. 7 (3) (2020) 361–364.
[9] G. Costamagna, E. Abati, N. Bresolin, G.P. Comi, S. Corti, Management of patients with neuromuscular disorders at the time of the SARS-CoV-2 pandemic, J. Neurol. 268 (5) (2021) 1580–1591.
[10] M.J. Page, J.E. McKenzie, P.M. Bossuyt, I. Boutron, T.C. Hoffmann, C.D. Mulrow, L. Shamseer, J.M. Tetzlaff, E.A. Akl, S.E. Brennan, R. Chou, J. Glanville, J. M. Grimshaw, A. Hróbjartsson, M.M. Lalu, T. Li, E.W. Loder, E. Mayo-Wilson, S. McDonald, L.A. McGuinness, L.A. Stewart, J. Thomas, A.C. Tricco, V.A. Welch, P. Whiting, D. Moher, The PRISMA 2020 statement: An updated guideline for reporting systematic reviews, PLOS Med. 18 (3) (2021), e1003583.
[11] A. Liberati, D.G. Altman, J. Tetzlaff, C. Mulrow, P.C. Gotzsche, J.P. Ioannidis, M. Clarke, P.J. Devereaux, J. Kleijnen, D. Moher, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration, BMJ 339 (2009) b2700.
[12] A. Jaretzki 3rd, R.J. Barohn, R.M. Ernstoff, H.J. Kaminski, J.C. Keesey, A.S. Penn, D.B. Sanders, Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America, Neurology 55 (1) (2000) 16–23.
[13] S. Balduzzi, G. Rücker, G. Schwarzer, How to perform a meta-analysis with R: a practical tutorial, Evid. -Based Ment. Health 22 (4) (2019) 153–160.
[14] P. Anand, M.C.C. Slama, M. Kaku, C. Ong, A.M. Cervantes-Arslanian, L. Zhou, W. S. David, A.C. Guidon, COVID-19 in patients with myasthenia gravis, Muscle Nerve 62 (2) (2020) 254–258.
[15] A. Hubers, A.M. Lascano, P.H. Lalive, Management of patients with generalised myasthenia gravis and COVID-19: four case reports, J. Neurol. Neurosurg. Psychiatry 91 (10) (2020) 1124–1125.
[16] N. Rein, N. Haham, E. Orenbuch-Harroch, M. Romain, Z. Argov, A. Vaknin-Dembinsky, M. Gotkine, Description of 3 patients with myasthenia gravis and COVID-19, J. Neurol. Sci. 417 (2020), 117053.
[17] H. Kushlaf, COVID-19 in muscle-specific kinase myasthenia gravis: A case report, Muscle Nerve 62 (4) (2020) E65–E66.
[18] E. Aksoy, T. Oztutgan, COVID-19 Presentation in Association with Myasthenia Gravis: A Case Report and Review of the Literature, Case Rep. Infect. Dis. 2020 (2020), 8845844.
[19] A.E. Camelo-Filho, A.M.S. Silva, E.P. Estephan, A.A. Zambon, R.H. Mendonca, P.V. S. Souza, W. Pinto, A.S.B. Oliveira, I. Dangoni-Filho, A.F.P. Pouza, B.C.O. Valerio, E. Zanoteli, Myasthenia Gravis and COVID-19: Clinical Characteristics and Outcomes, Front Neurol. 11 (2020) 1053.
[20] P. Moschella, P. Roth, Isolated COVID-19 Infection Precipitates Myasthenia Gravis Crisis: A Case Report, Clin. Pr. Cases Emerg. Med 4 (4) (2020) 524–526.
[21] J.V. Wanschitz, M. Kaml, B. Pfausler, R. Helbok, S. Wildner, G. Widmann, S. Sahanic, F. Deisenhammer, W.N. Loscher, M. Reindl, J. Loffler-Ragg, R. Beer, Myasthenic crisis following SARS-CoV-2 infection and delayed virus clearance in a patient treated with rituximab: clinical course and 6-month follow-up, J. Neurol. 268 (8) (2021) 2700–2702.
[22] U. Hofstadt-van Oy, S. Stankovic, C. Kelbel, D. Oswald, S. Larrosa-Lombardi, T. Barchfeld, U. Cleff, Complement inhibition initiated recovery of a severe myasthenic crisis with COVID-19, J. Neurol. 268 (9) (2021) 3125–3128.
[23] F. Octaviana, H.P. Yugo, A.Y. Safri, L.A. Indrawati, W. Wiratman, T. Ayuningtyas, M. Hakim, Case series: COVID-19 in patients with mild to moderate myasthenia gravis in a National Referral Hospital in Indonesia, eNeurologicalSci 23 (2021), 100332.
[24] S. Zupanic, M. Peric Situm, M. Majdak, M. Karakas, S. Basic, D. Sporis, Case series of COVID-19 in patients with myasthenia gravis: a single institution experience, Acta Neurol. Belg. 121 (4) (2021) 1039–1044.
[25] B.J. Peters, A.A. Rabinstein, H.M. DuBrock, Use of Remdesivir in Myasthenia gravis and COVID-19, Pharmacotherapy 41 (6) (2021) 546–550.
[26] Z. Saied, A. Rachdi, S. Thamlaoui, F. Nabli, C. Jeridi, N. Baffoun, C. Kaddour, S. Belal, S. Ben Sassi, Myasthenia gravis and COVID-19: A case series and comparison with literature, Acta Neurol. Scand. 144 (3) (2021) 334–340.
[27] R. Yevgi, N. Bilge, F. Simsek, Favipiravir Experience in Covid-19 Positive Myasthenia Gravis Patients, Eurasia J. Med 53 (2) (2021) 164–165.
[28] P. Businaro, G. Vaghi, E. Marchioni, L. Diamanti, S. Arceri, P. Bini, E. Colombo, G. Cosentino, E. Alfonsi, A. Costa, S. Ravaglia, G. Mallucci, E. Ballante, D. Franciotta, M. Gastaldi, COVID-19 in patients with myasthenia gravis: Epidemiology and disease course, Muscle Nerve 64 (2) (2021) 206–211.
[29] M. Jakubikova, M. Tyblova, A. Tesar, M. Horakova, D. Vlazna, I. Rysankova, I. Novakova, K. Doleckova, P. Dusek, J. Pitha, S. Vohanka, J. Bednarik, Predictive factors for a severe course of COVID-19 infection in myasthenia gravis patients with an overall impact on myasthenic outcome status and survival, Eur. J. Neurol. 28 (10) (2021) 3418–3425.
[30] M. Huber, S. Rogozinski, W. Puppe, C. Framme, G. Hoglinger, K. Hufendiek, F. Wegner, Postinfectious Onset of Myasthenia Gravis in a COVID-19 Patient, Front Neurol. 11 (2020), 576153.
[31] S. Muppidi, J.T. Guptill, S. Jacob, Y. Li, M.E. Farrugia, A.C. Guidon, J.O. Tavee, H. Kaminski, J.F. Howard, Jr Cutter G., H. Wiendl, M.B. Maas, I. Illa, R. Mantegazza, H. Murai, K. Utsugisawa, R.J. Nowak, C.-M.S. Group, COVID-19-associated risks and effects in myasthenia gravis (CARE-MG), Lancet Neurol. 19 (12) (2020) 970–971.
[32] D.A. Restivo, D. Centonze, A. Alesina, R. Marchese-Ragona, Myasthenia Gravis Associated With SARS-CoV-2 Infection, Ann. Intern Med 173 (12) (2020) 1027–1028.
[33] S. Sriwastava, M. Tandon, S. Kataria, M. Daimee, S. Sultan, New onset of ocular myasthenia gravis in a patient with COVID-19: a novel case report and literature review, J. Neurol. (2020).

[34] J.M. Aragones, I. Bolibar, X. Bonfill, E. Bufill, A. Mummany, F. Alonso, I. Illa, Myasthenia gravis: a higher than expected incidence in the elderly, Neurology 60 (6) (2003) 1024–1026.
[35] J.M. Aragones, P. Roura-Poch, E.M. Hernandez-Ocampo, F. Alonso, M. Pont-Lluelles, I. Xandri, I. Bolibar, I. Illa, Myasthenia gravis: a disease of the very old, J. Am. Geriatr. Soc. 62 (1) (2014) 196–197.
[36] A.S. Carr, C.R. Cardwell, P.O. McCarron, J. McConville, A systematic review of population based epidemiological studies in Myasthenia Gravis, BMC Neurol. 10 (2010) 46.
[37] A. Vincent, L. Clover, C. Buckley, J. Grimley Evans, P.M. Rothwell, U.K.M.G. Survey, Evidence of underdiagnosis of myasthenia gravis in older people, J. Neurol. Neurosurg. Psychiatry 74 (8) (2003) 1105–1108.
[38] J.P. Sieb, Myasthenia gravis: an update for the clinician, Clin. Exp. Immunol. 175 (3) (2014) 408–418.
[39] J.M. Statland, E. Ciafaloni, Myasthenia gravis: Five new things, Neurol. Clin. Pr. 3 (2) (2013) 126–133.
[40] D. Wang, B. Hu, C. Hu, F. Zhu, X. Liu, J. Zhang, B. Wang, H. Xiang, Z. Cheng, Y. Xiong, Y. Zhao, Y. Li, X. Wang, Z. Peng, Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China, JAMA 323 (11) (2020) 1061–1069.
[41] H. Yue, X. Bai, J. Wang, Q. Yu, W. Liu, J. Pu, X. Wang, J. Hu, D. Xu, X. Li, N. Kang, L. Li, W. Lu, T. Feng, L. Ding, X. Li, X. Qi, C. Gansu, Provincial Medical Treatment Expert Group of, Clinical characteristics of coronavirus disease 2019 in Gansu province, China, Ann, Palliat. Med 9 (4) (2020) 1404–1412.
[42] R.D. Melamed, H. Khiabanian, R. Rabadan, Data-driven discovery of seasonally linked diseases from an Electronic Health Records system, BMC Bioinforma. 15 (Suppl 6) (2014) S3.
[43] A. Ramos-Fransi, R. Rojas-Garcia, S. Segovia, C. Marquez-Infante, J. Pardo, J. Coll-Canti, I. Jerico, I. Illa, N.M.D.E.S.S.G. Myasthenia, Myasthenia gravis: descriptive analysis of life-threatening events in a recent nationwide registry, Eur. J. Neurol. 22 (7) (2015) 1056–1061.
[44] J.I. O'Riordan, D.H. Miller, J.P. Mottershead, N.P. Hirsch, R.S. Howard, The management and outcome of patients with myasthenia gravis treated acutely in a neurological intensive care unit, Eur. J. Neurol. 5 (2) (1998) 137–142.
[45] C.E. Thomas, S.A. Mayer, Y. Gungor, R. Swarup, E.A. Webster, I. Chang, T. H. Brannagan, M.E. Fink, L.P. Rowland, Myasthenic crisis: clinical features, mortality, complications, and risk factors for prolonged intubation, Neurology 48 (5) (1997) 1253–1260.
[46] L.C. Wendell, J.M. Levine, Myasthenic crisis, Neurohospitalist 1 (1) (2011) 16–22.
[47] L. Muhammed, A. Baheerathan, M. Cao, M.I. Leite, S. Viegas, MuSK Antibody-Associated Myasthenia Gravis With SARS-CoV-2 Infection: A Case Report, Ann. Intern Med 174 (6) (2021) 872–873.
[48] A. Assini, I. Gandoglia, V. Damato, K. Rikani, A. Evoli, M. Del Sette, Myasthenia gravis associated with anti-MuSK antibodies developed after SARS-CoV-2 infection, Eur. J. Neurol. 28 (10) (2021) 3537–3539.
[49] N.E. Gilhus, Myasthenia Gravis, N. Engl. J. Med 375 (26) (2016) 2570–2581.
[50] A. Marx, F. Pfister, B. Schalke, G. Saruhan-Direskeneli, A. Melms, P. Strobel, The different roles of the thymus in the pathogenesis of the various myasthenia gravis subtypes, Autoimmun. Rev. 12 (9) (2013) 875–884.
[51] F. Romi, L. Bo, G.O. Skeie, A. Myking, J.A. Aarli, N.E. Gilhus, Titin and ryanodine receptor epitopes are expressed in cortical thymoma along with costimulatory molecules, J. Neuroimmunol. 128 (1–2) (2002) 82–89.
[52] G.I. Wolfe, H.J. Kaminski, I.B. Aban, G. Minisman, H.C. Kuo, A. Marx, P. Strobel, C. Mazia, J. Oger, J.G. Cea, J.M. Heckmann, A. Evoli, W. Nix, E. Ciafaloni, G. Antonini, R. Witoonpanich, J.O. King, S.R. Beydoun, C.H. Chalk, A.C. Barboi, A. A. Amato, A.I. Shaibani, B. Katirji, B.R. Lecky, C. Buckley, A. Vincent, E. Dias-Tosta, H. Yoshikawa, M. Waddington-Cruz, M.T. Pulley, M.H. Rivner, A. Kostera-Pruszczyk, R.M. Pascuzzi, C.E. Jackson, G.S. Garcia Ramos, J.J. Verschuuren, J. M. Massey, J.T. Kissel, L.C. Werneck, M. Benatar, R.J. Barohn, R. Tandan, T. Mozaffar, R. Conwit, J. Odenkirchen, J.R. Sonett, A. Jaretzki, 3rd, J. Newsom-Davis, G.R. Cutter, M.S. Group, Randomized Trial of Thymectomy in Myasthenia Gravis, N. Engl. J. Med 375 (6) (2016) 511–522.
[53] W.G. Dixon, A. Kezouh, S. Bernatsky, S. Suissa, The influence of systemic glucocorticoid therapy upon the risk of non-serious infection in older patients with rheumatoid arthritis: a nested case-control study, Ann. Rheum. Dis. 70 (6) (2011) 956–960.
[54] L. Fardet, I. Petersen, I. Nazareth, Common Infections in Patients Prescribed Systemic Glucocorticoids in Primary Care: A Population-Based Cohort Study, PLoS Med 13 (5) (2016), e1002024.
[55] L. Rostaing, P. Malvezzi, Steroid-Based Therapy and Risk of Infectious Complications, PLoS Med 13 (5) (2016), e1002025.
[56] H. Li, L. Liu, D. Zhang, J. Xu, H. Dai, N. Tang, X. Su, B. Cao, SARS-CoV-2 and viral sepsis: observations and hypotheses, Lancet 395 (10235) (2020) 1517–1520.
[57] P. Mehta, D.F. McAuley, M. Brown, E. Sanchez, R.S. Tattersall, J.J. Manson, U. K. Hlh, Across Speciality Collaboration, COVID-19: consider cytokine storm syndromes and immunosuppression, Lancet 395 (10229) (2020) 1033–1034.
[58] L. Diez-Porras, C. Homedes, M.A. Alberti, V. Velez-Santamaria, C. Casasnovas, Intravenous immunoglobulins may prevent prednisone-exacerbation in myasthenia gravis, Sci. Rep. 10 (1) (2020) 13497.
[59] P. Keith, M. Day, L. Perkins, L. Moyer, K. Hewitt, A. Wells, A novel treatment approach to the novel coronavirus: an argument for the use of therapeutic plasma exchange for fulminant COVID-19, Crit. Care 24 (1) (2020) 128.
[60] X. Liu, W. Cao, T. Li, High-Dose Intravenous Immunoglobulins in the Treatment of Severe Acute Viral Pneumonia: The Known Mechanisms and Clinical Effects, Front Immunol. 11 (2020) 1660.
[61] M. Rojas, Y. Rodriguez, D.M. Monsalve, Y. Acosta-Ampudia, B. Camacho, J. E. Gallo, A. Rojas-Villarraga, C. Ramirez-Santana, J.C. Diaz-Coronado, R. Manrique, R.D. Mantilla, Y. Shoenfeld, J.M. Anaya, Convalescent plasma in Covid-19: Possible mechanisms of action, Autoimmun. Rev. 19 (7) (2020), 102554.
[62] W. Robberecht, J. Bednarik, P. Bourgeois, J. van Hees, H. Carton, Myasthenic syndrome caused by direct effect of chloroquine on neuromuscular junction, Arch. Neurol. 46 (4) (1989) 464–468.
[63] P. Goyal, J.J. Choi, L.C. Pinheiro, E.J. Schenck, R. Chen, A. Jabri, M.J. Satlin, T. R. Campion Jr., M. Nahid, J.B. Ringel, K.L. Hoffman, M.N. Alshak, H.A. Li, G. T. Wehmeyer, M. Rajan, E. Reshetnyak, N. Hupert, E.M. Horn, F.J. Martinez, R. M. Gulick, M.M. Safford, Clinical Characteristics of Covid-19 in New York City, N. Engl. J. Med 382 (24) (2020) 2372–2374.
[64] J.Y. Chen, G.R. She, S.M. Luo, W.R. Wu, T.F. Zhuang, S.W. Huan, N. Liu, Z.G. Zha, Hemiarthroplasty compared with internal fixation for treatment of nondisplaced femoral neck fractures in elderly patients: a retrospective study, Injury 51 (4) (2020) 1021–1024.
[65] S. Richardson, J.S. Hirsch, M. Narasimhan, J.M. Crawford, T. McGinn, K. W. Davidson, C.-R.C. the Northwell, D.P. Barnaby, L.B. Becker, J.D. Chelico, S. L. Cohen, J. Cookingham, K. Coppa, M.A. Diefenbach, A.J. Dominello, J. Duer-Hefele, L. Falzon, J. Gitlin, N. Hajizadeh, T.G. Harvin, D.A. Hirschwerk, E.J. Kim, Z. M. Kozel, L.M. Marrast, J.N. Mogavero, G.A. Osorio, M. Qiu, T.P. Zanos, Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area, JAMA 323 (20) (2020) 2052–2059.
[66] F. Zhou, T. Yu, R. Du, G. Fan, Y. Liu, Z. Liu, J. Xiang, Y. Wang, B. Song, X. Gu, L. Guan, Y. Wei, H. Li, X. Wu, J. Xu, S. Tu, Y. Zhang, H. Chen, B. Cao, Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study, Lancet 395 (10229) (2020) 1054–1062.
[67] T. Chiam, K. Subedi, D. Chen, E. Best, F.B. Bianco, G. Dobler, M. Papas, Hospital length of stay among COVID-19-positive patients, J. Clin. Transl. Res 7 (3) (2021) 377–385.
[68] E.M. Rees, E.S. Nightingale, Y. Jafari, N.R. Waterlow, S. Clifford, B.P. CA, C. W. Group, T. Jombart, S.R. Procter, G.M. Knight, COVID-19 length of hospital stay: a systematic review and data synthesis, BMC Med 18 (1) (2020) 270.