Predictive factors for a severe course of COVID-19 infection in myasthenia gravis patients with an overall impact on myasthenic outcome status and survival

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Abstract

Background and purpose: Myasthenia gravis (MG) patients could be a vulnerable group in the pandemic era of coronavirus 2019 (COVID-19) mainly due to respiratory muscle weakness, older age and long-term immunosuppressive treatment. We aimed to define factors predicting the severity of COVID-19 in MG patients and risk of MG exacerbation during COVID-19.

Methods: We evaluated clinical features and outcomes after COVID-19 in 93 MG patients.

Results: Thirty-five patients (38%) had severe pneumonia and we recorded 10 deaths (11%) due to COVID-19. Higher forced vital capacity (FVC) values tested before COVID-19 were shown to be protective against severe infection (95% CI 0.934–0.98) as well as good control of MG measured by the quantified myasthenia gravis score (95% CI 1.047–1.232). Long-term chronic corticosteroid treatment worsened the course of COVID-19 in MG patients (95% CI 1.784–111.43) and this impact was positively associated with dosage ($p = 0.005$). Treatment using azathioprine (95% CI 0.448–2.935), mycophenolate mofetil (95% CI 0.91–12.515) and ciclosporin (95% CI 0.029–2.212) did not influence the course of COVID-19. MG patients treated with rituximab had a high risk of death caused by COVID-19 (95% CI 3.216–383.971). Exacerbation of MG during infection was relatively rare (15%) and was not caused by remdesivir, convalescent plasma or favipiravir (95% CI 0.885–10.87).

Conclusions: As the most important predictors of severe COVID-19 in MG patients we identified unsatisfied condition of MG with lower FVC, previous long-term corticosteroid treatment especially in higher doses, older age, the presence of cancer, and recent rituximab treatment.

KEYWORDS
corticosteroids, COVID-19, immunosuppression, myasthenia gravis, rituximab

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The authors of this publication are members of the European Reference Network for Neuromuscular Diseases - Project ID No. 870177.
INTRODUCTION

Coronavirus disease 2019 (COVID-19) is caused by the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in which the host reaction can include antibody-mediated inflammation and a cytokine storm that is thought to have a major impact on the outcome [1]. Chen et al. [2] found that the risk of severe disease course increases with age and with certain types of comorbidities.

Myasthenia gravis (MG) is an autoimmune neuromuscular disease that carries the risk of respiratory muscle weakness, the treatment for which, for more than half the patients older than 60 years of age, is immunosuppressive therapy. These three main factors could play an important role in COVID-19 infection increasing the likelihood of SARS-CoV-2 complications in MG patients [3].

Among various trigger factors for MG exacerbation and crisis, infections are the most common cause [4,5]. Some drugs, which are being tested for COVID-19 treatment such as inosine pranobex [6], hydroxychloroquine and some antibiotics (azithromycin) [7,8], may also adversely affect MG patients, especially those with bulbar symptoms and/or with severe muscle weakness who are at greater risk for another destabilization of myasthenic symptoms due to such risk medication. Treatment considerations in MG with COVID-19 are even more complex. MG is treatable with corticosteroids (CS), long-term immunosuppressive drugs, intravenous immunoglobulins (IVIG) and plasmapheresis, or biologic treatment in refractory forms. CS normally used in MG are very controversial in COVID-19 cases. In the early stages, CS can prolong viremia [9], as they inhibit immune reactions by acting on migration and chemokine production, but in contrast they can be beneficial during acute respiratory distress syndrome. However, there is still scant evidence on the positive effect of CS treatment for this critical condition [10]. Immunosuppressive treatment can affect the risk of infections and some therapies are associated with an increased risk from particular types of pathogens. The use of biologic agents in generalized MG is generally limited to therapy-refractory cases [11] and long-term use of rituximab is also associated with an increased risk of severe infection [12]. Furthermore, there may be a reduction in the production of COVID-19 antibodies and the risk of a more severe disease course in patients who have developed this infection recently after administration of rituximab [13].

In contrast, IVIG therapy has the potential to be beneficial in conjunction with COVID-19 infection and acute myasthenic exacerbation [3,14,15] through its immunomodulatory effect, thereby suppressing cytokine storm syndrome [16]. However, we have to be aware of the risk of thromboembolic complications associated with IVIG treatment, which may accentuate the hypercoagulable state during COVID-19 [17].

In this second phase of severe COVID-19, some immunotherapies might have the potential to attenuate or even prevent critical illness [18]. A very promising cure also seems to be tocilizumab (interleukin 6 [IL-6] inhibitor), which is currently in clinical trials for the treatment of severe cases of COVID-19 [19] and offers the possibility of this therapy being used in myasthenic patients with a more severe course of COVID-19 in addition to IVIG therapy. This is because IL-6, which is also involved in the immunopathogenesis of MG [20] and COVID-19 and levels of IL-6 also correlated with increased mortality due to COVID-19 infection [21].

Our primary goal was to determine the important predictive factors of the severity of COVID-19 in 93 patients with MG including treatment modalities, comorbidities and degree of MG control, and identify which therapies should be modified in those patients with confirmed SARS-CoV-2 infection if possible. Secondly, we wanted to identify the impact of a severe course of COVID-19 and its therapy on MG patients and risk of MG exacerbation.

METHODS

All patients fulfilling diagnostic criteria for MG (based on positive antibodies against acetylcholine receptor [AChR] or muscle-specific tyrosine kinase [MuSK], or at least 10% decrement on repetitive stimulation studies) were followed up in two specialized centers for MG in the Czech Republic (in Prague and Brno). We informed all patients in the national myasthenia registry about our study by means of text messages. COVID-19 infection was confirmed by a positive throat/nose smear real-time polymerase chain reaction (RT-PCR) assay on SARS-CoV-2 viral RNA. Pre-infection data were obtained from the medical documentation for each patient, and patients or attending physicians were consulted by telephone about the post-infection course. The informed consent of all subjects was obtained according to the procedures of the Ethics Committee of the General University Hospital in Prague and University Hospital in Brno.

We were interested in risk factors for severe COVID-19 in patients suffering from MG. The severity of COVID-19 was classified on a seven-point scale (1 = asymptomatic COVID-19, 2 = isolated symptoms such as anosmia, headache, etc., 3 = mild infection such as fatigue, cold and cough, 4 = influenza-like infection without admission to hospital, 5 = hospitalized patients with proven COVID-19 pneumonia requiring oxygen therapy, 6 = severe COVID-19 pneumonia with artificial lung ventilation and 7 = death due to COVID-19). We defined severe COVID-19 as a value on the scale ≥5. Exacerbation of MG was measured as a deterioration of one category in the Myasthenia Gravis Foundation of America (MGFA) classification or as a deterioration on the Activity of Daily Living (ADL) scale of at least 2 points. All the statistics were processed using MATLAB R2018b statistic tools (MathWorks).

We applied the Shapiro–Wilk normality test for all parameters. With the exception of weight, height and forced vital capacity (FVC), the test values were below the level of significance (p = 0.05). Therefore, we used the median and interquartile range for the descriptive characteristics (see Table 1). An odds ratio (OR) with a 95% confidence interval (95% CI) was calculated to estimate the difference between defined subgroups for binomial variables. Values for p were calculated using Fisher’s exact test. The OR for continuous/ordinal variable was identified by univariate logistic regression
with the ordinal model of COVID-19 severity scale. We used the Benjamini–Yekutieli procedure to compensate for multiple comparisons problem (critical $p$ value > 0.005). The Wilcoxon rank-sum test was used to study the effect of immunosuppression on the severity of COVID-19. The dependence of the severity of COVID-19 on a dosage of CS was also calculated by univariate logistic regression for binary classification (severe COVID-19 vs. mild COVID-19) without respect to the exact value on the severity scale.

### RESULTS

**Descriptive characteristics**

We identified 93 MG patients with confirmed COVID-19. Some 35 patients (38%) were diagnosed with severe pneumonia and we recorded 10 deaths (11%) due to COVID-19. The majority of patients (72 subjects, 77%) were treated with acetylcholinesterase inhibitors and with CS (75 subjects, 80%). Forty-four patients (47%) had another type of immunosuppressive therapy, namely azathioprine, mycophenolate mofetil, cyclosporine or tacrolimus. Six patients were treated with biologic therapy (four with rituximab, one with the study drug anti-neonatal Fc receptor immunoglobulin and one with glatiramer acetate). Seven patients were also treated with IVIG due to worsening myasthenic symptoms during COVID-19. The results are summarized in Table 1.

Older patients had a higher chance of suffering from severe COVID-19 pneumonia (OR 1.062, 95% CI 1.037–1.088, $p$ < 0.001). Conversely, higher FVC (%) was associated with lower odds of severe pneumonia (OR 0.957, 95% CI 0.934–0.98), $p$ < 0.001. For a decrease of 1% in FVC, the odds of severe pneumonia was 4.5% higher (Figure 1).

CS medication increased the odds of contracting severe pneumonia (OR 14.098, 95% CI 1.784–111.43, $p$ = 0.002) and higher dosage of

### Table 1

Descriptive characteristics of the cohort of 93 patients suffering from myasthenia gravis and COVID-19 infection

| Parameter                                      | Median | Q1     | Q3     | Parameter                                      | n    | %    |
|------------------------------------------------|--------|--------|--------|------------------------------------------------|------|------|
| Age (years)                                    | 65.33  | 48.63  | 75.46  | Women                                          | 46   | 49   |
| Height (cm)                                    | 172    | 164    | 180    | Men                                            | 47   | 51   |
| Weight (kg)                                    | 82     | 70     | 96.5   | Anti-AChR positivity                           | 73   | 78   |
| MG duration (months)                           | 72     | 36     | 163.25 | Anti-MuSK positivity                           | 2    | 2    |
| CS dosage (mg)                                 | 5      | 5      | 10     | Thymoma                                        | 9    | 10   |
| FVC (%)                                        | 75     | 65.95  | 86.05  | Thymectomy                                     | 34   | 37   |
| MGFA scale before COVID-19 infection           | IIa    | IIa    | IIb    | Azathioprine                                   | 25   | 27   |
| MGFA scale during COVID-19 infection           | IIb    | IIa    | IIIa   | Mycophenolate mofetil                          | 11   | 12   |
| MGFA scale after COVID-19 infection            | IIa    | IIa    | IIb    | Ciclosporin                                    | 6    | 6    |
| ADL scale before COVID-19 infection            | 2      | 0      | 4      | Tacrolimus                                     | 2    | 2    |
| ADL scale during COVID-19 infection            | 3      | 1      | 6      | Change in medication due to COVID-19 infection | 12   | 13   |
| QMG score before COVID infection               | 2.75   | 9      |       | Number of patients admitted to hospital        | 34   | 37   |
| MGC scale before COVID-19 infection            | 5      | 2      | 9      | Non-myasthenic complications during COVID-19 infection | 23   | 25   |
| Duration of symptomatic COVID-19 infection     | 14     | 7      | 21     | Remdesivir therapy                             | 11   | 12   |
| Days with fever (n)                            | 2      | 0      | 5      | Acetylcholine inhibitors                       | 72   | 77   |
| Severity of COVID-19 infection scale           | 4      | 3      | 5      | Rituximab                                      | 4    | 4    |
| Severity of COVID-19 infection scale           |        |        |        | IVIG                                            | 7    | 8    |
| Exacerbation of MG                            | 14     | 15     |        |                                                                |      |      |

**Abbreviations:** AChR, acetylcholine receptor; ADL, Activity of Daily Living scale; CS, corticosteroid; FVC, forced vital capacity; IVIG, intravenous immunoglobulins; MG, myasthenia gravis; MGC, Myasthenia Gravis Composite scale; MGFA, Myasthenia Gravis Foundation of America; MuSK, muscle-specific tyrosine kinase; Q1, quarter 1; Q3, quarter 3; QMG, Quantitative Myasthenia Gravis score.
CS increased the odds of severe pneumonia (OR 1.059, 95% CI 1.014–1.107, \(p = 0.01\)), but the \(p\) value exceeded the level of significance. To clarify the dependence of the severity of COVID-19 infection on a dosage of CS, we calculated the logistic regression for two categories, namely severe COVID-19 pneumonia and a mild course of COVID-19 infection (OR 1.093, 95% CI 1.027–1.164, \(p = 0.005\)).
We tested whether any type of immunosuppressive treatment (azathioprine, mycophenolate mofetil, ciclosporin) caused more severe COVID-19. For every immunosuppressive drug, the median of the COVID-19 severity scale was 4 for treated as well for non-treated patients ($p = 0.24$). We observed similar results for individual types of immunosuppressives, namely azathioprine (OR 1.147, 95% CI 0.448–2.935, $p = 0.8$), mycophenolate mofetil (OR 3.375, 95% CI 0.91–12.515, $p = 0.1$) and ciclosporin (OR 0.255, 95% CI 0.029–2.212, $p = 0.3$).

The corresponding values in patients treated with rituximab for death caused by COVID-19 were OR 35.143, 95% CI 3.216–383.971 and $p = 0.004$.

Patients with an unsatisfied condition of MG status described using MGFA, Myasthenia Gravis Composite (MGC) and Quantitative Myasthenia Gravis (QMG) scales were at higher risk of severe pneumonia: OR MGFA status 1.936, 95% CI 1.217–3.081, $p = 0.005$; OR QMG 1.136, 95% CI 1.047–1.232, $p = 0.002$ and OR MGC 1.125, 95% CI 1.053–1.202, $p < 0.001$.

Finally, we tested the association of COVID-19 pneumonia with six different categories of comorbidities (cardiovascular diseases, arterial hypertension, diabetes mellitus type 2, cancer, bronchial asthma, and smoking). The majority of comorbidities increased the odds of severe pneumonia: (1) cardiovascular diseases: OR 3.669, 95% CI 1.117–12.057, $p = 0.04$, which exceeds the level of significance for multiple comparisons; (2) arterial hypertension: OR 5.136, 95% CI 1.99–13.257, $p < 0.001$; (3) diabetes mellitus type 2: OR 6.264, 95% CI 1.993–19.682, $p = 0.001$ and (4) cancer: OR 7.333, 95% CI 1.856–28.978, $p = 0.004$. Conversely, in asthma/COPD (OR 0.586, 95% CI 0.145–2.374, $p = 0.5$) as well as in smoking (OR 0.255, 95% CI 0.029–2.212, $p = 0.3$) we did not demonstrate any effect. The OR results are plotted in Figure 2.

The specific treatment of COVID-19 pneumonia did not pose a risk in MG (11 patients were treated using remdesivir, one with favipiravir, one with inosine pranobex and four with convalescent plasma). We did not register any adverse effects and treatment did not affect MG exacerbation (OR 3.1019, 95% CI 0.885–10.87) but $p = 0.1$ exceeded the level of significance and we also did not find significant changes in the ADL scale level during COVID-19 treatment (OR 1.709, 95% CI 0.590–4.953, $p = 0.4$). We observed a change in MGFA during infection, but MGFA status also increased due to respiratory insufficiency and general weakness.

**DISCUSSION**

Our research is, to the best of our knowledge, the largest cohort of 93 MG patients with COVID-19, and as the most important predictors of severe COVID-19 infection we identified unsatisfied condition of MG with lower FVC and previous long-term CS treatment especially in higher doses, older age, the presence of cancer, and recent rituximab treatment.

Similar smaller groups, but with only descriptive statistics of the cohort of patients with MG and COVID-19, were also reported by neurologists from the USA [22,23] and Brazil [24].

As demonstrated in our results, a significant finding was that higher FVC before COVID-19 in MG is associated with a lower risk of severe COVID-19 course (OR 0.957) and that the outcome of MG patients during COVID-19 is related to their premorbid MG status according to MGFA classification (OR 1.936), the values on the QMG scale (OR 1.136) and the MGC scale (OR 1.125). There are already many studies evaluating the long-term consequences of COVID-19, and FVC is considered to be a basic indicator of the outcome because shortness of breath is one of the persistent predominating symptoms in 43% of post-COVID-19 patients [25,26]. Since we measured FVC in MG patients by default as part of scoring their condition, we had this indicator available before infection and it clearly is an important predictive factor of the patients' outcome after COVID-19 disease.

Oral CS treatment was associated with severe pneumonia and an increase in CS dosage by 5 mg led to a 56% higher chance of severe COVID-19 pneumonia in MG patients. Patients with unsatisfactory control of MG before infection were also at a higher risk of severe pneumonia incidence. This result is related to the fact that patients with a worse MG score usually take a higher dose of CS. The reason may be faster deterioration of respiratory parameters in unstable MG patients during COVID-19 infection and faster progression of pneumonia in the field of impaired cellular immunity due to chronic CS therapy. It is known that long-term oral CS treatment clearly increases the risk of serious infections as a result of short-term lymphopenia due to suppressing T-cell activation and differentiation [27]. Equally, the use of CS seemed to protract SARS-CoV-2 viral clearance, and in MERS-CoV-infected patients (also from the group of beta coronaviruses related to SARS) the use of systemic CS was found to be one of the most significant factors that contributed to increased mortality [28].

Patients with immune-mediated inflammatory diseases in New York, USA who were treated with chronic CS were more likely to require hospitalization for COVID-19 than patients who were not receiving CS [29] as is also evidenced by our conclusions. However, these two parameters are strongly associated with each other, and from our statistical analysis we are not able to distinguish exactly what has a greater influence on the course of COVID-19 in MG patients, whether it is the severity of MG before infection or the dose of CS.

This is followed by the question of how to use CS in MG COVID-19 patients, at which disease stage, and at which dosage [21]. As reported by the World Health Organization (WHO) regarding COVID-19, steroids should not be routinely given for the treatment of viral pneumonia outside of clinical trials [30]. There is no conclusive evidence to support the use of CS in the treatment of viral respiratory infection and their use remains controversial in COVID-19. Analysis has revealed no beneficial effects and, in some cases, harmful effects [31] especially in the case of long-term oral CS treatment before COVID-19 as is also evidenced by our results. Other additional risk factors for infection during chronic treatment with CS are higher doses, longer durations of therapy and older age [32]. In our cohort, older MG patients had a slightly higher chance
of suffering from severe COVID-19 pneumonia, so age can be considered a significant risk factor for the severity of COVID-19 in myasthenic patients. Based on our observations, we suggest not increasing CS during COVID-19, even in the case of exacerbation of MG, and rather choosing the route of IVIG therapy.

None of the immunosuppressants we used (azathioprine, mycophenolate mofetil, ciclosporin) had a statistically significant effect on the course of COVID-19 in our MG patients, which means we did not prove that these immunosuppressants increased the likelihood of COVID-19 complications, affected the course of COVID-19 in our MG patients or worsened their outcome. Camelo-Filho et al. [24] support this hypothesis since in their observed group of 15 MG patients with COVID-19 infection, the previous use of immunosuppressive therapy did not seem to result in an unfavorable outcome. Previous smaller cohorts of MG and COVID-19 have also shown a favorable outcome in patients receiving low-dose prednisone combination immunosuppressive therapy [23,33]. In our study group, a total of 47% of 93 MG patients used immunosuppressive therapy, only a low number of MG patients exacerbated their underlying disease during COVID-19 infection (15%), as this treatment affects the long-term stabilization of their myasthenic state, and at the same time, as shown by various studies [34], it probably plays a certain protective role in COVID-19 infection, because it reduces the immune response that leads to inflammatory cytokine storm and clinical deterioration. Some drugs recently used to treat MG (e.g., tocilizumab) are being investigated as a possible anti-inflammatory treatment for cytokine storm caused by COVID-19 [19].

Based on our observations, we do not recommend reducing or even discontinuing these immunosuppressants in MG patients with COVID-19 infection.

A completely different situation occurred in our MG patients who became infected while on biologic therapy. COVID-19 and concomitant biologic therapy with rituximab in patients with MG resulted in a more severe course of COVID-19 infection with a high risk of death (OR 35.143, 95% CI 3.216–383.971). In the cohort, four patients were treated with rituximab before COVID-19 infection. One of them survived, but his course of COVID-19 was calculated to be grade 5 on our scale with the need for hospitalization and oxygen therapy for more than 48 hours. One of them survived, but his course of COVID-19 was calculated to be grade 5 on our scale with the need for hospitalization and oxygen therapy for more than 48 hours. Nevertheless, pausing rituximab therapy carries a risk of destabilizing MG control and might increase the requirement for CS, which could conversely worsen outcomes in MG patients with COVID-19. In multiple sclerosis patients, outcomes of COVID-19 during B-cell-depleting therapy range from mild disease to death, but rates of critical illness and death do not seem to be increased dramatically relative to the wider population [18]. Based on our results we recommend caution in myasthenic patients shortly after rituximab treatment. But due to the limited number of our patients on this therapy, the effect of rituximab on severity of COVID-19 infection needs to be assessed in a larger patient cohort.

Of all the comorbidities observed in myasthenic patients – pulmonary, cardiovascular, metabolic and oncologic – the course of COVID-19 is most adversely affected by cancer (OR 7.333). Similar findings have also been published in non-myasthenic patients [36]. Surprisingly, in our MG patients we did not prove that asthma/COPD or smoking affected their course of COVID-19 (95% CI 0.145–2.374 and 95% CI 0.029–2.212, respectively).

Only 14 patients (15%) from all the MG patients with COVID-19 had an exacerbation of MG during COVID-19 infection; three of these aggravated myasthenic patients died and all three were receiving biologic therapy with rituximab. We explain this mainly by the fact that these patients may experience a reduction in the production of antibodies to COVID-19 and the risk of a more serious course of this infection precisely because they become infected immediately or a few weeks after receiving rituximab. Statistically, the course of infection in MG worsened patients was not different from patients who did not worsen in MGFA or ADL (OR 1.821, 95% CI 0.578–5.721, p = 0.373). Of all the deceased patients, 30% were also worsened in their underlying disease; and of all the MG COVID-19 patients, 11% died as a result of COVID-19 infection. Different results were reported by the CARE-MG group [22], where worsening of myasthenic symptoms with the need for rescue therapy with IVIG or plasma exchange was documented in 40% of MG patients, unlike in our cohort where this figure was only 15%. In our seven MG patients whose condition worsened, we used IVIG treatment as the first option rescue therapy also due to this treatment being recommended for its positive impact on concomitant COVID-19 infection [3,14,15]. There is some evidence to suggest that IVIG might increase the risk of thrombosis including multifocal stroke in COVID-19 [17], so it is good to have these patients covered by anticoagulant therapy. Specific treatment of COVID-19 with remdesivir, favipiravir and convalescent plasma was not associated with MG exacerbation (95% CI 0.885–10.87). We documented persisting myasthenic worsening even after recovery from COVID-19 infection in six patients only.

In conclusion, based on our observations, long-term use of CS before COVID-19 infection in myasthenic patients predicts a worse course of COVID-19 infection that in all likelihood is also due to the instability of MG, which requires higher doses of CS. Conversely, immunosuppressive treatment in stable MG patients does not affect the course of COVID-19 infection and could lower the risk of exacerbation of MG during COVID-19. Therefore, based on our results, we do not recommend discontinuing chronically used treatment for cytokine storm caused by COVID-19 [19].

For patients with immunodeficiency secondary to rituximab who develop severe COVID-19. Nevertheless, pausing rituximab therapy carries a risk of destabilizing MG control and might increase the requirement for CS, which could conversely worsen outcomes in MG patients with COVID-19. In multiple sclerosis patients, outcomes of COVID-19 during B-cell-depleting therapy range from mild disease to death, but rates of critical illness and death do not seem to be increased dramatically relative to the wider population [18]. Based on our results we recommend caution in myasthenic patients shortly after rituximab treatment. But due to the limited number of our patients on this therapy, the effect of rituximab on severity of COVID-19 infection needs to be assessed in a larger patient cohort.

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immunosuppressants or reducing their doses rapidly. CD20 antibody treatment during the COVID-19 pandemic in MG patients is very risky and we recommend initiating it only in severe refractory forms of MG in suitable patients with no comorbidities, those of younger age, and in smaller doses than usual. IVIG and possibly tocilizumab appear to be the optimal treatment for exacerbations of MG during COVID-19 infection.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

AUTHOR CONTRIBUTIONS

Michala Jakubíková: Conceptualization (lead); Data curation (equal); Investigation (equal); Methodology (equal); Project administration (lead); Writing-original draft (lead); Writing-review & editing (lead). Michaela Týblová: Conceptualization (equal); Data curation (equal); Funding acquisition (lead); Investigation (equal); Methodology (equal); Project administration (equal). Adam Tesař: Formal analysis (lead); Methodology (equal); Software (lead); Validation (lead); Visualization (equal). Magda Horáková: Data curation (supporting); Funding acquisition (supporting); Investigation (supporting); Project administration (supporting). Daniela Vlažná: Data curation (supporting); Investigation (supporting). Irena Ryšánková: Data curation (supporting); Investigation (supporting). Iveta Nováková: Data curation (supporting); Investigation (supporting). Kristýna Dolečková: Data curation (supporting); Investigation (supporting). Pavel Dušek: Formal analysis (supporting); Software (supporting). Jiří Pitha: Supervision (equal). Stanislav Voháňka: Funding acquisition (equal); Supervision (equal). Josef Bednář: Resources (equal); Supervision (equal).

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Iwasaki A, Yang Y. The potential danger of suboptimal antibody responses in COVID-19. Nat Rev Immunol. 2020;20(6):339-341.
2. Chen T, Dai Z, Mo P, et al. Clinical characteristics and outcomes of older patients with coronavirus disease 2019 (COVID-19) in Wuhan, China: a single-centered, retrospective study. J Gerontol A Biol Sci Med Sci. 2020;75(9):1788-1795.
3. Guidon AC, Amato AA. COVID-19 and neuromuscular disorders. Neurology. 2020;94(22):959-969.
4. Gummi RR, Kukulkia NA, Deroche CB, Govindarajan R. Factors associated with acute exacerbation of myasthenia gravis. Muscle Nerve. 2019;60(6):693-699.
5. Gilhus NE, Romi F, Hong Y, Skeie GO. Myasthenia gravis and infectious disease. J Neurol. 2018;265:1251-1258.
6. Beran J, Špajdel M, Katzerová V, et al. Inosine pranobex significantly decreased the case-fatality rate among PCR positive elderly with SARS-CoV-2 at three nursing homes in the Czech Republic. Pathogens. 2020;9(12):1055.
7. Cadisch R, Streit E, Hartmann K. Exacerbation of pseudoparalytic myasthenia gravis following azithromycin (Zithromax). Schweiz Med Wochenschr. 1996;126:308-310 (in German).
8. Jalouli M, Saadoun D, Eymard B, et al. The association of systemic lupus erythematosus and myasthenia gravis: a series of 17 cases, with a special focus on hydroxychloroquine use and a review of the literature. J Neurol. 2012;259(7):1290-1297.
9. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020;395(10223):497-506.
10. Lewis SR, Pritchard MW, Thomas CM, Smith AF. Pharmacological agents for adults with respiratory distress syndrome. Cochrane Database Syst Rev. 2019;23:7.
11. Brauner S, Eriksson-Dufva A, Hietala AM, et al. Comparison between rituximab treatment for new-onset generalized myasthenia gravis and refractory generalized myasthenia gravis. JAMA Neurol. 2020;77(8):974-981.
12. Safavi F, Nourbakhsh B, Azimi AR. B-cell depleting therapies may affect susceptibility to acute respiratory illness among patients with multiple sclerosis during the early COVID-19 epidemic in Iran. Mult Scler Relat Disord. 2020;43:102195.
13. Yasuda H, Tsukune Y, Watanabe N, et al. Persistent COVID-19 pneumonia and failure to develop anti-SARS-CoV-2 antibodies during rituximab maintenance therapy for follicular lymphoma. Clin Lymphoma Myeloma Leuk. 2020;20(11):774-776.
14. International MG/COVID-19 Working Group, Jacob S, Muppidi S, et al. Guidance for the management of myasthenia gravis (MG) and Lambert-Eaton myasthenic syndrome (LEMS) during the COVID-19 pandemic. J Neurol Sci. 2020;25:116803.
15. Herth FJF, Sakoulas G, Haddad F. Use of intravenous immunoglobulin (prevagin or octagam) for the treatment of COVID-19: retrospective case series. Respiration. 2020;99:1145-1153.
16. Buszko M, Park JH, Verthelyi D, Sen R, Young HA, Rosenberg AS. The dynamic changes in cytokine responses in COVID-19: a snapshot of the current state of knowledge. Nat Immunol. 2020;21(10):1146-1151.
17. van Dam LF, Kroft LJ, van der Wal LI, et al. Clinical and computed tomography characteristics of COVID-19 associated acute pulmonary embolism: a different phenotype of thrombotic disease? Thromb Res. 2020;193:86-89.
18. Amor S, Baker D, Khoury SJ, Schmieri K, Giovanoni G. SARS-CoV-2 and multiple sclerosis: not all immune depleting DMTs are equal or bad. Ann Neurol. 2020;87(6):794-797.
19. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A. 2020;117(20):10970-10975.
20. Cohen-Kaminski S, Delattre RM, Devengre O, et al. High IL-6 gene expression and production by cultured human thymic epithelial cells from patients with myasthenia gravis. Ann NY Acad Sci. 1993;681:97-99.
21. Perricone C, Triggiani P, Bartoloni E, et al. The anti-viral facet of anti-rheumatic drugs: lessons from COVID-19. J Autoimmun. 2020;111:102468.
22. Muppidi S, Guptill JT, Jacob S, et al. COVID-19-associated risks and effects in myasthenia gravis (CARE-MG). Lancet Neurol. 2020;19(12):970-971.
23. Anand P, Slama MCC, Kaku M, et al. COVID-19 in patients with myasthenia gravis. Muscle Nerve. 2020;62:254-258.
24. Camelo-Filho AE, Silva AMS, Estephan EP, et al. Myasthenia gravis and COVID-19: clinical characteristics and outcomes. Front Neurol. 2020;11:1053.
25. Carfì A, Bernabei R, Landi F. Gemelli against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA*. 2020;324(6):603-605.
26. Arnold DT, Hamilton FW, Miline A, et al. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. *Thorax*. 2020;76(4):399-401.
27. Korsukewitz C, Reddel WS, Bar-Or A, Wiendl H. Neurological immunotherapy in the era of COVID-19 — looking for consensus in the literature. *Nat Rev Neurol*. 2020;16(9):493–505.
28. Alfaraj SH, Al-Tawfiq JA, Assiri AY, Alzahrani NA, Alanazi AA, Memish ZA. Clinical predictors of mortality of Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection: a cohort study. *Travel Med Infect Dis*. 2019;29:48-50.
29. Haberman R, Axelrad J, Chen A, et al. Covid-19 in immune-mediated inflammatory diseases - case series from New York. *N Engl J Med*. 2020;383(1):85-88.
30. World Health Organization. (2020). Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected: interim guidance. World Health Organization.
31. Russell CD, Millar JE, Baille JC. Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *Lancet*. 2020;395:473-475.
32. Youssef J, Novosad SA, Winthrop KL. Infection risk and safety of corticosteroid use. *Rheum Dis Clin North Am*. 2016;42:157-176.
33. Ramaswamy SB, Govindarajan R. COVID-19 in refractory myasthenia gravis - a case report of successful outcome. *J Neuromuscul Dis*. 2020;7:361-364.
34. Li H, Liu L, Zhang D, et al. SARS-CoV-2 and viral sepsis: observations and hypotheses. *Lancet*. 2020;395(10235):1517-1520.
35. von Oertzen TJ, Macerollo A, Leone MA, et al. EAN consensus statement for management of patients with neurological diseases during the COVID-19 pandemic. *Eur J Neurol*. 2021:28(1):7-14.
36. Guan WJ, Liang WH, Zhao Y, et al. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. *Eur Respir J*. 2020;55(5):2000547.

How to cite this article: Jakubíková M, Týblová M, Tesař A, et al. 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*. 2021:00:1–8. [https://doi.org/10.1111/ene.14951](https://doi.org/10.1111/ene.14951)