Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Clinical Outcomes in Covid-19 Patients with Pre-Existing Myasthenia Gravis - a Systematic Analysis of Reported Cases

Ahmad Daif
University of Illinois at Chicago
Tejal Gapchup
University of Illinois at Chicago
Pritikanta Paul (pritikanta.paul@gmail.com)
University of Illinois at Chicago

Research Article

Keywords: Covid-19, Myasthenia gravis, outcome

Posted Date: March 31st, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2635861/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

INTRODUCTION: Myasthenia gravis (MG) presents an additional challenge in managing COVID-19 as outcomes potentially depend on prior disease control and treatment. Yet the role of pre-existing MG in COVID-19 outcomes has not been established.

METHODS: We searched PubMed, Scopus, and Web of Science databases for reports of MG patients with confirmed COVID-19 until March 2022. We analyzed data on patient demographics, chronicity, and MG control at baseline pre-COVID, treatment history and outcome following COVID infection.

RESULTS: Twenty-nine publications with 119 patients (females n=75, age range 20-93 years, AChR Ab positive n= 65, MuSK Ab positive n= 5, seronegative n=14, unknown n=35) were included. Eighty-three (70%) were hospitalized, more than half with MG exacerbation. There was no significant difference in disease duration or control of MG symptoms at baseline between hospitalized and non-hospitalized. Hospitalization was associated with higher dose of daily prednisone but a comparable proportion of patients were on steroid-sparing agents. Among hospitalized patients, 40% were intubated uncorrelated with MG baseline control. Unfavorable outcome was not always associated with MG exacerbation. Amongst those discharged,75% received intravenous immunoglobulin (IVIG) or Plasmapheresis (PLEX) for MG exacerbation as compared to 67% with a fatal outcome didn't receive either.

CONCLUSION: Preexisting MG does not appear to be associated with severe COVID-19 outcomes. Higher dose of prednisone prior to COVID-19 infection is associated with increased risk of hospitalization but MG control at baseline did not determine worse outcome. IVIG/PLEX appears safe and potentially can reduce fatality in patients with COVID-19 experiencing MG exacerbation.

Introduction

Myasthenia gravis (MG), an autoimmune disease affecting the neuromuscular junction, commonly requires immunosuppressive treatment putting patients at a potentially increased risk for infections[1]. Patients with MG are susceptible to respiratory infections such as COVID-19 due to their neuromuscular weakness[2]. These patients can develop respiratory insufficiency, therefore may have a perilous clinical course from COVID-19 pneumonia. Furthermore, COVID-19 can itself precipitate MG exacerbation since infections are known to be common triggers[3]. Antibiotics used to treat secondary pneumonia and possibly medications such as Hydroxychloroquine, used early in the pandemic, can potentially worsen MG[4]. Given the uncertainties surrounding COVID-19, especially at the beginning of pandemic and the persistent emergence of new variants and treatment protocols, treating COVID-19 patients with known MG has remained an ongoing challenge[5]. The fluctuating course of MG and the wide variations seen between MG patients further complicated this challenge.

Over the course of the pandemic, several case reports of COVID-19 in patients with known MG have been described. These have suggested highly variable clinical courses with some attributing pre-existing

myasthenia to worsen COVID-19 whereas others speculating that COVID-19 itself was responsible for the eventual outcome. Yet systematic evidence on the factors such as the role of steroids taken for MG control, which could alter COVID-19 outcomes in this population, remains scarce. This study thus attempts to aggregate information presented across all such published cases in order to investigate predictors of outcomes in MG patients with concomitant COVID-19 infection.

We performed a systematic review of the relevant literature with key aims to assess two specific outcomes of COVID-19 in patients with pre-existing MG. First outcome is hospitalization, for which we compared clinical characteristics of patients who were hospitalized with those who did not require hospitalization. Second, among hospitalized patients we identified factors associated with severe outcomes of requiring subsequent invasive ventilation and/or mortality.

Methods

Following the recommendations of Preferred Reporting Items for Systematic Review and

Meta-Analysis checklist (PRISMA)[6] for conducting systematic reviews we searched PubMed, Scopus, and Web of Science databases for reports of MG patients with confirmed COVID-19 infection until March 2022 with keywords “COVID-19” and “myasthenia gravis”. For our analysis, we excluded registries or studies with little details of individual patients which were insufficient to answer our research question. Additionally, exclusion of those studies helped us to ensure we are not including duplicate cases. We systematically collated a dataset including patient demographics, chronicity, and MG control at baseline pre-COVID, treatment history and outcome following COVID infection.

We used two widely accepted MG outcome measures, Myasthenia Gravis Foundation of America (MGFA) class and or Myasthenia Gravis Activities of Daily Living (MGADL) scores to define MG control[7]. We defined MG controlled at baseline or milder disease for MGFA classes I, IIA and IIB or MGADL score of < 6[8,9]. Further, to determine favorable vs unfavorable outcome amongst hospitalized patients, we defined favorable outcome as patients who were discharged to home or facility. Death and continued hospitalized with intubation were considered unfavorable outcomes,. When information was inadequate or unavailable for certain parameters for individual cases, those were excluded from the denominator for analysis.

Statistical analyses were performed with the following details. For continuous variables of normal distribution, the reported statistic is mean ± standard deviation, while the median is reported for variables with skewed distributions. For categorical variables frequencies and percentages are reported. Continuous variables were compared by Student's t-test and categorical variables were compared by two sample Z-test of proportions. A p-value < 0.05 was considered statistically significant.

Results

We found a total 124 articles based on keyword search and after reviewing all abstracts, following the criteria described in ‘methods;, 37 were reviewed in detail (Fig. 1). Eight of these were further excluded because they were aggregated analysis of registries or studies with little details of individual patients. Finally, we were able to include 23 publications with case reports or case series, and 6 studies (observational or cross-sectional) describing 62 patients cumulatively with individual details. The final dataset comprised of 119 patients (Fig. 1) whom we analyzed assessing their outcome and potential predictors for Covid-19 outcomes.

Out of 119 patients, the majority (N = 83 (70%) was hospitalized (median age of 56 years, 54% females) (Table 1). Non-hospitalized patients were more commonly females (83%, $p < 0.05$) and younger (median age 43.5 years, $p < 0.05$) and more frequently noted to have a history of thymectomy (94%. $p < 0.05$). Patients who were hospitalized more likely had comorbidities (72%, $p < 0.05$). Although a comparable proportion of patients were on steroid-sparing agents for both groups, hospitalization was associated with a higher dose(prednisone > 20mg/day or equivalent) of daily oral steroids (53% vs 21%, $p < 0.05$). Unlike age, disease duration of myasthenia was not different between hospitalized and non-hospitalized patients (Fig. 2).

Table 1
Comparison between hospitalized and non-hospitalized patients

Demographic and clinical characteristics	**Non hospitalized N = 36**	**Hospitalized N = 83**	***p* value**
Female	30/36 (83)	45/83(54)	**0.003**
Mean Age (Range) (yrs)	48.1 (21–86) (Median 43.5) (N = 36)	56.4 (25–93) (Median 56) (N = 68)	**0.013**
Mean Duration of MG (Range) (yrs)	8.7 (0.75-35) (Median 6) (N = 24)	6.7 (0.25-25) Median (4.2) (N = 64)	Mean Duration of MG (Range) (yrs)
AChR Ab positive	17/23 (74)	48/61 (79)	0.638
MuSK Ab positive	0/23 (0)	5/61(8)	0.156
Double seronegative	6/23 (26)	8/61 (13)	0.156
History of thymoma	9/16 (56)	6/24 (25)	**0.045**
History of thymectomy	15/16 (94)	25/61 (41)	**0.001**
Comorbidities	11/36 (31)	48/67 (72)	**< 0.001**
On oral steroids at baseline	21/36 (58)	59/83 (71)	0.174
On high dose prednisone or equivalent (> 20mg/day)	5/24 (21)	32/60 (53)	**0.007**
On steroid sparing agent	18/36 (50)	47/83(57)	0.503
MG controlled at baseline	28/35 (80)	60/69 (87)	0.352
Evidence of MG exacerbation	1/36 (3)	45/80 (56)	**< 0.001**
Received antibiotic or antiviral	18/36 (50)	64/81 (79)	**0.0015**
Received HCQ for covid?	0/37 (0)	12/82 (15)	**0.014**
Received tocilizumab for covid?	0/37 (0)	5/82 (6)	0.126

Ab: antibody, AChR: Acetylcholine receptor, HCQ: Hydroxychloroquine, IVIG: Intravenous immunoglobulin, MuSK: Muscle specific kinase, PLEX: Plasma exchange

Demographic and clinical characteristics	Non hospitalized N = 36	Hospitalized N = 83	*p* value
Intubation	0/37 (0)	38/83 (46)	**< 0.001**

Ab: antibody, AChR: Acetylcholine receptor, HCQ: Hydroxychloroquine, IVIG: Intravenous immunoglobulin, MuSK: Muscle specific kinase, PLEX: Plasma exchange

Among hospitalized patients, males (86%) and elderly (median age 68yrs, $p < 0.05$) were more likely to have unfavorable outcome and prior disease duration was unrelated (Table 2, Fig. 3). Usage of antibiotics or antivirals was not significantly different amongst hospitalized patients with favorable or unfavorable outcome. Interestingly, 18/30 (60%) patients who received azithromycin; and 4/5 (80%) patients who received fluoroquinolones showed evidence of MG exacerbation. However, only 4/12 patients who took HCQ reported MG exacerbation.

Table 2
Comparison between favorable and non-favorable outcome among hospitalized patients

Demographics and clinical characteristics	Favorable outcome N = 49	Non favorable outcome N = 17	*p* value
Female	20/36 (56)	1/7 (14)	0.046
Mean Age (Range) (yrs)	52.4 (25–90) (Median = 54) N = 40	68.5 (34–93) (Median = 68) N = 16	**0.007**
Duration of MG (Range) (yrs) (mean duration?)	6.9 (0.16-22) (Median = 4.5) N = 44	6.8 (1.2–15) (Median = 6) N = 12	0.493
AChR Ab positive	31/41 (76)	11/12 (92)	0.226
MuSK Ab positive	3/41 (7)	1/12 (8)	0.904
Double seronegative	7/41 (17)	0/12 (0)	0.124
History of thymoma	3/15 (20)	1/4 (25)	0.825
History of thymectomy	16/38 (42)	2/9 (22)	0.271
Comorbidities	22/34 (65)	13/16 (81)	0.234
On oral steroids at baseline	33/48 (69)	13/17 (77)	0.548
On high dose prednisone or equivalent (> 20mg/day)	21/37 (57)	9/17 (53)	0.795
On steroid sparing agent	25/48 (52)	9/17 (53)	0.952
MG controlled as baseline	36/41 (88)	11/14 (79)	0.395
Evidence of MG exacerbation	28/45 (62)	10/13 (77)	0.327
Received antibiotic or antiviral	34/48 (71)	15/16 (94)	0.061
Received tocilizumab/HCQ	9/48 (19)	2/16 (13)	0.569
Extra steroids administered during hospitalization	25/40 (63)	6/14 (43)	0.201

Ab: antibody, AChR: Acetylcholine receptor, HCQ: Hydroxychloroquine, IVIG: Intravenous immunoglobulin, MuSK: Muscle specific kinase, PLEX: Plasma exchange

Demographics and clinical characteristics	Favorable outcome N = 49	Non favorable outcome N = 17	*p* value
Received IVIG or PLEX For MG exacerbation	21/28 (75)	4/10 (40)	**0.045**
Intubation	19/48 (40)	15/17 (88)	**0.001**

Ab: antibody, AChR: Acetylcholine receptor, HCQ: Hydroxychloroquine, IVIG: Intravenous immunoglobulin, MuSK: Muscle specific kinase, PLEX: Plasma exchange

Forty six percent of hospitalized patients required intubation, but this was not associated with MG baseline control (68% vs 76%, $p > 0.05$). More than half (56%) of the hospitalized patients showed evidence of MG exacerbation. Unfavorable outcome was not always associated with MG exacerbation (62% vs 77%, $p < 0.05$). Amongst 38 hospitalized patients with MG exacerbation whose outcomes could be determined, 28 had a favorable outcome with 21 (75%) of them having received either IVIG or PLEX. On the contrary, only 4 out of 10 with unfavorable outcome received either therapy (40%). Among the remaining 6 with unfavorable outcome who received neither, death was confirmed for 4 patients.

Discussion

MG patients who contract COVID-19 are expectedly at increased risk of hospitalization and likely to have longer duration of hospital stay, which recent studies analyzing data from registries have confirmed [10][11][12]. However, determinants for risk of hospitalization and poor outcome in hospitalized MG patients were not well-established. The limited studies on MG patients with COVID-19 have documented diverse clinical course with only few potential predictors of outcome[13][14]. To address this gap, we compared between hospitalized and non-hospitalized patients and further compared between hospitalized patients with or without favorable outcomes. There was no significant difference in MG disease duration (Fig. 2(b)) and antibody positivity status between hospitalized and non-hospitalized groups. We found male and elder myasthenics are more likely to be hospitalized and more likely to have poor outcome when hospitalized. Studies worldwide similarly have shown elderly[15] and men are likely to have worse COVID-19 outcome[16][17][18] including patients with neuromuscular disorders[19]. On the contrary, myasthenia tends to have a more severe course in females[20]. Thus, COVID-19 appears to be the dominant factor in shaping outcomes in patients with concomitant MG and Covid infection. Unsurprisingly, comorbidities found previously to be significant risk factors for severe Covid-19 infection[21][22] were more common amongst hospitalized MG patients in our dataset. Additionally, MG control at baseline was unrelated to hospitalized patients being intubated. Unfavorable outcome in hospitalized patients was not always associated with MG exacerbation. Our analysis thus suggest pre-existing MG did not appear to be major factor in worsening outcome from Covid-19 infection.

We found high dose of oral steroids to be associated with increased risk for hospitalization. Baseline long-term corticosteroid treatment especially in high dose has been noted to predict severe course of COVID-19 in a study on MG patients[23]. This highlights why reducing or discontinuing steroids without losing MG control should be the therapeutic goal when managing MG. Interestingly high dose of prednisone at baseline didn't predict poor outcome amongst hospitalized patients in our analysis. Furthermore, administration of extra steroids during hospitalization did not also seem to affect the outcome (Table 2). The lack of such association could possibly be explained by potential beneficial role of steroids in severe COVID-19 infection[24] but not in mild Covid[25]. Majority of non-hospitalized patients had h/o thymectomy and 85% patients with thymectomy in our cohort had MG controlled. While a protective role of thymus gland has been suggested in viral infection like COVID-19[26], thymectomy is known to render improved clinical outcome in MG[27] and perhaps accounted for a lesser risk for a severe clinical course. No significant association of poor outcome was noted with non-steroid sparing agent, as observed in COVID-19 and other autoimmune conditions[28].

Both IVIG and PLEX are effective treatments for myasthenic crisis. Beneficial role of therapeutic plasma exchange[29] and IVIG[30] also has been observed in severe Covid-19 infection, although debate continues with concern for increased thromboembolic events particularly in relation to IVIG[3132]. Further, administration of IVIG historically has been speculated to put patients at increased risk of infection or adverse outcome in severe infection but evidence is sparse[33]. In the cases we reviewed, most hospitalized patients with COVID-19 appeared to have benefitted from IVIG/PLEX for MG exacerbation. These regimens appear safe and potentially reduce fatality in COVID-19 patients who experience MG exacerbation.

One of the major limitations of the study is reporting bias since our review is primarily based on published case reports and case series. Additionally, marked heterogeneity of study population due to variation in geographical origin, practiced standard of care as well as often limited information due to non-uniform reporting could not be adjusted for. Nevertheless, several of our study findings including more favorable Covid-19 outcomes in females and increased risk for hospitalization due to comorbidities, lend face validity to our dataset. Additional studies may utilize data from MG cohorts from individual institutions or databases. None of the studies we reviewed reported whether patients were vaccinated. Given these studies were published prior to March 2022, it is highly plausible that most cases occurred before vaccines for COVID-19 were widely available around the world. While it is true that vaccines could alter the course of COVID-19 in MG patients and having that information would be helpful. Yet studies like ours provide clinical implications of managing MG should any future pathogens result in epidemics for whom vaccines may not become immediately available.

Conclusion

Pre-existing myasthenia gravis is potentially a risk factor for worse outcomes in COVID-19. Yet, given MG itself is a disease with a highly variable course, it is important to establish the specific factors among MG

patients that could alter COVID-19 outcomes. We aggregated data combining a large number of published cases of MG patients diagnosed with COVID-19 and found that pre-existing MG itself does not predict a worse COVID-19 outcome. Rather the factors typically associated with worse COVID-19 outcomes irrespective of MG diagnosis, also led to poorer outcomes in MG patients who contracted COVID-19.

Declarations

Ethics approval and consent to participate - Not Applicable

Consent for publication - Not Applicable

Availability of Data and Materials

The datasets used and/or analyzed during the current study available from the corresponding author on reasonable request.

Competing Interests: The authors have no conflict of interest.

Funding: None

Author Contributions

Ahmad Daif analyzed the data; drafted the manuscript.

Tejal Gapchup analyzed the data; drafted the manuscript.

Pritikanta Paul designed and conceptualized study; analyzed the data; drafted the manuscript, revised the manuscript for intellectual content.

Acknowledgments None

References

1. Kassardjian CD, Widdifield J, Paterson JM, et al. Serious infections in patients with myasthenia gravis: population-based cohort study. *Eur J Neurol*. 2020;27(4):702-708. doi:10.1111/ene.14153
2. Guidon AC, Amato AA. COVID-19 and neuromuscular disorders. *Neurology*. 2020;94(22):959-969. doi:10.1212/WNL.0000000000009566
3. Gilhus NE, Romi F, Hong Y, Skeie GO. Myasthenia gravis and infectious disease. *J Neurol*. 2018;265(6):1251-1258. doi:10.1007/s00415-018-8751-9
4. Galassi G, Marchioni A. Myasthenia gravis at the crossroad of COVID-19: focus on immunological and respiratory interplay. *Acta Neurol Belg*. 2021;121(3):633-642. doi:10.1007/s13760-021-01612-6

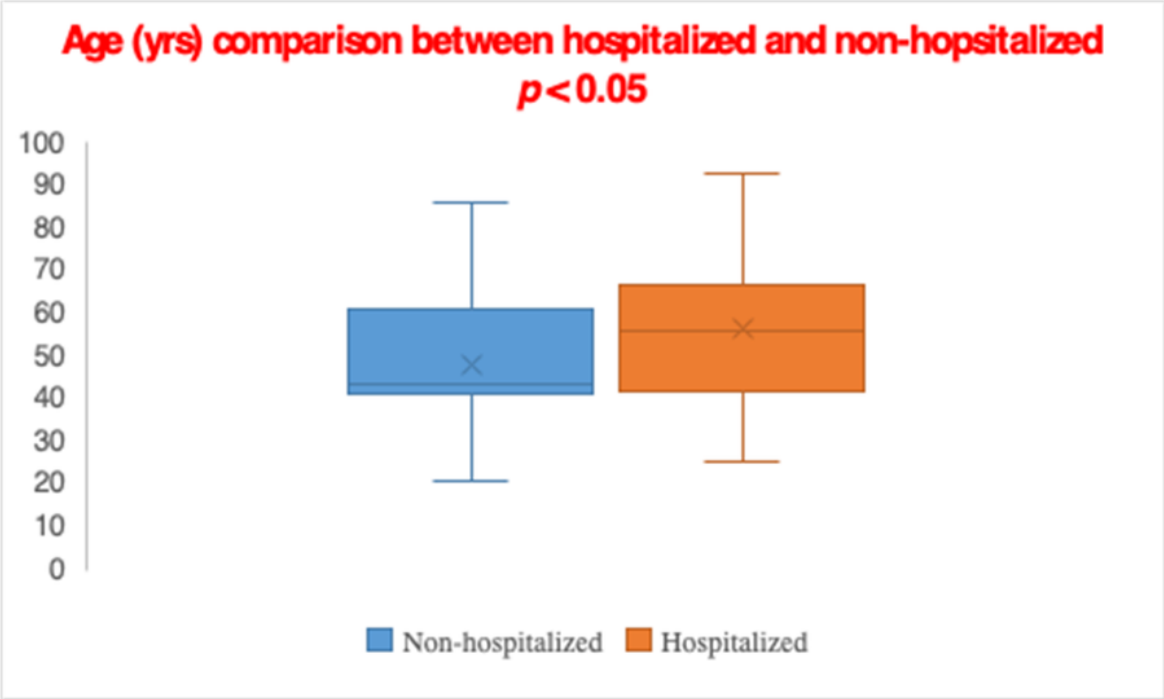
5. Županić S, Lazibat I, Rubinić Majdak M, Jeličić M. TREATMENT OF MYASTHENIA GRAVIS PATIENTS WITH COVID-19: REVIEW OF THE LITERATURE. *Acta Clin Croat*. 2022;60(3):496-509. doi:10.20471/acc.2021.60.03.21
6. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ*. 2009;339:b2700. doi:10.1136/bmj.b2700
7. Thomsen JLS, Andersen H. Outcome Measures in Clinical Trials of Patients With Myasthenia Gravis . *Front Neurol* . 2020;11. https://www.frontiersin.org/article/10.3389/fneur.2020.596382.
8. Barnett C, Herbelin L, Dimachkie MM, Barohn RJ. Measuring Clinical Treatment Response in Myasthenia Gravis. *Neurol Clin*. 2018;36(2):339-353. doi:10.1016/j.ncl.2018.01.006
9. Tuan V, Andreas M, Renato M, et al. Terminal Complement Inhibitor Ravulizumab in Generalized Myasthenia Gravis. *NEJM Evid*. 2022;1(5):EVIDoa2100066. doi:10.1056/EVIDoa2100066
10. 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. doi:10.1016/S1474-4422(20)30413-0
11. Roy B, Kovvuru S, Nalleballe K, Onteddu SR, Nowak RJ. Electronic health record derived-impact of COVID-19 on myasthenia gravis. *J Neurol Sci*. 2021;423:117362. doi:10.1016/j.jns.2021.117362
12. Digala LP, Prasanna S, Rao P, Qureshi AI, Govindarajan R. Impact of COVID-19 infection among myasthenia gravis patients- a Cerner Real-World DataTM study. *BMC Neurol*. 2022;22(1):38. doi:10.1186/s12883-022-02564-x
13. Saied Z, Rachdi A, Thamlaoui S, et al. Myasthenia gravis and COVID-19: A case series and comparison with literature. *Acta Neurol Scand*. 2021;144(3):334-340. doi:10.1111/ane.13440
14. Abbas AS, Hardy N, Ghozy S, et al. Characteristics, treatment, and outcomes of Myasthenia Gravis in COVID-19 patients: A systematic review. *Clin Neurol Neurosurg*. 2022;213:107140. doi:10.1016/j.clineuro.2022.107140
15. Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) - United States, February 12-March 16, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(12):343-346. doi:10.15585/mmwr.mm6912e2
16. Jin JM, Bai P, He W, et al. Gender Differences in Patients With COVID-19: Focus on Severity and Mortality. *Front Public Heal*. 2020;8(April):1-6. doi:10.3389/fpubh.2020.00152
17. Peckham H, de Gruijter NM, Raine C, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. *Nat Commun*. 2020;11(1):6317. doi:10.1038/s41467-020-19741-6
18. Pivonello R, Auriemma RS, Pivonello C, et al. Sex Disparities in COVID-19 Severity and Outcome: Are Men Weaker or Women Stronger? *Neuroendocrinology*. 2021;111(11):1066-1085. doi:10.1159/000513346
19. Pisella LI, Fernandes S, Solé G, et al. A multicenter cross-sectional French study of the impact of COVID-19 on neuromuscular diseases. *Orphanet J Rare Dis*. 2021;16(1):450. doi:10.1186/s13023-021-02090-y

20. Thomsen JLS, Vinge L, Harbo T, Andersen H. Gender differences in clinical outcomes in myasthenia gravis: A prospective cohort study. *Muscle Nerve*. 2021;64(5):538-544. doi:https://doi.org/10.1002/mus.27331
21. Yang J, Zheng Y, Gou X, et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. *Int J Infect Dis IJID Off Publ Int Soc Infect Dis*. 2020;94:91-95. doi:10.1016/j.ijid.2020.03.017
22. Liu B, Spokes P, He W, Kaldor J. High risk groups for severe COVID-19 in a whole of population cohort in Australia. *BMC Infect Dis*. 2021;21(1):685. doi:10.1186/s12879-021-06378-z
23. 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;28(10):3418-3425. doi:10.1111/ene.14951
24. Horby P, Lim WS, Emberson JR, et al. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med*. 2021;384(8):693-704. doi:10.1056/NEJMoa2021436
25. Bradley MC, Perez-Vilar S, Chillarige Y, et al. Systemic Corticosteroid Use for COVID-19 in US Outpatient Settings From April 2020 to August 2021. *JAMA*. 2022;327(20):2015-2018. doi:10.1001/jama.2022.4877
26. Wang W, Thomas R, Oh J, Su D-M. Thymic Aging May Be Associated with COVID-19 Pathophysiology in the Elderly. *Cells*. 2021;10(3). doi:10.3390/cells10030628
27. Wolfe GI, Kaminski HJ, Sonnett JR, Aban IB, Kuo HC, Cutter GR. Randomized trial of thymectomy in myasthenia gravis. *J Thorac Dis*. 2016;8(12):E1782-E1783. doi:10.21037/jtd.2016.12.80
28. Freites Nuñez DD, Leon L, Mucientes A, et al. Risk factors for hospital admissions related to COVID-19 in patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis*. 2020;79(11):1393-1399. doi:10.1136/annrheumdis-2020-217984
29. Faqihi F, Alharthy A, Abdulaziz S, et al. Therapeutic plasma exchange in patients with life-threatening COVID-19: a randomised controlled clinical trial. *Int J Antimicrob Agents*. 2021;57(5):106334. doi:10.1016/j.ijantimicag.2021.106334
30. Cao W, Liu X, Bai T, et al. High-Dose Intravenous Immunoglobulin as a Therapeutic Option for Deteriorating Patients With Coronavirus Disease 2019. *Open forum Infect Dis*. 2020;7(3):ofaa102. doi:10.1093/ofid/ofaa102
31. Kindgen-Milles D, Feldt T, Jensen BEO, Dimski T, Brandenburger T. Why the application of IVIG might be beneficial in patients with COVID-19. *Lancet Respir Med*. 2022;10(2):e15. doi:10.1016/S2213-2600(21)00549-X
32. Mazeraud A, Wolff M, Lucas B, Sharshar T. Why the application of IVIG might be beneficial in patients with COVID-19 - Authors' reply. *Lancet Respir Med*. 2022;10(2):e16. doi:10.1016/S2213-2600(21)00550-6
33. Tagami T, Matsui H, Fushimi K, Yasunaga H. Intravenous Immunoglobulin and Mortality in Pneumonia Patients With Septic Shock: An Observational Nationwide Study. *Clin Infect Dis*. 2015;61(3):385-392. doi:10.1093/cid/civ307

Figures

Figure 1

Flowchart showing search process, outcomes and included studies conducted in accordance with PRISMA guidelines for systematic reviews[6]



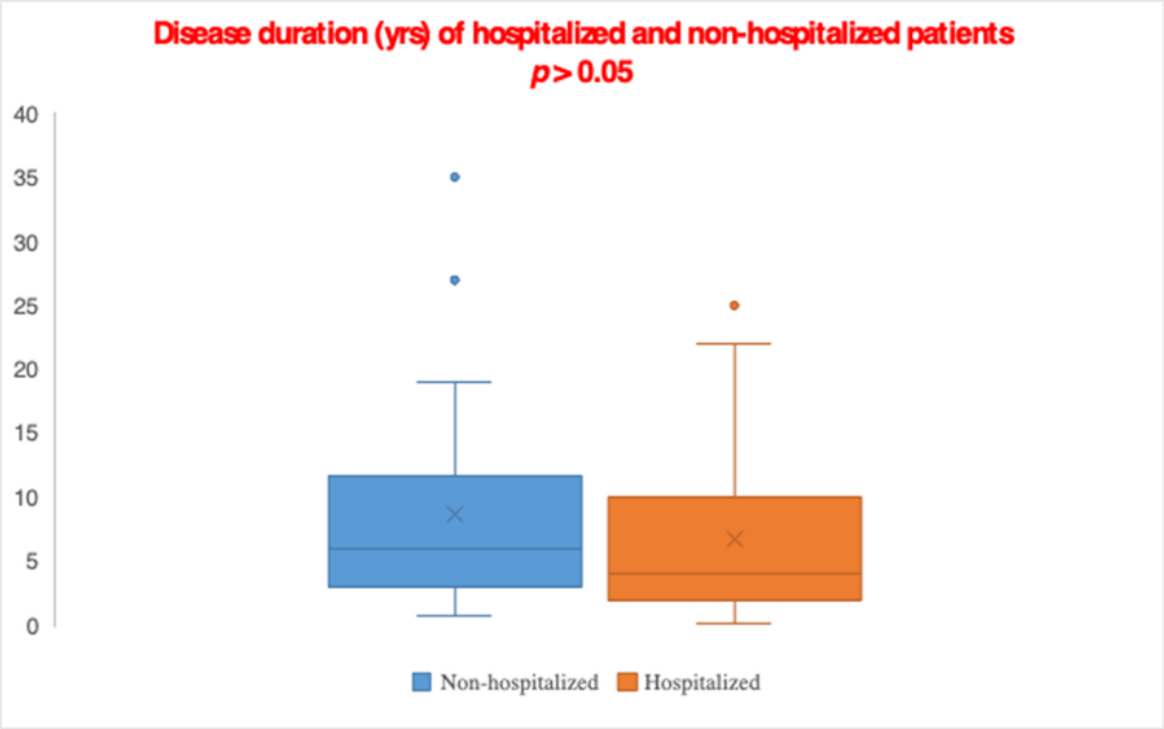
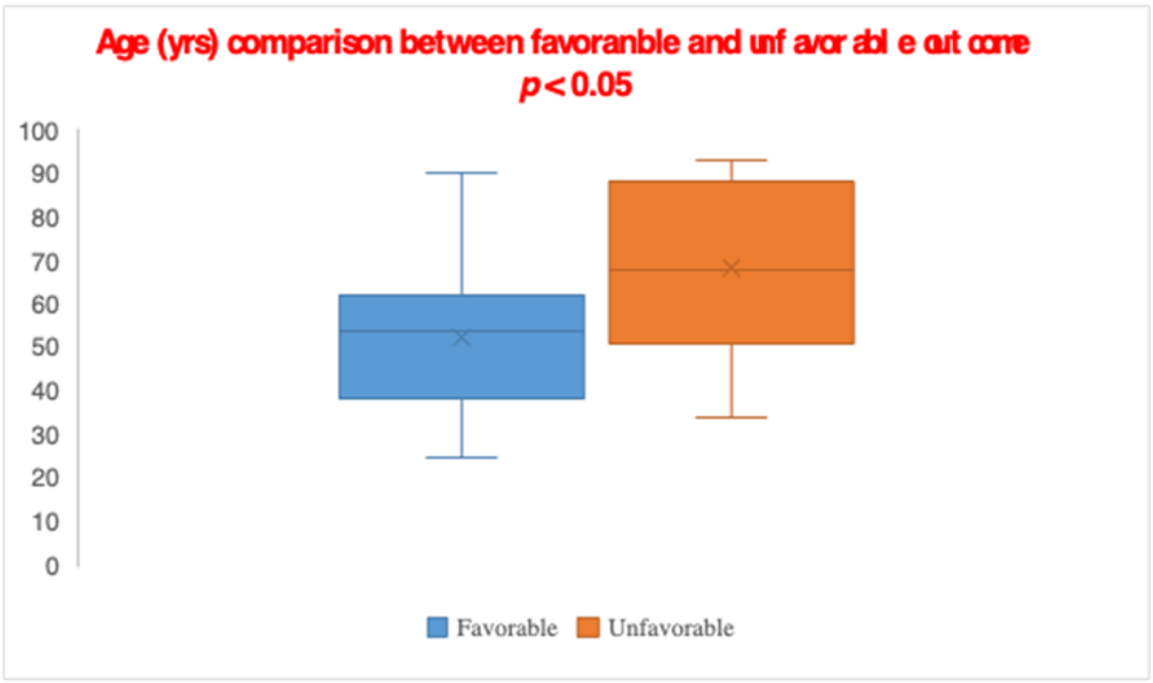


Figure 2

Differences in hospitalized vs non-hospitalized patients based on age (top) and disease duration (bottom)



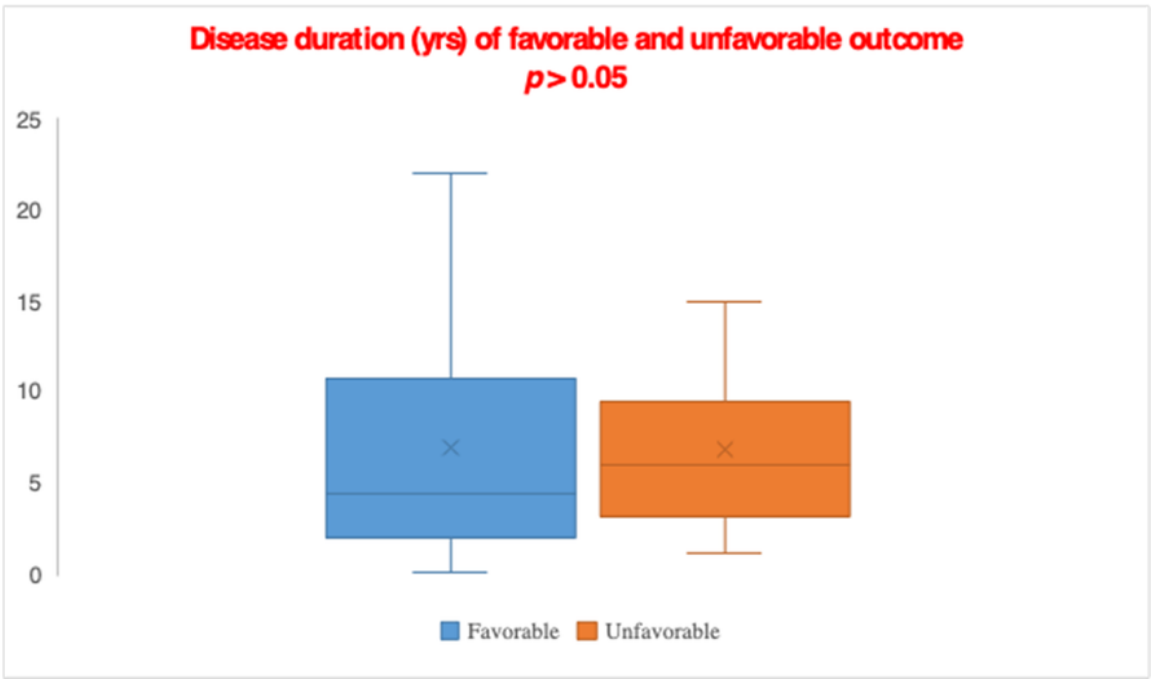


Figure 3

Differences in hospitalized patients' favorable vs un-favorable outcomes based on age (top) and disease duration (bottom)