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CLINICAL RESEARCH SHORT REPORT

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The impact of SARS-CoV-2 immunization on COVID-19 disease course in people with myasthenia gravis

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Abstract

Introduction/Aims: There is limited knowledge regarding the impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines on coronavirus disease 2019 (COVID-19) disease course in people with myasthenia gravis. In this study, we aimed to investigate whether SARS-CoV-2 vaccination influences hospitalization and mortality due to COVID-19 in this population.

Methods: This is a retrospective analysis of administrative data extracted from the Greek nationwide database that holds the COVID-19 disease and vaccination registry, as well as all medical prescription records. The study period extended from the onset of the pandemic (February 2020) until the 10th of January 2022.

Results: We identified 278 people with myasthenia gravis (mean age 58.1 ± 17.2, 47.5% males) who tested positive for SARS-CoV-2. Of those, 139 (50%) were not vaccinated at the time of infection. Multivariable binary logistic regression analysis showed that the probability of hospitalization increased with age (odds ratio [OR]: 1.058; 95% confidence interval [CI], 1.036–1.080; $p < .001$) and immunosuppressive treatment (OR: 2.872; 95% CI 1.412–5.839; $p = .004$), and decreased with vaccination (OR: 0.244; 95% CI 0.132–0.453; $p < .001$). The probability of a fatal outcome increased with age (OR: 1.085; 95% CI 1.043–1.129; $p < .001$) and decreased with vaccination (OR: 0.315; 95% CI 0.125–0.791; $p = .014$).

Discussion: SARS-CoV-2 vaccination significantly reduces hospitalization and mortality due to COVID-19 in people with myasthenia gravis. This study regarding the efficacy of these vaccines, together with previous studies regarding their safety, provide evidence to support their use in people with myasthenia gravis.

KEYWORDS
myasthenia gravis, mortality, epidemiology, infection, COVID-19

Abbreviations: CI, confidence interval; COVID-19, coronavirus disease 2019; MMF, mycophenolate mofetil; OR, odds ratio; pwMG, people with myasthenia gravis; PCR, polymerase chain reaction; RAT, rapid antigen test; RTX, rituximab; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

1 | INTRODUCTION

People with myasthenia gravis (pwMG) are considered to be at high risk for a severe coronavirus disease 2019 (COVID-19) disease course.[1] Advanced age and chronic comorbid conditions may have an additive effect on the risk of a severe respiratory syndrome.[2] There is currently limited knowledge about the impact of SARS-CoV-2 immunization on the COVID-19 disease course in pwMG.[3] In this study, we aimed to investigate the effect of SARS-CoV-2 vaccination on hospitalization and mortality in pwMG who tested positive for SARS-CoV-2 infection.

2 | METHODS

We retrospectively analyzed pseudo-anonymized data from the Greek nationwide digital database of IDIKA S.A., in order to identify pwMG who tested positive for SARS-CoV-2 infection. The database holds all medical prescriptions, as well as the national COVID-19 disease and SARS-CoV-2 vaccination registries, in Greece. The study period extended from the onset of the pandemic in Greece (26th February 2020) until the 10th of January 2022. The identification of MG cases was performed using the criterion of a minimum of 2 consecutive prescriptions, during this study period, with the ICD-10 code for myasthenia gravis (G70). In order to be included in this study, participants must have tested positive for SARS-Cov-2 via polymerase chain reaction (PCR) or rapid antigen test (RAT), and must have received prescriptions for MG-related treatments (pyridostigmine, steroids or other immunosuppressants) with the ICD-10 code G70, for a minimum of 6 consecutive months prior to the day of positive testing for SARS-CoV-2, in order to ensure that the MG diagnosis preceded the SARS-CoV-2 infection. We additionally collected data regarding age, hospitalization, and death due to COVID-19.

Descriptive statistics was performed for quantitative (mean andSD) and qualitative (frequency, percentage) variables. Appropriate hypothesis testing was applied for specific comparisons (t-test, chi-squared test) related to hospitalization and death from COVID-19. The corresponding p-values were corrected using the Bonferroni correction. Univariable and multivariable binary logistic regression analysis was applied to assess the impact of different factors, separately, on hospitalization and death from COVID-19.

This study was performed in accordance with the national laws on personal data (32,129/24-04-2019) and was approved by the local ethical committee (7.381/7/20.04.21). Informed consent of the participants was waived by the regulatory authority.

3 | RESULTS

We identified 278 pwMG who tested positive (147 with PCR, 131 with RAT) for SARS-CoV-2 infection during this study period. Of those, 139 pwMG were not vaccinated, 10 were partly vaccinated (they tested positive for SARS-CoV-2 infection after receiving only one dose of a vaccine that requires 2 doses for full vaccination), and 129 were fully vaccinated at the time they tested positive. Vaccines used were BNT162b2 (n:122), mRNA-1273 (n:8), ChAdOx1-S (n:5), and Ad26.COV2-S (n:4). All pwMG were treated either with pyridostigmine monotherapy (n:88) or with various combinations of steroids, pyridostigmine and other immunosuppressants (n:190) at the time of COVID-19 infection. Descriptive statistics of the study sample are presented in Table 1.

As expected, pwMG who required hospitalization due to COVID-19 were older (67.8 ± 13.9 vs 53.6 ± 16.7, 95% CI: (10.41, 17.98), $p < .001$; Figure S1). With regard to sex, 40.2% of males and 24.0% of females (95% CI: (0.05, 0.28), $p = .006$) were hospitalized, while 83.0% of the hospitalized pwMG and 61.6% of non-hospitalized were receiving immunosuppression (95% CI: (0.10, 0.33), $p = .001$). Admission to hospital occurred more often in pwMG who were not vaccinated than in pwMG who were partly or fully vaccinated at the time of infection.

Thirty pwMG died from COVID-19 during the study period. Age was a significant factor for mortality (73.0 ± 10.8 vs 56.3 ± 17.0, 95% CI: (10.48, 22.99), $p < .001$; Figure S1). Fatal outcome was observed in 15.9% of males and in 6.2% of females (95% CI: (0.02, 0.18), $p = .015$), while 83.3% of those pwMG who died were receiving immunosuppression ($p < .001$). Fatal outcome occurred more often in the non-vaccinated group.

According to the univariable binary logistic regression analysis, the probability of hospitalization increased with increasing age (OR: 1.060, $p < .001$), male sex (OR: 2.128, $p = .004$), and immunosuppression (OR: 3.036, $p = .001$), while it decreased with vaccination (OR: 0.265, $p < .001$). All four factors (age, sex, vaccination status, presence of immunosuppression) were included in a multivariable logistic regression model, and the probability of hospitalization still increased with increasing age and immunosuppression and decreased with vaccination (Table 2).

With regard to death due to COVID-19, the univariable analysis showed that the probability of a fatal outcome increased with increasing age (OR: 1.088, $p < .001$) and male sex (OR: 2.880, $p = .011$), and decreased with vaccination (OR: 0.325, $p = .009$). Immunosuppression marginally increased the probability of a fatal outcome (OR: 2.515, $p = .069$). Multivariable analysis demonstrated that the probability of a fatal outcome increased with increasing age and decreased with vaccination (Table 2).

We further examined the impact of various immunosupressive agents on the course of COVID-19. The study sample was subdivided in 4 groups according to the type of immunosupression (Table S1). Treatment with rituximab (RTX) or mycophenolate mofetil (MMF) exhibited the highest odds ratio regarding both hospitalization and death; however, the OR was statistically significant only with regards to hospitalization (Table 3). High ORs were still observed when the RTX/MMF group was compared to all other pwMG regardless of the type of treatment they received, but without leading to a statistically significant result (Table S2).

TABLE 1 Demographic and disease characteristics of the study sample

Variable	Total (n:278)	Unvaccinated pwMG (n:139)	Vaccinated pwMG (n:139)	*P*-Value
Age, mean (SD), y	58.1 (17.2)	59.5 (17.4)	56.7 (17.0)	*.182*
Males, n (%)	132 (47.5)	64 (46.0)	68 (48.9)	*.719*
Receiving immunosuppressive treatment	190 (68.3)	100 (71.9)	90 (64.7)	*.246*
COVID-19 outcome				
Hospitalization, n (%)	88 (31.7)	63 (45.3)	25 (18.0)	*<.001*
Death, n (%)	30 (10.8)	22 (15.8)	8 (5.8)	*.012*
Vaccination status at COVID-19 testing				
Non-vaccinated, n (%)	139 (50)	139 (100)		
Partially vaccinated, n (%)	10 (3.6)		10 (7.2)	
Fully vaccinated, n (%)	96 (34.5)		96 (69.1)	
Fully vaccinated + booster, n (%)	33 (11.9)		33 (23.7)	

Abbreviation: pwMG, people with myasthenia gravis.

TABLE 2 Multivariable binary logistic regression analysis for hospitalization and mortality

Outcome	Independent factors	OR	95% CI for OR	*P*-Value
Hospitalization				
	Partially or fully vaccinated	0.244	0.132–0.453	<.001
	Age	1.058	1.036–1.080	<.001
	Presence of immunosuppresion	2.872	1.412–5.839	.004
	Male sex	1.586	0.860–2.925	.140
Death due to COVID-19	Partially or fully vaccinated	0.315	0.125–0.791	.014
	Age	1.085	1.043–1.129	<.001
	Presence of immunosuppresion	2.152	0.738–6.278	.161
	Male sex	2.136	0.869–5.252	.098

TABLE 3 Multivariable binary logistic regression analysis for hospitalization and mortality, on the basis of immunosupressive treatment

Outcome	Independent factors	OR	95% CI for OR	*P*-Value
Hospitalization				
	Age	1.057	1.036–1.079	<.001
	Male sex	1.624	0.874–3.016	.125
	Presence of immunosuppresion			.019
	Steroids only[a]	2.963	1.324–6.628	.008
	Azathioprine[a]	2.482	1.112 - 5.538	.026
	Rituximab or Mycophenolate mofetil[a]	4.932	1.455–16.713	.010
	Partially or fully vaccinated	0.242	0.130–0.451	<.001
Death due to COVID-19				
	Age	1.081	1.039–1.124	<.001
	Male sex	2.350	0.936–5.898	.069
	Presence of immunosuppresion			.034
	Steroids only[a]	3.391	1.080–10.640	.036
	Azathioprine[a]	0.856	0.221–3.313	.822
	Rituximab or Mycophenolate Mofetil[a]	3.458	0.742–16.108	.114
	Partially or fully vaccinated	0.322	0.126–0.823	.018

[a]vs no immunosupression.

4 | DISCUSSION

According to the results of this study, following partial or full SARS-CoV-2 vaccination, a 60.3% reduction in hospitalizations and a 63.6% reduction in deaths due to COVID-19 were observed. The findings of this study are in accordance with previous studies that suggest that these vaccines reduce hospitalization rates and COVID-19 severity,[4] although the effects of this protection may wane within a few months.[5] Furthermore, in agreement with other studies,[2,6] this study demonstrates that age and immunosuppression are risk factors for a severe COVID-19 disease course. Male sex is considered another risk factor,[7] and the tendency for worse disease course for male PwMG was observed in this study as well.

Several reports of new onset or worsening of myasthenia gravis following COVID-19 vaccination,[8,9] have raised concerns about their use in pwMG.[10,11] However, preliminary studies with a limited number of participants suggested that their use in pwMG is safe.[3,12,13] In a recent study of 294 pwMG, only 1% of them developed a flare of the disease attributed to COVID-19 vaccination.[14] Furthermore, in a study with 100 pwMG, Reyes-Leiva et al found that a therapeutic intervention was required in only 2% of them to control MG deterioration attributed to mRNA vaccines.[15] In addition, they demonstrated that mRNA vaccines can generate strong humoral and cellular immune responses, although at a lower rate in highly immunosuppressed pwMG. Immunosuppressive agents such as B cell depletion therapies and MMF may hinder the development of immune responses to vaccines,[15,16] leading to worse COVID-19 outcomes.[17,18] Therefore, people being treated with these therapies are considered to be at high risk for severe COVID-19 disease.[19,20] According to our study, the use of RTX or MMF was associated with increased hospitalization rates but not deaths due to COVID-19. However, this association was observed only when the RTX/MMF group was compared with pwMG who did not receive any immunosuppression. In addition, for all these analyses, the very wide confidence intervals indicate imprecision, likely due to the small sample size of the RTX/MMF group (n:21).

Disease coding misclassifications by clinicians may implicate the results of health administrative data analyses[21]; therefore, the results of this study should further be confirmed by studies using registries of pwMG. Disease severity may be one important variable affecting hospitalization and mortality rates due to COVID-19. In this study, data about MG severity, timing and duration of hospitalization, and data concerning risk factors for severe respiratory syndromes such as comorbid conditions, obesity and smoking were not available. Potential adverse events of immunization, levels of SARS-CoV-2 spike antibodies and data regarding the strains of SARS CoV-2 virus in the study sample were not available either. However, since the first case due to the Omicron variant in Greece was detected in December 2021, we assume that most of the cases may be attributed to the other variants of the virus. Finally, a number of hospitalizations might have been performed out of an abundance of caution, especially during the first months of the pandemic.

The current study does not address the risk reduction of overall COVID-19 infection by these vaccines in pwMG. Nevertheless, this study demonstrates the beneficial effects of SARS-CoV-2 immunization in pwMG, by significantly reducing the risk of hospitalization and death due to COVID-19. This study regarding the efficacy of these vaccines and previous reports on their safety, provide evidence to support their use in pwMG.

AUTHOR CONTRIBUTIONS

Prof Grigoriadis and Dr Bakirtzis had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Bakirtzis, Karakasi, Grigoriadis.
Acquisition, analysis, or interpretation of data: all authors.
Drafting of the manuscript: Bakirtzis, Moysiadis, Karakasi.
Critical revision of the manuscript for important intellectual content: Boziki, Grigoriadis.
Statistical analysis: Moysiadis, Bakirtzis, Boziki.
Administrative, technical, or material support: Karakasi, Grigoriadis.
Supervision: Grigoriadis.

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DATA AVAILABILITY STATEMENT

Data availability Statement;Raw data used in this study are property of the Greek Ministry of Health. Requests to access the datasets should be directed to https://www.moh.gov.gr/.;

DECLARATION OF COMPETING INTEREST

None of the authors has any conflict of interest to disclose.

ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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