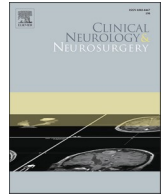




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# Impact of COVID-19 pandemic and lockdown in a cohort of myasthenia gravis patients in India

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## ABSTRACT

**Objective:** Myasthenia gravis (MG) is characterized by fluctuating muscle weakness due to immune mediated damage of acetylcholine receptor (AChR). COVID-19 infection, mental stress and non-availability of drugs following lockdown may worsen myasthenic symptoms. We report the impact of COVID 19, and lockdown on the physical and mental health, and quality of sleep in a cohort of MG.

**Methods:** Thirty-eight MG patients were telephonically interviewed 2months after the declaration of lockdown in India. The difficulty in procuring drugs, complications, and worsening in the MG Foundation of America (MGFA) stage were noted. The patients were enquired about MG Quality of Life 15 (MGQOL15), MG Activity of Daily Living (MGADL), Hospital Anxiety and Depression Scale (HADS) and Pittsburgh Sleep Quality Index (PSQI) using a prefixed questionnaire. Their pre-COVID parameters were retrieved from our earlier trial data, which was completed 4months back. The scores of the above mentioned parameters before and after COVID were compared.

**Results:** Their median age was 45 years, and the median duration of treatment for MG was 4.5years. Eleven (28.9 %) patients were hypertensive and 3(7.9 %) diabetic. All were on prednisolone and 18(47.4 %) received azathioprine. None developed COVID, but three had other infections. Two patients needed hospitalization because of wrong medication in one and severe anxiety-insomnia in another. Following COVID19 and lockdown, MG patients had worsening in MGQOL15, MGADL, HADS and PSQI scores. Pittsburgh Sleep Quality Index score correlated with MGQOL15 and dose of acetylcholine esterase inhibitors.

**Conclusion:** COVID-19 and lockdown were associated with anxiety, depression, poor MGQOL and sleep especially in severe MG patients.

## 1. Introduction

Myasthenia gravis (MG) is an autoimmune disease affecting the acetylcholine receptor (AChR) in the post synaptic membrane of neuromuscular junction by antibodies against AChR, muscle specific kinase (MuSK), low-density lipoprotein receptor-related protein 4 (LRP-4), or agrin [1]. MG is characterized by fluctuating muscle weakness which worsens with exertion and improves with rest. About two-third of MG patients manifest weakness of extrinsic ocular muscles, and later it may progress to involve bulbar and limb musculature resulting in generalized MG. The patients with autoimmune MG are treated with immuno-modulating drugs such as prednisolone, azathioprine, mycophenolate mofetil, cyclophosphamide or rituximab [2]. The patients on these drugs are prone to infections leading to worsening of weakness. About 15–20 % of MG patients may develop myasthenic crisis, and

infection is the leading cause in the reported series [3–5]. The other precipitating causes of the myasthenic crisis are stress, extremes of temperature, surgery, or inadvertent prescription of offending drugs [6, 7].

Recent COVID-19 pandemic is associated with pneumonia, cytokine storm, and myositis which may aggravate the myasthenic symptoms [8]. COVID-19 pandemic has impacted mental health all across the globe especially in children, the elderly, health care workers and with pre-existing medical diseases [9]. In India, the impact of COVID-19 on mental and physical health is more complex due to the large proportion of the vulnerable population with diabetes, hypertension or tuberculosis, and limited health infrastructure [10]. Fear and anxiety among people are likely to increase due to social and electronic media covering news on COVID-19 with daily spikes in cases and mortality [11]. People are made aware of preventive measures for disease control, and the

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vulnerable population groups through various government advisories. Misinformation about the nature and course of COVID-19 has caused panic among people, more so in the elderly and those who are having pre-existing medical conditions [12]. This is likely to affect the mental health, especially in MG patients who have experienced or aware of the impact of infection on worsening of symptoms. The impact of COVID-19 on various neurological diseases including multiple sclerosis, epilepsy, and Parkinson disease has been reported [13–15]. The impact of COVID-19 and lockdown on mental and physical health has not been reported in patients with MG. In the present study, we report the impact of COVID-19 and lockdown on the MG status, mental health, and quality of sleep in a cohort of patients with MG from India.

## 2. Materials and methods

This study is an extension of our earlier study (CTRI/2019/11/021869), which was completed 4 months before the declaration of the COVID-19 epidemic and lockdown in India [16]. The study was approved by the Institute Ethics committee (PGI/BE/632/2018). The MG patients in the RESTOREX trial were in close physical or telephonic follow up ever since the above mentioned trial. We have made a MG WhatsApp group, through which their day today problems were shorted out, and instructions about the preventive measures of COVID-19 were communicated. Two months after the declaration of lockdown in India, these patients were telephonically communicated by a neurology resident (ND) and a PhD student (AT) under the supervision of a faculty member (JK).

### 2.1. Inclusion criteria

The diagnosis of MG was based on fatigable muscle weakness and at least two of the following criteria: a) positive prostigmine test, b) decremental response on 3 Hz repetitive nerve stimulation test at least in two muscles, and c) detection of serum anti AchR or Anti-MuSK antibody.

### 2.2. Exclusion criteria

Patients with congenital myasthenia, ocular or stage V MG, children, pregnancy, malignancy, end stage renal failure or hepatic failure were excluded. The patients with incomplete preCOVID-19 information regarding Myasthenia Gravis Foundation of America (MGFA) stage, Hospital Anxiety and Depression Scale (HADS) score, MG Quality of Life (MGQoL)15 and MG Activity of Daily Living (MG ADL) were also excluded.

### 2.3. Clinical evaluation

Pre COVID clinical details were extracted from the RESTOREX trial data sheet including demographic details, duration of illness, MGFA stage, medication details, MGQOL 15, MGADL, HADS score. After 8 weeks of lockdown, patients were contacted telephonically and were enquired about working condition, their medications, difficulty in procuring prescribed medicine, drug compliance, and infection (COVID or non-COVID). They were also enquired whether they were aware about COVID-19 pandemic and its possible impact on their health. The preventive measures of COVID-19 infection such as mask, distancing and hand washing were also enquired. Almost all the questions were asked in Hindi. The patients answered themselves; however, while interviewing the patient, we also interacted with the care giver if needed to verify the relevant inputs.

The following information scales were applied for measuring MG status, mental health, and quality of sleep:

### 2.4. Myasthenia Gravis Foundation of America (MGFA) staging

The severity of MG was assessed by MGFA scale [17]. This classification divides MG into 5 main classes as follows:

<b>Class I</b>	Any ocular muscle weakness. Other muscle strength is normal.
<b>Class II</b>	Mild weakness of non-ocular muscles. Ocular muscle weakness may be of any severity.
a.	Mild weakness of limb muscle, axial or both with or without oropharyngeal weakness.
b.	Predominant oropharyngeal weakness, respiratory muscle or both with or without weakness of limb, axial or both.
<b>Class II</b>	Moderate weakness, distribution of weakness is similar to Class II
a.	Moderate weakness, the involvement of muscle is similar to IIa.
b.	Moderate weakness, the involvement of muscle is similar to IIb
<b>Class III</b>	Severe weakness of non-ocular muscles, ocular muscle weakness may be of any severity
IVa.	Severe weakness, distribution of muscle weakness is similar to IIa.
IVb.	Severe weakness, distribution of muscle weakness is similar to IIb.
<b>Class IV</b>	Intubation with or without mechanical ventilation except for postoperative management. Feeding tube without intubation categorized in Class IVb

### 2.5. Myasthenia gravis (MG) quality of life 15 scale

The quality of life was assessed by a 15 points self-administered disease-specific questionnaire. Each point is scored on a 0–4 scale (0 = none, 1 = a little bit, 2 = somewhat, 3 = quite a bit and 4 = very much respectively) [18].

### 2.6. MG activities of daily living (MGADL) score

Activities of daily living were evaluated using MGADL scale. This is a self-reported scale having 8 items including talking, chewing, swallowing, breathing, brushing teeth or combing hair, rising from a chair, double vision, and eyelid drooping. Each item is scored on a 0 (normal) to 3 (severe) scale [19].

### 2.7. Hospital anxiety and depression scale (HADS)

The HADS is a self-assessed 14 points scale including seven questions for the assessment of anxiety and another seven for depression [20]. The response to each question was scored on a 0–3 scale (0 = none and 3 = definite) with a total score ranging between 0–21 for HADS-A and HADS-B. Both the individual and total scores were noted. A score of 7 or below was considered normal, 8–10 borderline and >10 clinical ‘case-ness’ [21].

### 2.8. Pittsburgh Sleep Quality Index (PSQI)

Quality of sleep was assessed by PSQI, which includes subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, daytime sleepiness, day time enthusiasm and roommate or bed mate reporting of loud snoring, long pauses, leg movement, confusional state or restlessness during sleep dysfunction [22].

### 2.9. Treatment

All the patients received acetyl choline esterase inhibitors (AChEIs), and those with thymic enlargement on CT thorax had undergone thymectomy. Patients without thymic enlargement or those having moderate to severe symptoms after thymectomy received prednisolone. We practice gradual reduction of dose of corticosteroid after 3 months if the patient is stabilized. If there was corticosteroid intolerance or no improvement, steroid sparing or additional immunosuppressant such as azathioprine or mycophenolate mofetil was added. Prednisolone

**Table 1**  
Baseline clinical characteristics of the patients with myasthenia gravis.

Parameters	Number of patients 38
Age (median, range) years	45 (16–73)
Gender (female)	16 (42.1 %)
Education (years of schooling)	
8–10 years	6(15.85)
10–12 years	11(28.9 %)
12–15 years	11(28.9 %)
15–17 years	10(26.3 %)
Duration of illness in years	4.5 (range 1.2–24)
Working status	
Online	7(18.4 %)
At home	31(81.6 %)
Complication during COVID	
Non-COVID infection	3 (7.9 %)
Deterioration	3 (7.9 %)
Drug noncompliance	1(2.6 %)
Wrong drug	1(2.6 %)
None	31(81.5 %)
Myasthenic crisis	1(2.6 %)
Prednisolone (mg) (n = 38) in median and IQR	11.25 (7.5, 16.25)
Azathioprine (mg) (n = 18) in median and IQR	100 (100, 100)
AChEIs (mg) (n = 38) in median and IQR	180 (142, 240)

**AChEIs** = acetyl choline esterase inhibitors (pyridostigmine and or prostigmine), **IQR** = inter quartile range.

withdrawal was only attempted if the patient was stabilized on low dose of prednisolone for 6–12 months without requiring AChEIs. Such patients were very few.

2.10. Statistical analysis

The pre and postCOVID-19 status of MGFA stage, MGQOL 15, HADS-A, HADS-D, MGADL and PSQI scores were compared using Mann Whitney U test. The categorical data were compared by chi-square test. The post COVID MGFA stage, MGQOL 15, HADS-A, HADS-B, MGADL and PSQI scores were correlated by Spearman or Karl-Pearson correlation test. These parameters were also correlated with age, gender, education, duration of illness, the dose of AChEIs, corticosteroid, and azathioprine using Spearman rank correlation. An exact two tailed p value of < 0.05 in the statistics was considered significant. The statistical analysis was done using Statistical Package for Social Sciences version 20 and graphs were prepared by graph Pad prism 5.

2.11. Data availability statement

Data will be available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. Patient-related data will be shared upon request from any

**Table 2**  
Change in Severity of myasthenia gravis, quality of life, activity of daily living, anxiety, depression and quality of sleep a cohort of myasthenia gravis before and after COVID 19 and lockdown.

	Before COVID 19	After COVID 19	P value
<b>HADS score</b> in median and IQR	6 (5,7)	7 (5,8)	0.001
<b>HADS –A</b> in median and IQR	4 (3,5)	2 (1,3.2)	<0.001
<b>HADS –D</b> in median and IQR	2 (1,3)	3 (2,4)	< 0.001
<b>PSQI score</b> in median and IQR	3 (2,4)	4 (3,5)	< 0.001
<b>MGADL score</b> in median and IQR	0.50 (0, 2)	1 (0,3)	<0.001
<b>MGQOL 15 score</b> in median and IQR	6.5 (6,8)	7.5 (610)	0.036
MGFA stage			
IIA	11(28.9 %)	11(28.9 %)	
IIB	10(26.3 %)	10(26.3 %)	
IIIA	17(44.7 %)	15(39.5 %)	0.71
IIIB	0 (0%)	1(2.653 %)	
V	0 (0%)	1(2.65 %)	

**A** = anxiety, **D**= depression; **HADS** = Hospital Anxiety and Depression Scale; **IQR** = Inter quartile range; **MGFA** = Myasthenia Gravis Foundation of America; **MG ADL** = Myasthenia Gravis Activity of Daily Living; **MGQOL**= Myasthenia Gravis Quality of Life; **PSQI** = Pittsburgh Sleep Quality Index.

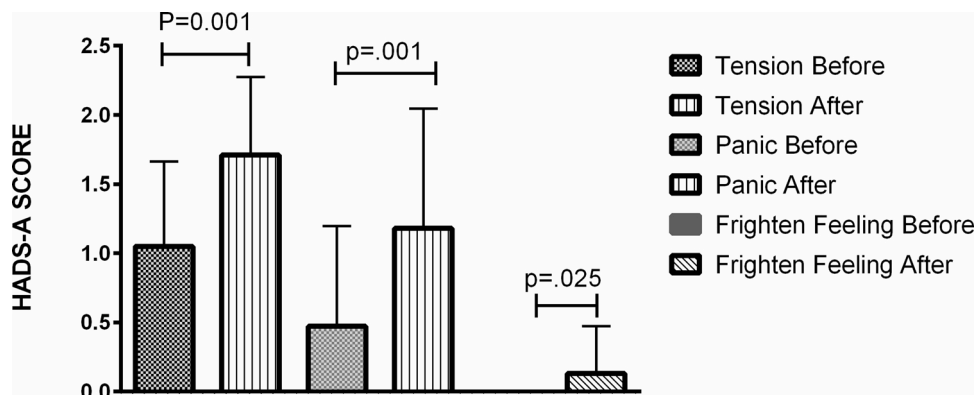
qualified investigator, maintaining anonymisation of the individual patients.

3. Results

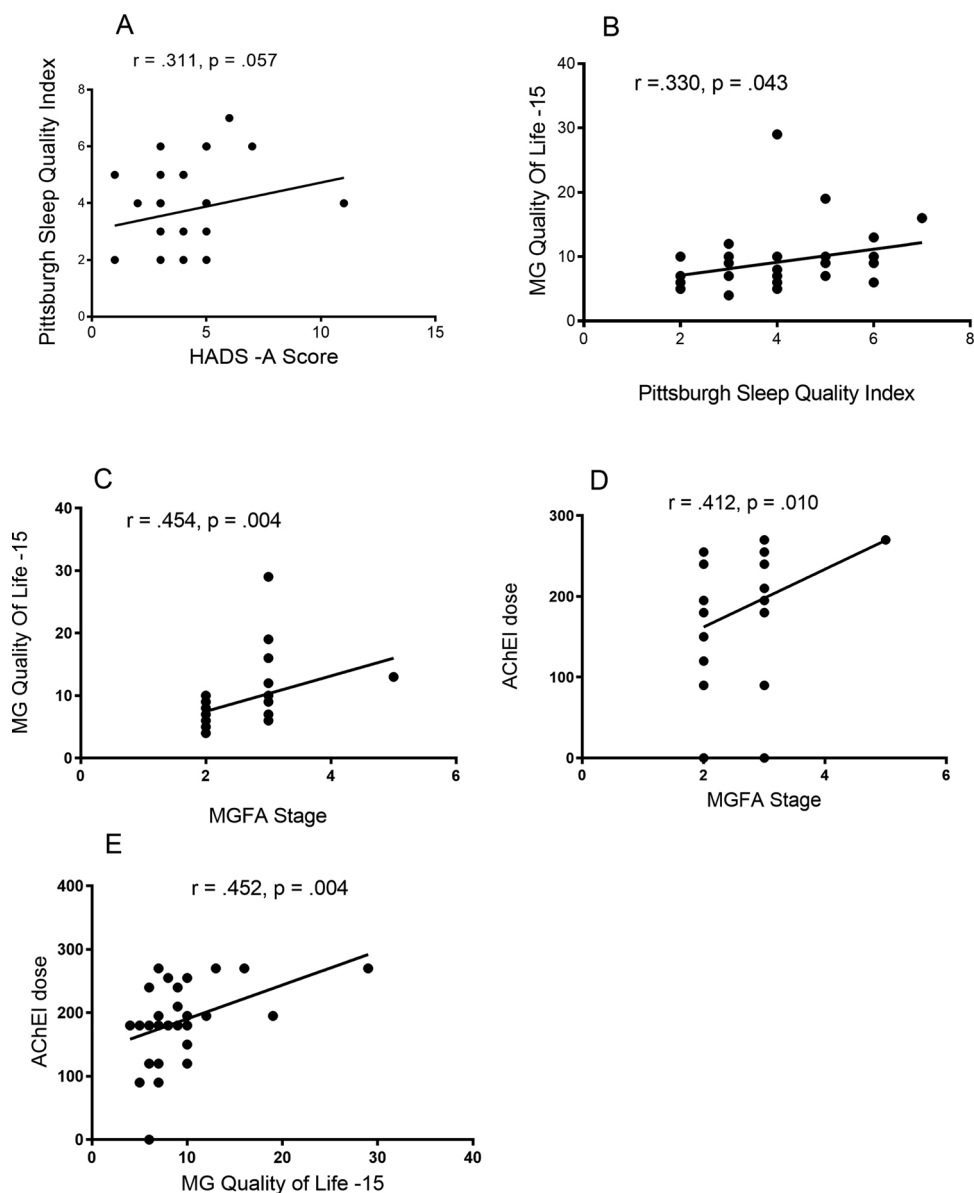
Thirty-eight patients with MG have been included, whose median age was 45 years (16–73 years), and 12 (31.6 %) were above the age of 50 years at the time of diagnosis. All the patients had eight or more years of schooling. The median duration of illness was 4.5 (range 1.2–24) years. 19(50 %) patients had comorbidities including hypertension in 11 (28.9 %), diabetes mellitus in 3(7.9 %) and thyroid disorder in 5(13.2 %) patients. The demographic and clinical details before COVID 19 are presented in Table 1.

3.1. Effect of COVID 19

None of the patients had COVID 19 infection. They have been following instructions about isolation, mask and distancing, and were doing moderate exercise or yoga at home regularly as conveyed them through chat messages in WhatsApp group. Seven (18.4 %) patients were working from home. Three patients developed infections (urinary tract 1, upper respiratory tract 2). Two patients had drug related problems; drug noncompliance in one due to inability to procure during lockdown and another purchased phenobarbitone tablet (60 mg) wrongly instead of pyridostigmine (60 mg) from local pharmacy. The remaining patients continued medication which they procured prior to



**Fig. 1.** There was increased tension, frightening feeling and panic in myasthenia gravis patients after COVID-19 and lockdown. HADS-A= Hospital Anxiety and Depression Scale- Anxiety.



**Fig. 2.** Spearman- regression curves show variables with significant correlation. There was correlation of (A). Pittsburgh Sleep Quality Index (PSQI) with Hospital Anxiety Depression Scale - A (HADS-A) score; (B) PSQI with Myasthenia Gravis Quality of Life (MGQoL)-15, (C) Myasthenia Gravis Foundation of America (MGFA) stage with MGQoL-15; (D) MGFA stage with acetylcholine esterase inhibitor (AChEI) dose and E) MGQoL-15 with AChEI dose.

the lockdown. Three patients deteriorated - one had ptosis, one was excessively sedated following wrong medication (phenobarbitone) who deteriorated from stage IIIa to IIIb needing hospitalisation, and third patient developed myasthenic crisis requiring hospitalisation and non-invasive ventilation. Myasthenic crisis in the third patient was triggered by severe anxiety and insomnia for one month.

The median and Inter Quartile range (IQR) of total HADS score [6 (IQR 5, 7) vs 7 (IQR 5, 8);  $P = 0.001$ ] was increased after COVID 19 especially HADS-D score [2 (IQR 1, 3) vs 3 (IQR 2, 4);  $P < 0.001$ ]. Post COVID HADS-A total score although was reduced but tension, frightening feeling and panic were significantly higher after COVID (Fig. 1). Two patients had depression with caseness on the HADS (HADS-D > 11). The quality of sleep was also worsened during pandemic as evidenced by PSQI [median 4(IQR 3, 5) vs median 3 (IQR 2, 4);  $P < 0.001$ ]. Similarly MGQOL 15 (median 7.5 Vs 6.5;  $P = 0.036$ ) and MGADL [median 1 (IQR 0, 3) vs median 0.5 (IQR 0, 2);  $P < 0.001$ ] were also worsened during post-COVID period. The comparison of pre and post COVID scores is presented in Table 2.

**Correlation:** MGQOL15 correlated with PSQI ( $r = 0.33$ ;  $P = 0.04$ ), MGFA stage ( $r = 0.40$ ,  $p = 0.012$ ) and dose of AChEIs ( $r = 0.45$ ;  $P = 0.004$ ), Pittsburgh Sleep Quality Index also correlated with dose of AChEIs ( $r = 0.41$ ;  $P = 0.01$ ). Correlation between HADS-A and PSQI is trending to significance ( $r = 0.311$ ,  $P = 0.057$ ), while HADS-D score did not correlate with MGFA stage, MGQOL15, MGADL, PSQI, age, duration of illness, education or dose of AChEIs. The significant variables are shown in Fig. 2 and correlation data are presented in Table 3.

#### 4. Discussion

In this cohort of MG patients, the impact of COVID-19 pandemic and lockdown in India is contemporaneous with quality of life, the activity of daily living, sleep quality, and increased depression along with tension, frightening and panic. Anxiety and insomnia resulted in a myasthenic crisis in one, and another patient was admitted due to deterioration following the wrong medication. Though this error was not directly related to COVID 19 and lockdown, but had there been normal situation,



**Table 3**

Correlation (correlation co-efficient) of quality of life, activity of daily living, anxiety, depression and quality of sleep with various clinical parameters (r values are provided).

	HADS-A	HADS-D	PSQI	MGQOL15	MGADL	MGFA
HADS-A		.275	.311*	.231	-.003	.055
HADS-D	.275		.095	-.042	.157	-.134
PSQI	.311*	.095		.330*	.102	.182
MGQOL 15	.231	-.042	.330*		.171	.454**
MGADL	-.003	.157	.102	.171		.124
MGFA	.055	-.134	.182	.454**	.124	
Age	-.137	.125	-.042	.007	.212	.054
Duration of illness	-.193	.191	-.186	.222	-.031	.008
Prednisolone	.031	-.286	.090	.116	.207	.240
AChEIs	.234	.161	.294	.452**	.112	.412*
Education	-.057	-.116	-.041	-.116	-.103	.030

A = anxiety; AChEIs = acetyl choline esterase inhibitors; D= depression; HADS = Hospital Anxiety and Depression Scale; MGFA = Myasthenia Gravis Foundation of America; MG ADL = Myasthenia Gravis Activity of Daily Living; MGQOL = Myasthenia Gravis Quality of Life; PSQI = Pittsburgh Sleep Quality Index.

\* P < 0.05.

\*\* P < 0.01 (2 tailed).

the patient might have got correct medicine from our hospital pharmacy in follow up visit. Inability to procure drug due to close down of market also caused deterioration in one patient but did not require hospitalisation. This study comprehensively evaluated physical and mental health and quality of sleep in the patient with MG. We could compare effect of COVID-19 with pre-COVID data because the same cohort participated in a recently completed trial [16]. We have used telephonic interviews for evaluation of the impact of COVID-19 and lockdown. Some studies have validated telephonic interviews for evaluation of MGQOL, MGADL15, and HADS scales [23–25]. PSQI is a self-administered questionnaire; therefore, it could potentially be completed by the patient himself, through telephonic call or during a visit to the clinic.

A number of studies have reported COVID-19 infection in MG patients. Anand et al. reported 5 MG patients who acquired COVID-19 infection; two of them needed mechanical ventilation and one high flow oxygen. Two were treated with IVIg and one with tocilizumab. None of the patients however had deterioration in weakness [26]. Apart from isolated studies, COVID 19 Associated Risk and Effect in Myasthenia Gravis (CARE-MG) study has reported worsening/crisis in 36 out of 91 (40 %) patients requiring rescue therapy (intravenous immunoglobulin, plasmapheresis or steroids), 22(24 %) died and 39(43 %) patients were discharged [27]. None of our patients had COVID-19 infection during the initial 2 months, but one developed myasthenic crisis due to severe anxiety and insomnia. Emotional stress and insomnia might have depleted neurotransmitters leading to physical and mental fatigue [28]. Therefore, patients with MG should be considered as vulnerable group, and need health education regarding prevention of COVID 19, and counselling and psychological support. We have counselled our MG patients regarding masking, hand washing and physical distancing through dedicated “MG WhatsApp group” in which MG patients and treating physicians were included.

We have correlated HADS score with myasthenia status, but also age, years of schooling, duration of illness, hypertension, diabetes and dose of AChEIs, and steroids. Educated patients having long duration of illness may be able to follow preventive measures better. A number of co-morbidities have been reported in MG including thyroid disorder, autoimmune disease, pernicious anaemia, diabetes and hypertension. The older patients are having hypertension and diabetes more frequently which may be due to the association of age related increasing frequency of use of corticosteroid [29]. Moreover, lack of treatment

options and non-availability of vaccine are responsible for anxiety and depression [30,31]. In China, evaluation of health-related quality of life in general population revealed discomfort in 19 % and anxiety/depression in 17.6 %. The QOL was related to age, chronic disease, low income and worry about getting COVID infection [31]. COVID-19 infection has also affected different patient groups such as in patients with multiple sclerosis (MS); infection can cause more severe disease because of disease-modifying therapies that have immunosuppressive effects in MS patients [13]. Similarly in Parkinson disease, COVID-19 pandemic has also increased stress, depression and anxiety along with deterioration in quality of life, as compared to controls [15].

After the diagnosis, MG patients were briefed about the possible triggers of worsening and offending drugs. They were advised to come for follow up at regular interval; therefore, they were usually aware about the nature of disease and factor that precipitates worsening. Many of them experienced worsening due to infections in the past. All these factors might have resulted MG patients anxious and fearful. In our study, MG patients had worsening with respect to QOL, ADL, HADS and PSQI scores. The worsening in these parameters however was not related to age, but QOL and MGFA were related to the dose of AChEIs. Higher score in MGQOL suggests more severe illness, and likely to receive higher dose of AChEIs. PQSI score related to MGQOL, duration of MG and dose of AChEIs. Severely affected individuals are likely to receive high titrated dose of AChEIs and corticosteroid which may affect sleep [32,33]. Autoimmune MG needs longer immunosuppression.

The pooled prevalence of sleep disturbance in Chinese health worker was 39.2 %, [34], which has increased to 78.4 % in front line COVID-19 health workers and 51.7 % of them had insomnia. The present study supports that MG patients are also one of the vulnerable population groups for impact of COVID-19 pandemic and lockdown.

#### 4.1. Limitations

We have not compared the results of MG patients with normal controls and other vulnerable groups; rather we have compared their post COVID parameters with pre-COVID data. This might have given, more valid effect of COVID-19 pandemic and lockdown in these patients. The pre-COVID data are not from the immediate past but 4 months before to COVID. These patients however were on regular physical or telephonic consultation and were stable. Using self-reported questionnaire and collecting information over the phone are limitations, but we have also consulted caregivers if needed. The sample size is small because of the rarity of the disease and data are from a single centre. However, the strength of this study is the evaluation of pre and post COVID-19 effect by the same investigators (AT and ND), and the patients were from a homogenous socio-cultural background. This study does not address the interventions needed to avert the impact of this pandemic on physical and mental health; hence, more comprehensive interventional studies are required.

#### 4.2. Conclusion

In patients with MG, COVID 19 pandemic and lockdown have been associated with poor quality of life, impaired activity of daily living, and poor sleep quality. There is increased depression along with tension, frightening, and panic, especially in severe MG patients.

#### Credit author’s statement

**Jayantee Kalita:** Concept, formulation, execution, writing the script.

**Abhilasha Tripathi:** Data collection and analysis.

**Nikhil Dongre:** Data collection and analysis.

**Usha K Misra:** Supervision and language editing.

**Statistical analysis:** Abhilasha Tripathi has done the statistical analysis for this paper.

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## Ethical approval

This study was approved by the Institute Ethics Committee, SGPGIMS.

## Informed consent

Informed consent was obtained from all individual participants included in the study.

## Declaration of Competing Interest

The authors report no declarations of interest.

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