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Myasthenia Gravis-Activities of Daily Living (MG-ADL) score is the strongest predictor of the MG quality of life (MG-QoL15r) among the other clinical scales for myasthenia gravis: a cross-sectional study

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Abstract. Background: The increasing incidence worldwide of autoimmune diseases in general, including myasthenia gravis (MG), requires the recognition of the burden of these diseases on the quality of the patients' lives. Myasthenia gravis, with its unique fluctuating symptoms that exacerbate with effort, interferes greatly with daily life activities. The aim of this work is to study various factors that influence the quality of life in MG patients.
Methods: This is a cross-sectional study that included a sample of Egyptian MG patients attending Alexandria University hospital neuromuscular clinic. The recruited patients were evaluated clinically, using MG Foundation of America (MGFA) classification, the Quantitative Myasthenia Gravis (QMG) scale, the MG Composite (MGC) scale, the MG-Activities of Daily Living (MG-ADL), and the MG-Quality of Life 15 (MG-QoL15r). The data collected was analyzed to correlate between the different parameters and the MG-QoL15r total score.
Results: Forty-Five MG patients are included; of which thirty-five patients have acetylcholine receptors antibodies positive results. Various factors as neck and jaw weakness, long disease duration, high scores of the MG-ADL, MGC, QMG and more severe MGFA status were positively correlated with the MG-QoL15r total score. However, multivariant regression analysis showed that MG-ADL score is the sole strong predictor of the quality of life in MG patients.
Conclusion: MG-ADL score is the strongest predictor of the quality of life in MG patients among the other clinical scales of MG.

Keywords: Myasthenia Gravis, MG-QoL15r, quality of life, MGFA, MG-ADL.

Introduction

Myasthenia Gravis (MG) is an autoimmune disease, where autoantibodies target different components of the postsynaptic membrane of the neuromuscular junction (NMJ), impairing the neuromuscular transmission and leading to fluctuating weakness and fatigue of the skeletal muscles.[1,2] The symptoms can range from restricted ocular symptoms, mainly of ptosis and diplopia, to generalized fatigue, proximal weakness, dysphagia, nasal tone dysarthria, nasal regurgitation and dyspnea.[1–3]

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About 85% of generalized MG is attributed to the presence of acetylcholine receptor antibodies (AChR Ab) and the remaining are due to the presence of muscle specific kinase autoantibodies (Anti-Musk), low-density lipoprotein receptor-related protein 4 autoantibodies (Anti-LRP4) or other yet-to-be discovered autoantibodies. About 10–20% of MG is a paraneoplastic syndrome caused by thymomas.[1–3]

The global estimated incidence of MG ranges from 0.3 to 2.8 per 100,000. Most studies conducted in Europe addressing incidence rates showed a wide range from 4.1 to 30 cases per million person-years. [2,4,5] The global estimated prevalence is 10 per 100,000. In Egypt, the estimated prevalence of MG is 3.2 in Al Kharga district and 9.57 in Assiut per 100,000 people.[2,4,6–9] MG incidence and prevalence rates are believed to have increased worldwide over the past 50 years. Improvements in diagnosis leading to earlier recognition together with the improvements in treatment and the overall increase in life expectancy might be the cause.[2,4,6–8]

The age of onset varies to include all age groups, with peaks in younger adult women, with bimodal incidence rates peaking around the age of 30 and 50 in women, and older men with the highest rates between the age of 60 and 89. Before age of 40, female: male ratio is around 3:1 for early-onset MG (EOMG), with equal affection in women and men around the fifth decade and higher affection of men after age 50 demonstrating a male: female ratio of 3:2 for late-onset MG (LOMG). Moreover, around 10% of cases have a pediatric age of onset, which is before the age of 18.[2,3,10]

Knowing that MG is predominantly a disease of young adults and middle-aged adults during their most productive years of lives, special attention should be paid to the impact of the disease's symptoms on their daily life activities. Disease control and achieving complete remission should be the goal. However, complete remission in MG patients with no continuous need for immunotherapy is only seen in 10-20% of generalized MG patients, and in about 30% following thymectomy.[3,11]

Moreover, refractory MG is encountered in approximately 10-15% of generalized MG. Refractory MG is identified when failure of corticosteroids and one or two additional immunosuppressive agents of adequate dose and duration occurs or an ongoing need for the rescue therapies as intravenous immunoglobulins (IVIG) or plasma exchange is mandatory.[3,12,13] Treatment of refractory MG include highly efficacious DMTs as complement inhibitors, neonatal fragment crystallizable receptor (FcRn) modulators, rituximab and cyclophosphamide.[11–16]

Therefore, accurate assessment of the current MG disease status and its impact on the quality of life are necessary for choosing the best available therapeutic approaches to achieve disease remission or at least control of the most bothering symptoms as much as possible. Hence, the aim of this work is to study various factors that influence the quality of life in MG patients and to focus on how to modify them for the sake of a better quality of life.

Patients and Methods:

This is a cross-sectional study that was conducted on Egyptian MG patients attending Alexandria University hospital neuromuscular clinic, from September 2023 to February 2024.

Patients with clinically definite myasthenia gravis (MG), with none of the exclusion criteria mentioned below, were included. The diagnosis of myasthenia gravis in the recruited patients was based on the typical clinical features of fluctuating weakness in voluntary muscles and at least one of the following three supportive criteria; (a) positive response to neostigmine injection, (b) repetitive motor nerve stimulation (RNS) significant decrement of 10% or greater

or abnormal mean jitter or abnormal jitter in two muscle fibers on the single-fiber electromyography (SFEMG), or (c) Seropositive serology for anti-AChR or Anti-MuSk autoantibodies.[17]

Patients with comorbid neoplastic -other than thymoma- or other autoimmune diseases were excluded from this study. Ethical approval from the institutional ethics committee (number 0201746) was obtained in December 2022. Written informed consent from the patients were obtained as well.

Demographic and clinical data were collected, and the recruited patients were evaluated clinically, using MG Foundation of America (MGFA) classification, the Quantitative Myasthenia Gravis (QMG) scale, the MG Composite (MGC) scale, the MG-Activities of Daily Living (MG-ADL), and the MG-Quality of Life 15 (MG-QoL15r) in the same setting, after cessation of symptomatic anticholinesterase inhibitors medications for 12 hours as long as the patient's clinical status permits so.

The revised MG-QoL15 version consists of 15 questions with answers either 0,1, or 2 for each. Thus, total MG-QoL15r score ranges from 0 to 30, with the higher the score, the poorer is the quality of life.[18] MGFA classification is an ordinal scale of 5 categories of clinical severity ranging from ocular to myasthenic crisis and subdivisions of either extremity or bulbar weakness predominance.[19]

QMG and MGC scales are 13-item and 10-item scoring systems, respectively, of direct physician assessment of various MG symptoms.[20,21] MG-ADL scale is an 8-item patient-reported scale, with total MG-ADL score ranging from 0 to 24. It assesses the MG symptoms and their impact on daily life activities via a linear scoring on each item that ranges from 0 to 3. [21,22]

Tests as sustained upward gaze to provoke ptosis (up to >61 seconds), sustained horizontal gazes to provoke diplopia (up to >61 seconds), and outstretched arms (up to 240 seconds), head lift (up to 120 seconds), outstretched legs (up to 100 seconds) and hand grips, to test for weakness and induce fatigue, were done during applying the QMG scale.

The sample size for this study was calculated using G*Power software package (version 3.1.9.4, Department of Psychology, University of Düsseldorf, Düsseldorf, Germany, 2019), employing correlation analysis with a Pearson's correlation coefficient approach. The calculation was based on a coefficient of determination (R^2) of 0.1849, which represents the strength of the relationship between Myasthenia Gravis-Quality of Life (MG-QOL15) score and Myasthenia Gravis-Activities of Daily Living (MG-ADL) as reported by Diez Porras et al in 2022.[23] A statistical power of 80% and a 95% confidence level were set for the analysis. Based on these parameters, the minimum required sample size was determined to be 32 patients. The sample size was increased to 45 patients to enhance the precision of the results.

The data collected was analyzed and correlated with the MG-QoL15r total score, using IBM SPSS software package version 20.0 (Armonk, NY: IBM Corp).[24] Qualitative data were illustrated using number and percent. The normality of distribution was tested for using the Shapiro-Wilk test. Mean, standard deviation, range (minimum and maximum), median and interquartile range (IQR) were used to describe quantitative data. The results were considered significant at the 5% level. The used statistical tests included Chi-square test, Fisher's Exact or Monte Carlo correction test, Student t-test, F-test (ANOVA), Mann Whitney test, Kruskal Wallis test, Spearman coefficient and univariate and multivariate Linear Regression analysis.

Results:

Forty-Five patients with myasthenia gravis are included; of which thirty-five patients are AChR-MG, and ten patients tested seronegative for AChR-Ab. All the recruited patients are of

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the generalized type. The predominant sex is female (thirty-five patients; 77.8%). Thirteen patients (28.9%) have juvenile onset of the disease; before the age of 18, twenty-two patients (78.9%) have early onset MG (EOMG), three patients (6.7%) have late onset MG (LOMG), and seven patients (15.6%) have thymoma-associated MG (Table 1).

Table (1): Demographic and clinical data and comparison between the AChR seropositive and seronegative subgroups regarding the different parameters

Demographic data of the MG cases	Total cases (n = 45)		AchR +ve (n = 35)		AchR –ve (n = 10)		Test f sig.	p
	No.	%	No.	%	No.	%		
Sex								
Male	10	22.2	10	28.6	0	0.0	FET=3.673	0.058
Female	35	77.8	25	71.4	10	100.0		
Age (years)								
Min. – Max.	10.0 – 68.0		10.0 – 68.0		15.0 – 46.0		t= 0.326	0.746
Mean ± SD.	32.80 ± 14.13		33.17 ± 15.30		31.50 ± 9.49			
Median (IQR)	31.0 (20.0 – 43.0)		30.0 (20.0 – 43.0)		33.0 (27.0 – 37.0)			
Educational level								
Illiterate	12	26.7	11	31.4	1	10.0		
Primary	2	4.4	2	5.7	0	0.0		
Preparatory	7	15.6	6	17.1	1	10.0	FET =3.765	0.446
Secondary / diploma	16	35.6	10	28.6	6	60.0		
College / university	8	17.8	6	17.1	2	20.0		
Residency								
Alexandria	30	66.7	24	68.6	6	60.0	FET =0.257	0.710
Outside Alexandria	15	33.3	11	31.4	4	40.0		
Occupation								
Employed	9	20.0	9	25.7	0	0.0	c^2 =3.214	^{FE}p=0.173
Unemployed	36	80.0	26	74.3	10	100.0		
Marital status								
Single	13	28.9	9	25.7	4	40.0		
Married	31	68.9	25	71.4	6	60.0	FET =1.246	0.571
Divorced	1	2.2	1	2.9	0	0.0		
Age of onset of illness								
Min. – Max.	8.0 – 64.0		8.0 – 64.0		10.0 – 34.0			
Mean ± SD.	26.91 ± 14.33		28.51 ± 15.08		21.30 ± 10.03		U=130.50	0.228
Median (IQR)	23.0 (15.0 – 32.0)		23.0 (18.0 – 40.0)		19.50 (12.0 – 31)			
Age of onset of illness (categorized)								
Juvenile onset	13	28.9	8	22.9	5	50.0		
Early onset	27	60.0	22	62.9	5	50.0	c^2=3.020	^{FE}p=0.167
Late onset	5	11.1	5	14.3	0	0.0		
Duration of illness								
Min. – Max.	0.10 – 34.0		0.10 – 19.0		0.60 – 34.0			
Mean ± SD.	5.78 ± 6.74		4.55 ± 4.42		10.11 ± 11.03		U= 123.0	0.162
Median (IQR)	3.0 (2.0 – 6.0)		3.0 (1.75 – 5.0)		5.0 (3.0 – 18.0)			
MG Type according to age								
Juvenile MG	13	28.9	8	22.9	5	50.0		
EOMG	22	48.9	17	48.6	5	50.0	FET= 3.948	0.206
LOMG	3	6.7	3	8.5	0	0.0		
Thymoma-associated MG	7	15.6	7	20.0	0	0.0		

χ^2: Chi square test, FE: Fisher exact test, U: Mann Whitney test, t: student T test, IQR: **Inter quartile range**, SD: **Standard deviation,** p: p value for comparing between the two groups (**AchR +ve and –ve**)

The symptoms that the patients experienced include -in order according to frequency- diurnal variation (100%), fatigue (97.8%), ptosis (88.9%), nasal tone (88.9%), dysphagia (88.9%), extremity weakness (86.7%), diplopia (84.4%), nasal regurgitation (68.9%), mastication weakness (60%) and lastly neck weakness (46.7%). Seventeen patients (43.6%) experienced

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generalized symptoms at the onset of the disease, and the remaining (56.4%) had ocular symptoms at the beginning of illness, of which fourteen patients (35.9%) transitioned into generalized MG within the first year of illness, six patients (15.4%) transitioned within 1 to 3 years after the onset and two patients (5.1%) transitioned 4 and 6 years after the onset (Table 2). Five patients (11.1%) have a family history of MG, and six patients (13.3%) have family history of other autoimmune diseases including systemic lupus, rheumatoid arthritis and thyroiditis. Nine patients (20%) have comorbidities other than MG, including hypertension, diabetes, gout, ischemic heart disease and gastritis, some of which -in some patients- are comorbidities induced by steroids such as hypertension, diabetes, osteoporosis and gastritis reported in about four patients (8.9%) (Table 2).

Table (2): symptomatology and thymectomy history and comparison between the AChR seropositive and seronegative subgroups regarding these parameters:

Symptoms	Total cases (n = 45)		AchR +ve (n = 35)		AchR –ve (n = 10)		Test of sig.	p
	No.	%	No.	%	No.	%		
Symptoms experienced throughout the illness:								
Ptosis	40	88.9	32	91.4	8	80.0	c^2=1.029	^{FE}p=0.309
Diplopia	38	84.4	29	82.9	9	90.0	c^2=0.302	^{FE}p=1.000
Jaw weakness/ chewing	27	60.0	20	57.1	7	70.0	c^2=0.536	^{FE}p=0.716
Neck drop/ weakness	21	46.7	16	45.7	5	50.0	c^2=0.057	^{FE}p=1.000
Nasal tone	40	88.9	31	88.6	9	90.0	c^2=0.016	^{FE}p=1.000
Nasal regurgitation	31	68.9	25	71.4	6	60.0	c^2=0.474	^{FE}p=0.700
Dysphagia	40	88.9	31	88.6	9	90.0	c^2=0.016	^{FE}p=1.000
UL & LL weakness	39	86.7	30	85.7	9	90.0	c^2=0.124	^{FE}p=1.000
Fatigue	44	97.8	34	97.1	10	100.0	c^2=0.292	^{FE}p=1.000
Diurnal variation	45	100.0	35	100.0	10	100.0	–	–
Time for transition from ocular to generalized (in years)	**(n = 39)**		**(n = 30)**		**(n = 9)**			
At onset	17	43.6	13	43.3	4	44.4	FET=2.348	0.494
<1 year	14	35.9	12	40.0	2	22.2		
1 – 3 years	6	15.4	4	13.3	2	22.2		
>3 years	2	5.1	1	3.3	1	11.1		
Min. – Max.	0.0 – 6.0		0.0 – 4.0		0.0 – 6.0		H= 0.257	0.612
Mean ± SD.	0.65 ± 1.29		0.52 ± 1.02		1.06 ± 1.97			
Median (IQR)	0.10 (0.0 – 0.25)		0.10 (0.0 – 0.25)		0.25 (0.0 – 1.0)			
Consanguinity	13	28.9	9	25.7	4	40.0	c^2=0.773	^{FE}p=0.441
Family history of MG	5	11.1	4	11.4	1	10.0	c^2=0.016	^{FE}p=1.000
Family history of other autoimmune diseases	6	13.3	4	11.4	2	20.0	c^2=0.495	^{FE}p=0.601
Comorbidities	9	20.0	6	17.1	3	30.0	c^2=0.749	^{FE}p=0.393
Complications due to steroids	4	8.9	2	5.7	2	20.0	c^2=1.960	^{FE}p=0.209
Thymectomy								
No	19	42.2	14	40.0	5	50.0	χ^2= 0.319	^{FE}p= 0.720
Yes	**26**	**57.8**	**21**	**60.0**	**5**	**50.0**		
Duration between onset and thymectomy (years)	**(n=26)**		**(n=21)**		**(n=5)**			
< 6 months	6	23.1	6	28.6	0	0.0	FET= 3.517	0.299
6 months to <1year	4	15.4	4	19.0	0	0.0		
1 to <3 years	11	42.3	7	33.3	4	80.0		
≥3 years	5	19.2	4	19.0	1	20.0		
Min. – Max.	0.25 – 19.0		0.25 – 4.0		1.0 – 19.0		U= 36.00	0.308
Mean ± SD.	2.01 ± 3.65		1.37 ± 1.26		4.70 ± 8.0			
Median (IQR)	1.0 (0.30 – 2.0)		1.0 (0.30 – 2.0)		1.0 (1.0 –1.50)			

χ^2: Chi square test, FE: Fisher Exact test, , U: Mann Whitney test, H: Kruskal Wallis test , IQR: Inter quartile range, SD: Standard deviation, UL: upper limb, LL: lower limb, p: p value for comparing between the different groups

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Twenty-six patients (57.8%) had thymectomy, of which 10 patients (38.5%) underwent thymectomy within the first year of illness, another eleven patients (42.3%) within 1 to 3 years after the onset, and five patients (19.2%) underwent thymectomy much later. (Table 2)

The number of relapses or exacerbations experienced by the patients ranged from 0 to 10 relapses, and taking the duration of illness into consideration, the annualized relapse rate (ARR) ranged from 0 to 5 relapses/ year. The number of hospitalizations and intensive care unit (ICU) admission ranged from 0 to 10 times as well. However, only eight patients have experienced myasthenic crises, with the number of myasthenic crises and intubation ranging from 1 to 2 times per patient (Table 3).

Table (3): Relapse history and comparison between the AChR seropositive and seronegative subgroups regarding it

Clinical history of MG	Total cases (n = 45)		AchR +ve (n = 35)		AchR –ve (n = 10)		Test of sig.	p
	No.	%	No.	%	No.	%		
No. of relapses/ exacerbations								
Min. – Max.	0.0 – 10.0		1.0 – 10.0		0.0 – 9.0			
Mean ± SD.	3.71 ± 2.42		5.10 ± 3.21		3.31 ± 2.03		U =126.50	0.189
Median (IQR)	3.0 (2.0 – 5.0)		5.0 (2.0 – 8.0)		3.0 (2.0 – 4.5)			
Annualized Relapse Rate (ARR)								
Min. – Max.	0.0 – 5.0		0.03 – 3.03		0.0 – 5.0			
Mean ± SD.	1.12 ± 0.93		1.18 ± 0.95		1.10 ± 0.94		U =164.50	0.778
Median (IQR)	1.0 (0.45 – 1.77)		1.03 (0.45 – 1.75)		1.0 (0.46 – 1.63)			
Hospitalization	**(n = 45)**		**(n = 35)**		**(n = 10)**			
No	29	64.4	24	68.6	5	50.0	c^2 =1.171	^{FE}p=0.455
Yes	**16**	**35.6**	**11**	**31.4**	**5**	**50.0**		
No. of hospitalizations due to relapses	**(n = 16)**		**(n = 11)**		**(n = 5)**			
Min. – Max.	1.0 – 10.0		1.0 – 10.0		1.0 – 3.0			
Mean ± SD.	2.0 ± 2.25		2.80 ± 4.02		1.64 ± 0.81		U= 23.0	0.661
Median (IQR)	1.0 (1.0 – 2.0)		1.0 (1.0 – 2.0)		1.0 (1.0 – 1.0)			
No. of ICU admission due to relapses	**(n = 16)**		**(n = 11)**		**(n = 5)**			
Min. – Max.	1.0 – 10.0		1.0 – 10.0		1.0 – 3.0			
Mean ± SD.	2.0 ± 2.25		2.80 ± 4.02		1.64 ± 0.81		U=23.0	0.661
Median (IQR)	1.0 (1.0 – 2.0)		1.0 (1.0 – 2.0)		1.0 (1.0 – 1.0)			
Myasthenic crises	**(n = 16)**		**(n = 11)**		**(n = 5)**			
No	8	50.0	6	54.5	2	40.0	c^2=0.291	^{FE}p=1.000
Yes	**8**	**50.0**	**5**	**45.5**	**3**	**60.0**		
No. of myasthenic crises / No. of times of intubation	**(n = 8)**		**(n = 5)**		**(n = 3)**			
Min. – Max.	1.0 – 2.0		1.0 – 2.0		1.0 – 1.0		U= 6.0	0.786
Mean ± SD.	1.13 ± 0.35		1.20 ± 0.45		1.0 ± 0.0			
Median (IQR)	1.0 (1.0 – 1.0)		1.0 (1.0 – 1.0)		1.0			

χ^2: Chi square test, FE: Fisher exact test, U: Mann Whitney test, IQR: **Inter quartile range,** SD: **Standard deviation**
p: p value for comparing between the different groups

About 95% of patients were on pyridostigmine, 84.4% of patients on steroids, and 77.8% currently on disease modifying therapy (DMT). The total duration of being on a steroid-sparing therapy in the recruited patients ranged from a few months to 8 years (Table 4).

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Table (4): Drug history of MG and comparison between the AChR seropositive and seronegative subgroups regarding the medications

Drug history of MG	Total cases (n = 45)		AchR +ve (n = 35)		AchR –ve (n = 10)		Test of sig.	p
	No.	%	No.	%	No.	%		
Pyridostigmine								
No	2	4.4	1	2.9	1	10.0	χ^2 =	^{FE}p=
Yes	**43**	**95.6**	**34**	**97.1**	**9**	**90.0**	0.934	0.399
Pyridostigmine Dose	**(n = 43)**		**(n = 34)**		**(n = 9)**			
Min. – Max.	120.0 – 960.0		120.0 – 960.0		180.0 – 720.0			
Mean ± SD.	341.9 ± 187.3		349.41 ± 192.86		313.3 ± 171.8		U= 0.279	0.597
Median (IQR)	300.0 (180.0 – 450.0)		330.0(180.0 – 480.0)		300.0 (180 - 300)			
Steroids								
No	7	15.6	5	14.3	2	20.0	χ^2 =	^{FE}p=
Yes	**38**	**84.4**	**30**	**85.7**	**8**	**80.0**	0.193	0.642
Steroids Dose								
Min. – Max.	1.0 – 80.0		10.0 – 80.0		1.0 – 60.0			
Mean ± SD.	30.36 ± 21.02		33.50 ± 20.73		18.56 ± 18.81		U = 65.50	0.050
Median (IQR)	20.0 (3.13 – 20.0)		20.0 (20.0 – 50.0)		20.0 (3.75 – 20.0)			
DMTs								
Patients on current DMTs								
No	10	22.2	7	20.0	3	30.0	χ^2 =0.450	^{FE}p=0.668
Yes	**35**	**77.8**	**28**	**80.0**	**7**	**70.0**		
Azathioprine	21	46.7	20	57.1	1	10.0	χ^2 =6.945*	^{FE}p=0.012*
Mycophenolate mofetil	6	13.3	4	11.4	2	20.0	χ^2 =0.495	^{FE}p=0.601
Methotrexate	5	11.1	3	8.6	2	20.0	c^2=1.029	^{FE}p=0.306
Rituximab	3	6.7	1	2.9	2	20.0	c^2=3.673	^{FE}p=0.119
Patients not on current DMTs	**(n= 10)**		**(n= 7)**		**(n= 3)**		c^2=	^{FE}p=1.000
Drug naïve	5	50.0	3	42.9	2	66.7	0.476	
DMT stopped for > 3 months	5	50.0	4	57.1	1	33.3		
Duration of current DMTs								
Min. – Max.	0.20 – 6.0		0.20 – 6.0		0.50 – 3.0			
Mean ± SD.	1.89 ± 1.55		1.93 ± 1.67		1.71 ± 0.99		U= 93.50	0.851
Median (IQR)	1.50 (0.50 – 3.0)		1.25 (0.50 – 3.0)		1.50 (1.0 – 2.50)			
No of DMTs tried								
Min. – Max.	0.0 – 3.0		0.0 – 3.0		0.0 – 2.0			
Mean ± SD.	1.02 ± 0.54		1.03 ± 0.51		1.0 ± 0.67		U=	0.989
Median (IQR)	1.0 (1.0 -1.0)		1.0 (1.0 – 1.0)		1.0 (1.0 – 1.0)		174.0	
History of other previous DMTs								
No	36	80.0	29	82.9	7	70.0	c^2=0.804	^{FE}p=0.393
Yes	**9**	**20.0**	**6**	**17.1**	**3**	**30.0**		
Total duration of steroid sparing DMT (years)								
Min. – Max.	0.20 – 8.0		0.20 – 6.0		0.50 – 8.0			
Mean ± SD.	2.10 ± 1.78		2.02 ± 1.60		2.44 ± 2.46		U=	0.778
Median (IQR)	1.75 (0.50 – 3.0)		1.75 (0.50 – 3.0)		1.75 (0.70 – 3.0)		119.00	

χ^2: Chi square test , FE: Fisher exact test , IQR: **Inter quartile range,** SD: **Standard deviation, U: Mann Whitney test, DMT: disease modifying therapy,** p: p value for comparing between the different groups

*: Statistically significant at $p \leq 0.05$

The current MG foundation of America classification (MGFA) status of the recruited

patients revealed 24 patients (53.3%) having MGFA classes I or II; mild disease condition, and 21 patients (46.7%) having MGFA classes III (moderate) or IV (severe). Total scores of QMG, MGC, MG-QoL15r and MG-ADL were estimated and a comparison between the AChR Ab seropositive and seronegative subgroups revealed no statistically significant difference. (Table 5)

Total QMG score ranged from 4 to 31, with a mean of 14.58. Total MG composite score ranged from 0 to 31, with a mean of 12.47. MG-ADL total score ranged from 0 to 17, with a mean of 7.31. The MG-QoL15r total score ranged from 1 to 30, with a mean of 17.56. There were no significant differences between the AChR Ab seropositive and seronegative groups regarding the total scores of these clinical severity scales (Table 5).

Table (5): Comparison between the AChR seropositive and seronegative subgroups according to clinical assessment of MG cases

Clinical assessment of MG cases	Total cases (n = 45)		AchR +ve (n = 35)		AchR –ve (n = 10)		Test of sig.	p
	No.	%	No.	%	No.	%		
MGFA classification								
I	9	20.0	7	20.0	2	20.0		
IIa	11	24.4	7	20.0	4	40.0		
IIb	4	8.9	3	8.6	1	10.0		
IIIa	8	17.8	6	17.1	2	20.0	FET = 3.443	0.680
IIIb	12	26.7	11	31.4	1	10.0		
Iva	0	0.0	0	0.0	0	0.0		
IVb	1	2.2	1	2.9	0	0.0		
MGFA classification								
I to II	24	53.3	17	48.6	7	70.0	c^2=1.435	^{FE}p = 0.296
III to IV	21	46.7	18	51.4	3	10.0		
QMG Total score								
Min. – Max.	4.0 – 31.0		4.0 – 22.0		9.0 – 31.0		**t** = 1.282	0.207
Mean ± SD.	14.58 ± 5.42		14.03 ± 5.0		16.50 ± 6.60			
Median (IQR)	15.0 (10 – 19)		14 (10.5 –18.5)		16.0 (10 –19)			
MG composite Total score								
Min. – Max.	0.0 – 31.0		0.0 – 26.0		4.0 – 31.0		**t** = 0.556	0.581
Mean ± SD.	12.47 ± 6.61		12.17 ± 6.29		13.50 ± 7.89			
Median (IQR)	12.0 (8 – 17)		12.0 (8 – 17)		12.50 (7 –17)			
MG-ADL Total score								
Min. – Max.	0.0 – 17.0		0.0 – 17.0		4.0 – 13.0		**t** = 0.678	0.502
Mean ± SD.	7.31 ± 3.62		7.11 ± 3.78		8.0 ± 3.09			
Median (IQR)	8.0 (4 – 10)		8.0 (4 – 9.5)		7.0 (6 – 10)			
MG-QoL15r Total score								
Min. – Max.	1.0 – 30.0		1.0 – 30.0		5.0 – 27.0		U = 173.50	0.968
Mean ± SD.	17.56 ± 8.30		17.34 ± 8.69		18.30 ± 7.13			
Median (IQR)	20.0 (13.0 – 24.0)		21.0 (13.0 – 24.0)		19.0 (12.0 – 25.0)			

t: Student t test, FET: Fisher exact test, χ^2: Chi square test, U: Mann Whitney test, IQR: **Inter quartile range**, SD: **Standard deviation,** p: p value for comparing between the two groups (**AchR +ve and –ve**)

Unemployed MG patients; consisting of 22 housewives, 5 students, 3 patients left their jobs due to MG symptoms, and 6 patients were unemployed from the start, were significantly associated with higher total scores of MG-QoL15r, compared with the employed MG patients. Similarly, late age of onset of MG, neck and/or jaw weakness and moderate and severe MGFA classes were associated with higher total scores of MG-QoL15r (Table 6).

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Table (6): Relation between Total of quality of life and different parameters for total MG patients' sample (n = 45)

Total sample (n = 45)	N	Total of quality of life			Test of sig.	p
		Min. – Max.	Mean ± SD.	Median		
Sex						
Male	**10**	2.0 – 28.0	14.10 ± 7.74	14.0	**U**= 120.000	0.139
Female	**35**	1.0 – 30.0	18.54 ± 8.30	21.0		
Educational level						
Illiterate	**12**	2.0 – 28.0	20.83 ± 7.22	23.0	H= 4.939	0.294
Primary	**2**	14.0 – 17.0	15.50 ± 2.12	15.50		
Preparatory	**7**	1.0 – 30.0	12.71 ± 9.88	11.0		
Secondary / diploma	**16**	1.0 – 26.0	17.44 ± 7.89	20.50		
College / university	**8**	1.0 – 27.0	17.63 ± 9.52	20.0		
Residency						
Alexandria	**30**	1.0 – 27.0	17.0 ± 8.29	18.50	**U**= 202.000	0.579
Outside Alexandria	**15**	1.0 – 30.0	18.67 ± 8.51	22.0		
Occupation						
Employed	**9**	1.0 – 23.0	11.11 ± 7.39	13.0	**U**= 72.500*	0.009*
Unemployed	**36**	1.0 – 30.0	19.17 ± 7.80	21.50		
Age of onset of illness (categorized)						
Juvenile and Early onset <50 ears	**40**	1.0 – 27.0	16.70 ± 8.22	19.0	**U**=161.000*	0.026*
Late onset >50 years	**5**	15.0 – 30.0	24.40 ± 5.77	25.0		
Steroids						
-On steroids	**38**	1.0 – 30.0	17.03 ± 8.70	19.50	**U**= 106.500	0.415
-Off steroids	**7**	13.0 – 25.0	20.43 ± 5.22	22.0		
Patients on current DMTs						
No	**10**	6.0 – 27.0	17.30 ± 6.27	17.50	**U**= 155.000	0.600
Yes	**35**	1.0 – 30.0	17.63 ± 8.88	21.0		
Thymectomy						
No	**19**	5.0 – 30.0	17.63 ± 8.08	19.0	**U**= 245.500	0.972
Yes	**26**	1.0 – 27.0	17.50 ± 8.62	20.50		
MGFA classification						
I to II	**24**	1.0 – 26.0	14.92 ± 8.75	16.0	**U**= 153.000*	0.024*
III to IV	**21**	6.0 – 30.0	20.57 ± 6.76	22.0		
Comorbidities						
No	**36**	1.0 – 27.0	16.44 ± 8.30	19	**U**= 229.500	0.054
Yes	**9**	7.0 – 30.0	22.00 ± 7.09	25		
Reported symptoms throughout the illness						
Ptosis					**U**= 73.500	0.349
No	**5**	11.0 – 25.0	21.20 ± 5.93	24.0		
Yes	**40**	1.0 – 30.0	17.10 ± 8.50	19.0		
Diplopia						
No	**7**	7.0 – 23.0	16.43 ± 5.56	18.0	**U**= 106.500	0.415
Yes	**38**	1.0 – 30.0	17.76 ± 8.76	21.0		
Jaw weakness/ chewing						
No	**18**	1.0 – 26.0	13.56 ± 8.70	15.50	**U**= 125.000*	0.006*
Yes	**27**	6.0 – 30.0	20.22 ± 6.98	23.0		
Neck drop/ weakness						
No	**24**	1.0 – 26.0	13.83 ± 7.97	14.0	**U**= 96.000*	<0.001*
Yes	**21**	6.0 – 30.0	21.81 ± 6.56	24.0		
Nasal tone						
No	**5**	17.0 – 26.0	21.80 ± 3.42	21.0	**U**= 74.000	0.368
Yes	**40**	1.0 – 30.0	17.03 ± 8.60	19.0		
Nasal regurgitation						
No	**14**	1.0 – 26.0	15.79 ± 9.29	18.0	**U**= 181.000	0.377
Yes	**31**	1.0 – 30.0	18.35 ± 7.85	21.0		
Dysphagia						
No	**5**	8.0 – 26.0	19.20 ± 7.12	21.0	**U**= 90.000	0.739
Yes	**40**	1.0 – 30.0	17.35 ± 8.50	19.50		
UL & LL weakness						
No	**6**	1.0 – 28.0	10.50 ± 9.73	7.0	**U**= 62.500	0.068
Yes	**39**	1.0 – 30.0	18.64 ± 7.63	21.0		

SD: Standard deviation, U: Mann Whitney test, H: H for Kruskal Wallis test. p: p value for comparing between the studied groups, *: Statistically significant at $p \leq 0.05$

Furthermore, longer disease duration, more frequent relapses, higher daily dose of pyridostigmine, higher number of DMTs tried throughout their illness, and higher total scores

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of the MG-ADL, MGC, and QMG scales were positively correlated with the higher total scores of MG-QoL15r (Table 7).

Table (7): Correlation between total of quality of life and different parameters for total MG patients' sample (n = 45)

	Total of quality of life	
	r_s	P
Age (years)	0.202	0.183
Age of onset of illness	0.145	0.342
Duration of illness	0.296*	0.049*
Time for transition from ocular to generalized (in years)	0.059	0.722
No of relapses/ exacerbations	0.297*	0.048*
ARR	-0.045	0.771
No of hospitalizations dt relapses	-0.021	0.938
No of ICU admission dt relapses	-0.021	0.938
No of myasthenic crises / No of times of intubation	0.249	0.552
Pyridostigmine Dose	0.355*	0.020*
Steroids Dose	0.125	0.455
Dose of Azathioprine	0.079	0.735
Duration of current DMTs	0.163	0.349
No of DMTs tried	0.349*	0.019*
Total duration of steroid sparing DMT (years)	0.235	0.144
Duration between onset and thymectomy (years)	0.164	0.422
MGFA grading	0.468*	0.001*
Total MG composite score	0.687*	<0.001*
Total MG-ADL score	0.748*	<0.001*
Total QMG score	0.398*	0.007*
QMG parameters (timer)		
Upward gaze/ ptosis	-0.029	0.851
Double vision	-0.248	0.101
Outstretched arms		
Right	-0.286	0.057
Left	-0.246	0.103
Outstretched legs		
Right	-0.313*	0.036*
Left	-0.369*	0.013*
Head lift	-0.250	0.098
Hand grip		
Right	-0.173	0.257
Left	-0.223	0.140

r_s: Spearman coefficient

*: Statistically significant at $p \leq 0.05$

Using univariate linear regression analysis, unemployed MG patients, late onset MG patients, and patients with jaw and/or neck weakness, higher pyridostigmine dose, and history of more than one DMT tried, shorter recorded time on the left QMG outstretched leg test, and/or higher total scores of QMG, MGC and MG-ADL scales were strongly associated with poor quality of life in MG patients. Multivariant regression analysis showed that MG-ADL score is the strongest predictor of the quality of life in MG patients (Table 8).

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Table (8): Univariate and multivariate Linear analysis for the parameters affecting quality of life for total cases (n = 45)

Quality of life	Univariate		#Multivariate	
	p	B(95%C.I)	P	B (95%C.I)
Occupation	**0.008***	8.056 (2.250 – 13.861)	**0.313**	2.888 (-2.847 – 8.624)
Late onset MG	**0.049***	7.700 (0.023 – 15.377)	**0.823**	0.850 (-6.835 – 8.534)
MGFA grading	**0.001***	4.951 (2.214 – 7.688)	**0.894**	0.126 (-1.782 – 2.035)
Jaw weakness/ chewing	**0.007***	6.667 (1.938 – 11.395)	**0.984**	-0.050 (-4.924 – 4.824)
Neck drop/ weakness	**0.001***	7.976 (3.549 – 12.403)	**0.349**	2.491 (-2.845 – 7.828)
Duration of illness	**0.287**	0.200 (-0.174 – 0.573)		
No of relapses/ exacerbations	**0.054**	0.992 (-0.019 – 2.003)		
Pyridostigmine dose	**0.005***	0.017 (0.005 – 0.029)	**0.932**	0.001 (-0.012 – 0.013)
No of DMTs tried	**0.042***	4.658 (0.179 – 9.136)	**0.235**	2.543 (-1.733 – 6.820)
Outstretched legs				
Right leg	**0.092**	-0.074 (-0.160 – 0.013)		
Left leg	**0.049***	-0.093 (-0.186 – 0.000)	**0.606**	-0.023 (-0.113 – 0.067)
Total QMG	**0.002***	0.688 (0.267 – 1.109)	**0.824**	-0.075 (-0.753 – 0.603)
Total MG composite	**<0.001***	0.824 (0.532 – 1.116)	**0.668**	-0.196 (-1.115 – 0.724)
Total MG ADL	**<0.001***	1.718 (1.251 – 2.184)	**0.022***	1.611 (0.251 – 2.972)

B: Unstandardized Coefficients
C.I: Confidence interval
#: All variables with p<0.05 was included in the multivariate
*: Statistically significant at p ≤ 0.05

Discussion

The recruited sample showed female predominance, with a female to male ratio of 3.5: 1, which is corresponding to the worldwide ratios.[2,10] Regarding the age of onset, pediatric onset in the recruited sample (28.9%) was higher than the usual reported percentage of the juvenile MG as 10-11% of all MG cases.[2,25] Thymoma-associated MG was found in 15.6% of the recruited sample, which is nearly corresponding to the percentage of paraneoplastic MG worldwide reported as 10-20% of MG patients.[2,3,26]

Transition of ocular to generalized myasthenia occurred in about 56.4% of the patients, mostly within 3 years after the onset of MG. However, two patients converted into the generalized type over 4-6 years. It's reported that 40-70% of ocular MG will convert into the generalized typer within 2 years of the onset, and about additional 5% will convert as well much later, while the rest remain with isolated ocular involvement.[2,3]

Eleven percent of the patients have a family history of MG, which is close to the previous studies' reported range of 1–7.1%.[26–29] Another multicentric study of 1032 MG patients showed that 5.6% of myasthenic patients reported a family history of MG and 26.6% reported a family history of autoimmune disease.[30] Our study showed that six patients (13.3%) of MG patients having a family history of autoimmune diseases other than MG, of which one patient has both a family history of MG and another autoimmune disease. A population-based study confirmed that the relatives of MG patients have an increased risk of MG and other autoimmune diseases

and showed a relative risk (RR) for MG of 17.85 in patients' siblings, and 5.33 and 5.82 for parents and offspring respectively.[27]

Comorbidities were found in 9 patients (20%) and four patients (8.9%) reported comorbidities induced by steroids. Several studies pointed out the different comorbidities that the myasthenic patients might have and reported wide ranges of 15 to 70% of MG patients having comorbidities.[31,32] On the other hand, other studies marked specifically the adverse effects of the long steroid therapy in MG patients, with the most two common comorbidities being prediabetes and weight gain, each reported in 43.6% of MG patients.[33,34]

Prior studies mostly showed that shorter duration of illness (<24 months) before undergoing thymectomy for non-thymomatus MG as well as younger age were associated with better outcome.[3,35,36] Most of our patients, who underwent thymectomy in our study, had thymectomy within the first three years of illness (80.8%).

There was no significant difference between AChR Ab seropositive and seronegative patients regarding MGFA classification, MG-ADL, MGC or QMG scales in the recruited patients. This is consistent with several studies that showed no difference regarding the disease severity between the seronegative MG and AChR MG.[2,26,37–39]

Mean MG-QoL15r total score ± standard deviation (SD) values (17.56 ± 8.30) were higher in our results than those of most of the other studies, maybe the generalized nature of all the included MG patients was a reason. For example, the mean total MGQOL15r scores in two Indian studies were 6.52 ± 7.7 and 10.34 ± 9.4, however, in the same studies, in severe generalized MG (MGFA – IV) subgroup the mean total score reached 25 ± 2.8.[40,41] In our study, mean MG-QoL15r scores were 14.92 ± 8.75 in MGFA classes I and II, and 20.57 ± 6.76 MGFA classes III and IV, with a statistically significant difference between both subgroups.

Aggelina et al. study in Greece reported a mean MG-QoL15r total score and an SD in all patients (13.50 ± 7.70.) and in generalized MG (14.60 ± 7.30) and mentioned a statistically significant worse MG-QoL15r total scores in generalized MG compared to ocular MG, however their study reported a statistically significant worse MG-QoL15r total scores as well in patients with history of myasthenic crisis compared to others who didn't experience a myasthenic crisis.[42]

Although the range of MG-QoL15r total scores, as well as the mean, were higher in patients with history of myasthenic crisis (min.-max.: 7-30, mean ± SD 20.5 ± 6.95, median 20.5) compared to those without (min.-max.: 1-28, mean ± SD 16.9 ± 8.52, median 20.0) in our study, no statistically significant difference was found (P=0.372). This might be due to the smaller sample size. Instead, a positive correlation was found with the number of relapses/ exacerbations and the MG-QoL15r total scores.

No significant difference between males and females was found regarding the MG-QoL15r total score, unlike Lee et al. study where the MG-QOL15r was worse in women compared with men, however Lee et al. found this difference is eliminated when comparing women who underwent thymectomy with men. Thus, maybe the fact that more than half our patients have underwent thymectomy explains this.[43]

Szczudlik et al. assessed quality of life in MG patients and similarly revealed that it was affected by the clinical severity, and also was reduced in unemployed patients and late age of onset MG. Szczudlik et al. showed that employed MG patients showed better physical and mental subscores in QoL SF-36 questionnaire compared to the unemployed patients.[44] Other studies as well showed a reduced quality of life in late onset MG.[45,46]

Other findings indicated that neck dropping and chewing difficulties were significantly associated with higher MG-QoL15r total scores compared with other patients who didn't

report such symptoms. Boldingh et al. showed also lower quality of life particularly in MG patients with bulbar symptoms.[47]

Longer duration of illness was found to be associated with higher MG-QoL15r total scores, denoting worse quality of life. Al-Ahmer et al. studied improvements in QOL and QMG in MG patients after plasmapheresis therapy and found greater improvement was significantly associated with shorter duration of the illness among other factors.[48]

Moreover, higher MG-QoL15r scores was positively correlated in our study with increased number of relapses, higher number of DMTs tried including refractory MG status, and higher daily doses of pyridostigmine, which denotes an uncontrolled symptomatic MG condition. Similarly, Alanzy et al. found similar factors significantly affecting MGQoL15R score as relapse within the last year, uncontrolled MG status, and higher number of current MG therapies.[49]

Several studies addressed the burden of refractory MG on the quality of life.(50,51) Boscoe et al. declared that refractory MG patients, who had received ≥2 previous and 1 current MG immunosuppressant therapy and had MG-ADL total score of ≥6, showed significantly higher mean MG-QOL15 total scores compared with non-refractory MG patients.[52]

A strong correlation and significant univariate regression analysis between the MG-QoL15r score and the other clinical severity scales were found in our MG patients. Burns et al., Yang et al., Mourao et al. and Kumar et al. studies also found similar correlations between MG-QOL15 score and MG-ADL, MGC, QMG and MFGA classification.[23,41,45,46,53–56]

In our study, multivariate regression analysis found that among all the factors with an impact on the MG-QoL15r total scores, MG-ADL total score was significantly the strongest predictor of the MG-QoL15r. MG-ADL is a patient-reported scale that addresses the impact of each MG symptom on daily life activities, which makes it correlate very well with the quality of life, and also makes it a useful tool to focus on the symptoms that bother the patient the most, aiming at including therapeutic or other assessment tools specific to such symptoms. For example, using a detailed deglutition assessment and rehabilitation program -if there are residual swallowing difficulties till a newly introduced therapeutic agent becomes effective- could contribute to improving the quality of life and daily life activities.

Yet, the small sample size and the unicentric nature of this study are limitations, which might call for further multicentric studies of larger sample sizes and prospective design for better understanding all possible predictors of the quality of life in MG patients and how to modify them.

In conclusion, our study found a significantly reduced quality of life in unemployed MG patients, late onset MG patients, and patients suffering of neck and/or jaw weakness, and clinically severe forms of the disease. The latter includes moderate and severe MGFA classes, longer disease duration, frequent relapses, frequent daily doses of pyridostigmine, more than one DMT tried, and higher total scores of the MG-ADL, MGC, and QMG scales, among which the MG-ADL scale was the strongest influencing factor. Special attention to these specific MG patient groups is required, using effective therapeutic interventions to improve their quality of life and reduce the physical, psychological and financial burden of the disease on MG patients.[57]

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Authors' contributions:

- H.S.A: Data collection, writing of the manuscript and the corresponding author.
- S.M.S: contributed to the idea of the research and revision of the results.
- H.M.M: contributed to the idea of the research.
- M.H.A: contributed to the idea of the research and revision of the writing.

All authors declare that the manuscript is originally written and that there's no data falsification.

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