Gender differences in clinical outcomes in myasthenia gravis

A prospective cohort study

Thomsen, Jan L.S.; Vinge, Lotte; Harbo, Thomas; Andersen, Henning

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FOR PEOPLE LIVING WITH **POMPE DISEASE,**

Not a real patient.

MOBILITY CAN'T TAKE A DAY OFF

People living with late-onset Pompe disease (LOPD) face obstacles that may challenge their well-being and livelihood. A 2011 Dutch survey of LOPD patients showed[1,2]:

40% (n=32/80) stopped working due to their disease

85% required support from more than 1 caregiver to help with household tasks such as cleaning and grocery shopping

As Pompe disease progresses, it can lead to irreversible loss of mobility, respiratory function, and ability to perform daily activities, as well as premature death.[3,4] In a 2007 international study[5]*:

42% of patients with LOPD depended on a wheelchair

46% required respiratory support

Regular evaluation is recommended in patients with Pompe disease to assess for disease progression and to understand the impact on daily activities and lifestyles.[3]

Explore Pompe disease and its impact on patients at

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*Mean disease duration of patients studied was 11 years.

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Thomsen Jan Lykke Scheel (Orcid ID: 0000-0003-2238-0406)

Gender differences in clinical outcomes in myasthenia gravis. A prospective cohort study

Authors: Jan L. S. Thomsen[1,2], MD; Lotte Vinge[2], MD, PhD; Thomas Harbo[1], MD, PhD; Henning Andersen[1], MD, DMSc

[1] Aarhus University Hospital, Department of Neurology, Aarhus, Denmark

[2] Aalborg University Hospital, Department of Neurology, Aalborg, Denmark

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Corresponding author:

Jan Lykke Scheel Thomsen, MD

Department of Neurology, Aarhus University Hospital

Palle Juul-Jensens Boulevard 165, DK-8200 Aarhus.

E-mail: jathms@rm.dk

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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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Jan Lykke Scheel Thomsen has received a speaking fee from Alexion. Henning Andersen has received research funding from Sanofi Genzyme and CSL Behring, travel funding and speaking fees from Novo, Alexion, Sanofi Genzyme, Octapharma and CSL Behring and served as consultant on the advisory board for NMD Pharma. The remaining authors have no conflicts of interest.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Gender differences in clinical outcomes in myasthenia gravis. A prospective cohort study

Abstract

Introduction/Aims

It is uncertain whether clinical outcomes differ between male and female patients with myasthenia gravis (MG) while receiving standard clinical care.

Methods

In a prospective cohort study of 107 patients with MG receiving standard of care from 2012 to 2019, the Quantitative MG (QMG), the MG Composite (MGC), the MG Activities of Daily Living (MG-ADL), and the MG Quality of Life 15-items (QOL15) were determined. Clinical outcomes were analyzed in relation to gender.

Results

Mean follow-up time was 4.8 (±0.4) years, and 70 patients completed all follow-up assessments. Patients improved on all clinical scores: QMG -1.8 (P<0.001), MGC -1.5 (P<0.001), MG-ADL -1.3 (P<0.001) and QOL15 -3.0 (P<0.001). Females improved less than males on the QMG (P=0.01), MGC (P<0.001), MG-ADL (P=0.006) and QOL15 (P<0.001) independent of potential confounders. Males had moderate to strong correlations between changes in all clinical scales (*r* range 0.52 to 0.73), whereas females had weak correlations between changes in the QMG and MG-ADL (*r*=0.13), the QMG and QOL15 (*r*=0.27), the

MGC and MG-ADL (r=0.21), the MGC and QOL15 (r=0.00), and the MG-ADL and QOL15 (r=0.31).

Discussion

Females improved less compared to males on objective and patient-reported outcomes. Moreover, females improved more on objective measures than on patient-reported outcomes. These gender differences should receive attention in clinical care and in the design of future trials.

Keywords: myasthenia gravis, outcome, gender, prospective, treatment

Introduction

Myasthenia gravis (MG) is an autoimmune neuromuscular disease with a heterogenous clinical presentation and course[1]. Severity of MG is assessed using validated objective clinical scales and patient-reported assessment tools. The most widely used include the Quantitative MG (QMG)[2](objective), the MG Composite (MGC)[3](composite), the MG Activities of Daily Living (MG-ADL)[4](patient-reported) and the MG Quality of Life 15-items (QOL15)[5,6](patient-reported). Female gender is more prevalent in patients with early-onset disease[1]. Furthermore, studies suggest that patient-reported outcome scores are more severe in females with MG[7–9] and females more often have refractory disease[10–12]. However, firm conclusions are limited due to cross-sectional and retrospective designs, patient-reported data collection, insufficient adjustments for potential confounders, or lack of objective assessments of the MG disease burden. Prospective studies examining gender differences in clinical outcomes are needed to establish whether females with MG improve less. This knowledge may identify unmet needs in the current management of MG and highlight a group of patients in whom persistent deficits increase the socioeconomic burden[13]. Further, identification of gender differences in clinical outcomes may help to optimize clinical trial design and thus increase the likelihood of demonstrating clinical efficacy. The recent increase in new therapeutic candidates for MG highlights the importance of examining whether gender plays a role in clinical outcome.

To test the hypothesis that gender is an independent factor in both patient-reported and objective outcomes, we conducted a prospective cohort study of patients with MG receiving standard of care.

Methods

Study design and population

This prospective, observational cohort study of patients with MG was conducted in the Department of Neurology, Aarhus University Hospital in Denmark. The baseline population included prevalent and incident patients from 2012 to 2014, which have been described previously[14,15]. Briefly, the clinical diagnosis of MG was based on typical symptoms and deficits, and verified by at least one of the following: autoantibodies against the acetylcholine receptor or muscle-specific tyrosine kinase, a positive edrophonium test, abnormal decrement on repetitive nerve stimulation, abnormal jitter on single-fiber electromyography, or unequivocal clinical response to pyridostigmine. We excluded 1) patients ≥ 90 years of age, and 2) patients with comorbidities directly affecting motor function. Comorbidities were identified by reviewing medical records and including detailed patient history of any concomitant diseases potentially affecting mobility and motor function as determined by the physician investigators of this study, such as myopathy, cancer, musculoskeletal diseases, etc. Furthermore, we identified significant comorbidities that may affect outcome scores, such as thyroid disease, lung diseases, other autoimmune diseases, etc. The patients were followed during routine standard of care initiated and adjusted at the discretion of the treating physician at outpatient visits and hospital admissions. Standard of care included treatment with pyridostigmine, steroids, azathioprine, methotrexate, mycophenolate, cyclosporine, rituximab, immunoglobulins, plasmapheresis, eculizumab and thymectomy.

In 2012, we identified 247 MG patients in the Central Denmark Region (one of five Danish regions with approximately 1.3 million inhabitants) in the Danish Civil Registration System and the Danish National Patient Registry. A critical review of the medical records of these patients (conducted by authors LV and HA) resulted in 175 prevalent patients with a verified MG diagnosis according to the criteria above. Recruitment letters were sent to all 175 patients

at baseline. A reminder was sent to non-responders. Furthermore, between 2012 and 2014, we consecutively enrolled incident patients diagnosed with generalized MG. Incident patients were enrolled at the time of diagnosis. They were examined prior to initiation of any treatment, and outcomes were assessed during one or two follow-up visits following initiation of standard of care. We used the most recent outcome assessment following initiation of treatment as baseline.

Follow-up assessments were made between 2017 and 2019. Patients were invited either at outpatient visits or by letter; a second reminder was sent to non-responders. Patients were eligible for follow-up assessments if they were ≤ 90 years of age and had no intercurrent comorbidities potentially affecting clinical outcome. Intercurrent comorbidities affecting outcome assessment during follow-up were identified by review of medical records and detailed patient history obtained by telephone prior to the follow-up assessments.

Patient characteristics

Clinical characteristics including date of MG diagnosis, prior and current MG treatments, comorbidities, thymectomy, antibody status, and neurophysiological assessment results were obtained from medical records and the detailed patient history both at baseline (LV) and follow-up (JLST). Retrospective data were validated and cross-checked; in case of discrepancies, a second critical review of the medical records was performed at follow-up by JLST to identify and validate the information. MG duration was calculated from the date of the physician-verified clinical diagnosis. Patients were stratified into refractory and non-refractory MG based on published criteria[16] and a MG-ADL ≥ 6.

Clinical scales

Validated MG scales were applied by the same trained physicians at baseline and follow-up (LV and JLST), using the QMG[2], and the MGC[3], the MG-ADL[4], and the QOL15[5]. The MG-ADL was administered as physician-assessed questions. Patients were examined while receiving current therapy including pyridostigmine. On the day of testing, the QMG was performed first, followed by MGC, MG-ADL and QOL15. Assessments were performed at visits independent of routine clinical follow up.

Statistical analyses

Normality was checked using histogram and QQ-plot. Gender frequencies, thymectomy rates, treatment frequencies and rates of refractory disease were compared using chi-squared test. Age, MG duration and baseline scores in participants compared to patients lost to follow-up were compared using Wilcoxon's rank-sum test. Treatment dosing at follow-up was compared using the t-test. Longitudinal assessments on clinical scales were analyzed as repeated measures using a generalized linear mixed-effects model to assess the independent effect of gender on outcome. To reduce potential bias, all data on all patients alive at follow-up were included in the main analysis. The statistical analyses used patient as random effect, and the analyses used normal (gaussian) distribution with log link due to positively skewed data. The statistical models were checked using residual plots. Gender differences were examined using gender as categorical fixed effect, and confounders including MG duration (continuous), age (continuous), refractory status (categorical), dichotomized onset (categorical, early-onset vs. late-onset), comorbidity (categorical), and prior thymectomy (categorical) were individually added as additional fixed effects.

Correlations between changes in clinical scales were analyzed using Spearman's correlation. An absolute correlation coefficient value between 0.00 and 0.29 was considered very weak,

0.30 to 0.49 weak, 0.50 to 0.69 moderate, 0.70 to 0.89 strong, and 0.90 to 1.00 very strong[17].

The change in patient-reported scores for any 1-point change in objective scores during follow-up was analyzed using linear regression. These analyses were restricted to patients completing follow-up assessments.

Analyses were made using STATA/IC 16.1 software for Windows (StataCorp LLC). The level of statistical significance was 0.05.

Standard approvals and patient consent

The study was approved by the Central Denmark Region Committee on Health Research Ethics. All patients provided written informed consent prior to inclusion.

Results

Population

A total of 107 patients with MG were assessed at baseline and complete follow-up was achieved in 70 patients corresponding to 78% of the patients who were alive at follow-up and did not have a comorbidity directly affecting motor function (Figure 1).

A total of 34.6% of included patients had at least one significant comorbidity that could affect outcome assessments, including chronic obstructive pulmonary disease or asthma (14.0%), diabetes mellitus (9.3%), thyroid disease (7.5%), restless legs or sensory neuropathy (5.6%), obstructive sleep apnea (0.9%), autoimmune rheumatic disease (3.7%), and other autoimmune or inflammatory diseases (1.9%). None of the patients had a clinical diagnosis of depression. Males (37.0%) and females (32.1%) did not differ in the prevalence of these comorbidities (P=0.59).

Other than age (patients lost to follow-up were older, median 66 vs. 61 years, P = 0.011), there were no significant differences in baseline characteristics between participants and patients lost to follow-up regarding gender, MG duration, rates of thymectomy, presence of comorbidities, QMG, MGC, MG-ADL or QOL15 scores.

Baseline scores did not differ significantly between participating females and females lost to follow-up, whereas participating males had higher baseline MGC scores than males lost to follow-up (P<0.05) (Supplemental table S1). Females lost to follow-up had higher baseline MGC (P=0.03) and MG-ADL (P=0.04) scores than males lost to follow-up (Supplemental Table 1). Incident and prevalent patients had the same baseline MGC (P=0.163) and MG-ADL (P=0.455) scores, whereas QMG (P=0.001) and QOL15 (P<0.001) scores were higher in incident patients. The proportion of females did not differ between incident (40%) and prevalent (51.7%) patients (P=0.344).

Female patients had longer MG duration (P = 0.008), were younger (P = 0.001), and more often had undergone thymectomy (P < 0.001) at baseline (Table 1).

Mean (± SD) follow-up duration was 4.8 (±0.44) years, and minimum follow-up was 3.6 years. During follow-up, 21.8% of males and 23.7% of females had initiated at least one type of new immunosuppressive therapy (P=0.857). At follow-up, 71.4% of patients received pyridostigmine, 54.3% received immunosuppressive agents, and 10.0% received maintenance plasmapheresis, immunoglobulins or eculizumab. More females than males received immunosuppressive agents other than azathioprine at follow-up (23.7% vs. 6.3%, P=0.045), including mycophenolate (13.2% vs. 3.1%), cyclosporine (7.9% vs. 0%), rituximab (10.5% vs. 0%), and plasmapheresis/immunoglobulins/eculizumab (15.8% vs. 3.1%). Dosing did not differ between females and males at follow-up regarding pyridostigmine (521.4±58.7 mg vs. 376.8±48.6 mg, P=0.07), corticosteroids (0.12 mg/kg vs. 0.17 mg/kg, P = 0.64), azathioprine

(2.1 mg/kg vs. 1.9 mg/kg, P = 0.60), methotrexate (7.5 mg vs. 15 mg, only 1 female), mycophenolate (1500 mg vs. 1500 mg) and cyclosporine (2.7±1.4 mg/kg, only females). A total of 10.0% were refractory at follow-up.

Clinical scales

Patients improved significantly during follow-up on all clinical scales (Table 2). There were no significant gender differences in baseline scores (Figure 2). Female patients improved less than males during follow-up on the QMG (-0.9 vs. -2.7, P = 0.01), the MGC (-0.1 vs. -3.0, P < 0.001), the MG-ADL (-0.6 vs. -2.0, P = 0.006), and the QOL15 (0.0 vs. -6.2, P < 0.001) (Figure 2). Female patients were more severely affected on the QMG (P = 0.01), the MGC (P < 0.001), the MG-ADL (P = 0.003), and the QOL15 (P = 0.001) at follow-up (Figure 2). A sub-analysis of objective subitems in the MGC scale showed female patients improved less compared to males (P < 0.001). These gender differences in change and follow-up scores were unrelated to whether patients were incident or prevalent at baseline (all P<0.001).
The effect of confounders on gender difference in change during follow-up was tested. Female patients improved less than males during follow-up on all clinical scales independent of MG duration (all P < 0.02), patient age (all P < 0.02), refractory MG (all P < 0.05), dichotomized onset (early- vs. late-onset, cut-off at 55 years) (all P < 0.007), and prior thymectomy (all P < 0.02). Compared to patients with non-refractory disease, patients with refractory disease improved less on all clinical scales during follow-up (all P < 0.03) and they were more severely affected on all clinical scales at follow-up (all P < 0.001). Gender-differences in change were unaffected by presence of significant comorbidities (all P > 0.05), and females had more severe disease than males on all clinical scales at follow-up independent of whether they had significant comorbidities or not (all P < 0.05).

Correlations and ratios

There was moderate to strong agreement between scores on all clinical scales at baseline (*r* range 0.56 to 0.74). At baseline, correlations were moderate to strong in males (*r* range 0.60 to 0.78) and weak to moderate in females (*r* range 0.49 to 0.68).

The clinical scales changed in the same direction during follow-up (Table 3). When stratified by gender, males had moderate to strong correlations between changes in all clinical scales, whereas females had weak to very weak correlations between change in the QMG and the MG-ADL, in the QMG and the QOL15, in the MGC and the MG-ADL, in the MGC and the QOL15, and in the MG-ADL and the QOL15 (Table 3).

A change of 1 point in the QMG or the MGC scale during follow-up was accompanied by less change in the MG-ADL or the QOL15 scale in female compared to male patients. The predictive value was low in female patients (Supplemental Table S2).

Discussion

In this study of patients with MG receiving standard of care, female patients improved significantly less than males on all 4 clinical scales during follow-up. Previous cross-sectional[7–9,11] or retrospective[10,12] studies have reported more severe disease in females using mostly registry-based and patient-reported data. We provide prospective results on both patient-reported and objective outcomes, supporting the existence of a link between female gender and less clinical improvement among patients receiving standard of care. Further, this gender difference in disease severity is evident on both objective measures, level of disability and quality of life.

Those with early-onset MG are more frequently female[1], and this may confound population-based studies examining gender differences in disease severity. Theoretically, younger age at onset and longer disease duration in females might result in fixed deficits due to ongoing complement-mediated destruction of the neuromuscular junction; however, neither younger age nor longer disease duration accounted for the gender differences in outcomes in our study. Thymus hyperplasia is more frequent in early-onset MG[1], and thymectomy effectively improves clinical outcomes[18]. In our population, more female than male patients had prior thymectomy. Accordingly, thymectomy frequencies should not attenuate gender differences in our study, which was confirmed in our analyses.

Although the mechanisms responsible for the higher frequency of females with early-onset MG are uncertain, sex hormones may influence antibody production in MG[1] as well as onset[19] and severity[20]. Our results provide further evidence of gender differences in the underlying mechanisms of MG, potentially affecting onset and course of disease as well as the therapeutic efficacy of treatments that impact clinical outcomes.

Previous studies on gender differences in MG severity have focused on patients with refractory disease[10–12]. In accordance with previously reported frequencies[1,10–12,21,22], 10% of our population was refractory at follow-up; however, females who were not refractory also improved less. Hence, these gender differences in outcomes apply to the broader MG population and are not restricted to refractory patients. Females did not change immunosuppressive therapy less often during follow-up. Further, females did not receive lower doses of pyridostigmine or immunosuppressive agents at follow-up, and they more often received a second- or third-line therapy at follow-up. Accordingly, the observed gender differences in clinical outcomes are seemingly not related to less intensive therapy or suboptimal dosing in females. It is unclear whether further therapeutic optimization or

initiation of novel treatments can improve symptoms in females and diminish gender differences in outcomes.

Several of the larger randomized, controlled trials of immunomodulators in MG have failed to clearly demonstrate efficacy[23], and most of the currently ongoing phase 3 trials in MG use the MG-ADL as the primary outcome[23]. Our results stress the importance of balancing inclusion in MG treatment trials by gender. Skewed populations consisting mostly of females may potentially mask beneficial treatment effects observed in males. Moreover, our results highlight the discrepancies between objective improvements and continued disease burden as assessed by the QOL15 or the MG-ADL. This stresses the importance of investigating and confirming beneficial treatment effects through patient-reported outcomes.

Our between-scale correlations are comparable to previous studies[4,5,24–28]. However, correlations between patient-reported and objective scores were weaker in females than in males, and females improved more on objective than on patient-reported scores during follow-up. Whereas the QMG may be more sensitive to changes in ocular, limb and axial weakness[29], the MG-ADL may be more sensitive to ocular and bulbar weakness[30]. Hence, more improvement in limb and axial symptoms than in bulbar symptoms in females may result in a weak correlation between the QMG and the MG-ADL. However, the correlation between the MGC and MG-ADL was also weaker in females than in males. The bulbar subitems were similar across these two scales, hence objective improvements in extremity deficits on the MGC are not mirrored by equal improvements in self-reported extremity disability in the MG-ADL. Some subitems of the QOL15 scale (e.g. family) and the MG-ADL (e.g. comb hair) may have an inherent gender bias, which may explain some of the weaker correlations observed in females. Furthermore, increased rates of fatigue among female patients with MG[31,32] may worsen assessments of disease burden using patient-reported

outcomes, resulting in a larger discrepancy between objective and patient-reported outcome measures in females. Whether fatigue has an impact on objective measures such as QMG and MGC scoring is uncertain.

We do not have data on patients who declined baseline participation, which might have resulted in selection bias due to gender differences in reasons for not participating (e.g. disease severity). However, the general characteristics regarding gender and age distribution, antibody type, treatment frequencies, MG duration, MGFA Classification and rates of patients with refractory disease are similar to previous reports[1,7–12,21,22,25,26,33], suggesting external validity of our findings. Although it is unknown whether gender differences influenced those who were lost during follow-up, the statistical analyses should reduce any bias as a consequence of this. Moreover, females lost to follow-up had higher baseline scores than males on some of the clinical scales, and this has likely attenuated the observed gender differences rather than increased them. The overall improvements seen in our population are comparable to improvements during routine care in other populations[25,33]. MG duration was defined as time from clinical diagnosis, and a longer duration from onset of symptoms to diagnosis and treatment in females could theoretically confound the results due to fixed deficits. However, we could not detect any effect of disease duration on outcome, and the presence of fixed deficits in MG is thus unsettled. Further studies are needed to clarify whether longer pre-existing disease duration can result in less improvement.

Conclusion

Our results show that female patients with MG improved less on both objective measures and patient-reported outcomes during routine standard care. The underlying reasons and mechanisms remain unknown and warrant further research. Current standard of care appears

to improve objective signs of disease burden more than patient-reported outcomes in females. Our results stress the importance of using patient-reported outcomes as a primary efficacy parameter in clinical trials. Attention should be given to gender differences in clinical outcome in daily clinical practice and in the design of future trials.

List of abbreviations

MG = myasthenia gravis

MG-ADL = myasthenia gravis activities of daily living

MGC = myasthenia gravis composite

QMG = quantitative myasthenia gravis

QOL15 = myasthenia gravis quality of life 15-items

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Fig. 1

Flow-chart

Legend:

Nationwide registry data identified 247 potential myasthenia gravis (MG) patients in Central Denmark Region. Review of medical records resulted in a population of 175 patients with a confirmed diagnosis; recruitment letters were sent to these patients. Further, 24 patients were diagnosed with generalized MG, of which 22 were consecutively enrolled.

† Due to traumatic tetraplegia (1) and cerebral palsy (1).

‡ Due to concomitant sarcoidosis at baseline (1) and revision of diagnosis (1).

§ Dementia (1), cancer (1), lower extremity ischemia (1), bilateral leg amputation (1), recent bilateral knee surgery (1), subarachnoid hemorrhage (1), and severe rheumatic disease (1).

Fig. 2

Baseline and follow-up scores stratified by gender (mean ± SE)

Legend:

Gender-stratified baseline and follow-up scores in (A) Quantitative Myasthenia Gravis, (B) Myasthenia Gravis Composite, (C) Myasthenia Gravis Activities of Daily Living, and (D) Myasthenia Gravis Quality of Life 15-items.

Table 1

Table 1. Baseline characteristics	
Male gender, %	50.5%
Age*, years (range)	62 (19-88)
Male	66 (19-88)
Female	54 (22-82)
MG duration*, years (range)	7 (0-62)
Male	5 (0-62)
Female	10 (0-54)
Antibody type, %	
Acetylcholine receptor	84.1%
Muscle-specific kinase	1.9%
Negative	14.0%
Thymectomy, %	30.8%
Male	14.8%
Female	47.2%
MGFA Classification, %	
Class I	16.8%
Class II	60.8%
Class III	21.5%
Class IV	0.9%

Abbreviations: MG = myasthenia gravis; MGFA = Myasthenia Gravis Foundation of America

* Displayed as median (range)

Table 2

Table 2. Baseline, follow-up and change in MG scales (mean and 95% CI).

	Baseline	**Follow-up**	**Change**	**P-value**
QMG	6.4 (5.52;7.18)	4.6 (3.79;5.38)	-1.8 (-2.59;-0.94)	< 0.001
MGC	5.9 (4.94;6.81)	4.4 (3.50;5.28)	-1.5 (-2.34;-0.63)	< 0.001
MG-ADL	3.5 (2.97;4.04)	2.3 (1.76;2.74)	-1.3 (-1.83;-0.68)	< 0.001
QOL15	11.5 (9.46;13.56)	8.5 (6.66;10.32)	-3.0 (-4.81;-1.23)	< 0.001

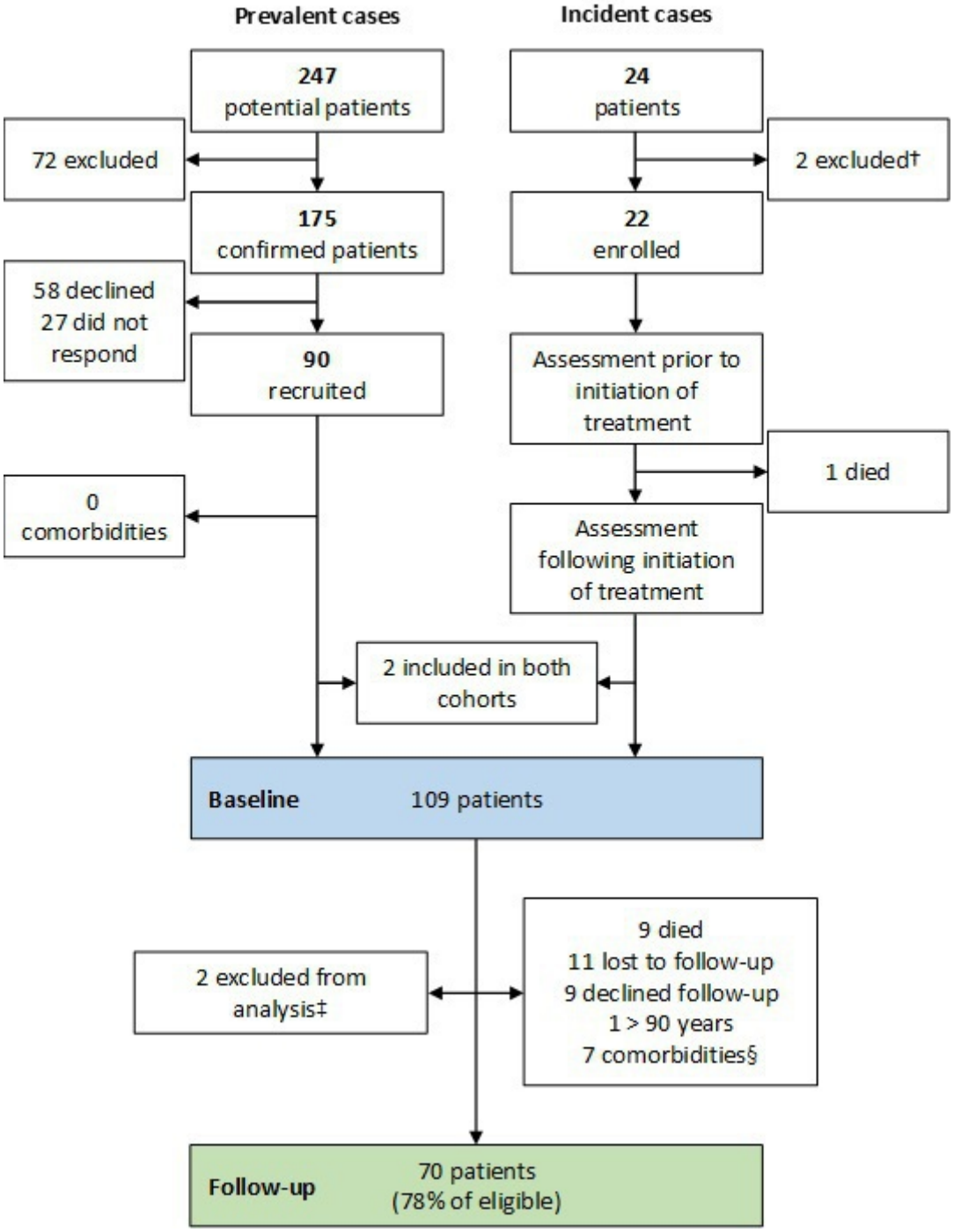
Abbreviations: QMG = Quantitative Myasthenia Gravis; MGC = Myasthenia Gravis Composite; MG-ADL = Myasthenia Gravis Activities of Daily Living; QOL15 = Myasthenia Gravis Quality of Life 15-items.

Table 3

Table 3. Correlations between change in clinical scales during follow-up, stratified by gender (correlation coefficient *r*).

	QMG	MGC	MG-ADL
MGC	0.68		
Male	0.73		
Female	0.64		
MG-ADL	0.37	0.46	
Male	0.64	0.72	
Female	0.13	0.21	
QOL15	0.45	0.27	0.49
Male	0.64	0.52	0.70
Female	0.27	0.00	0.31

Abbreviations: QMG = Quantitative Myasthenia Gravis; MGC = Myasthenia Gravis Composite; MG-ADL = Myasthenia Gravis Activities of Daily Living; QOL15 = Myasthenia Gravis Quality of Life 15-items.



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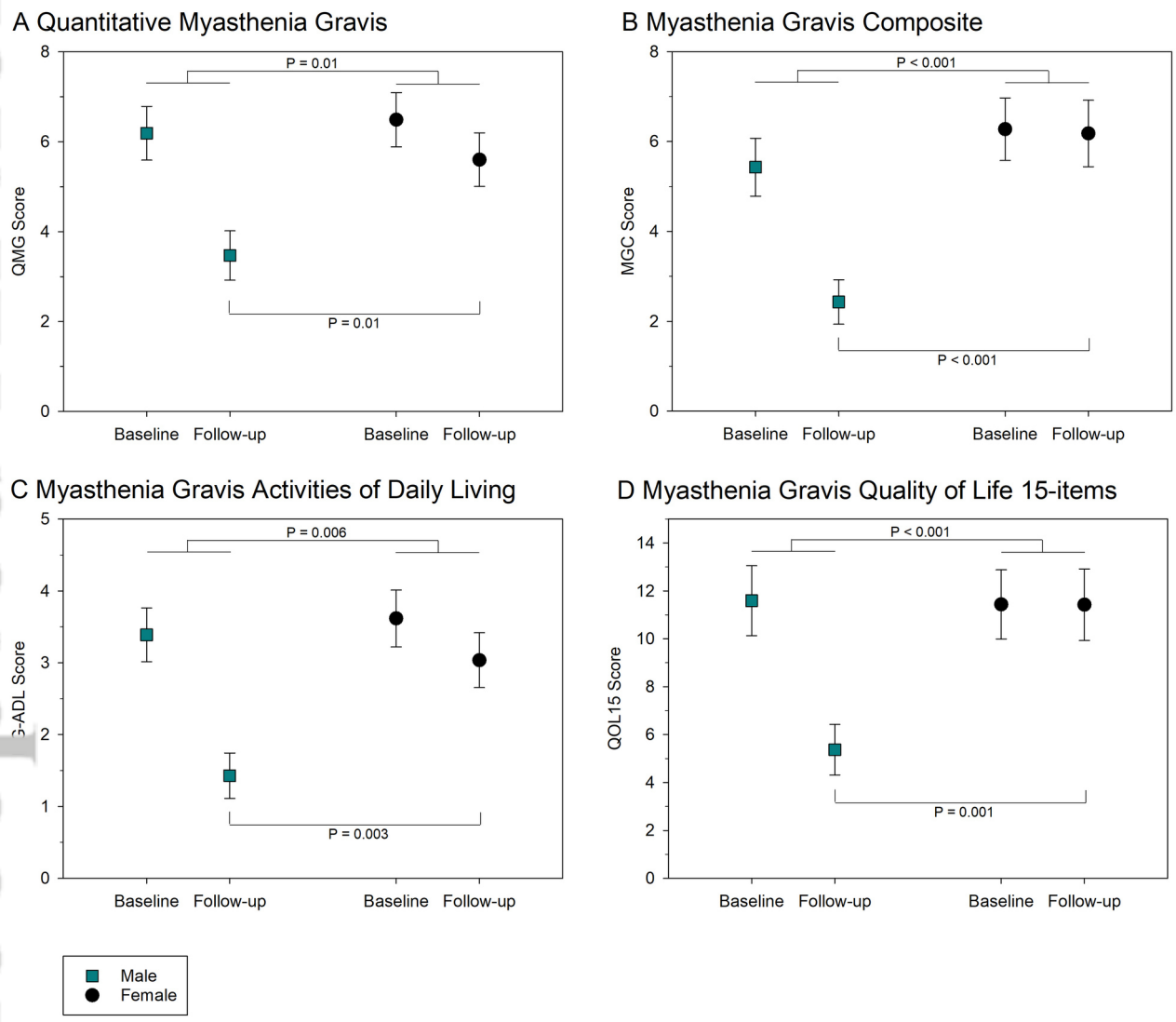

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