Survival Analysis of Myasthenia Gravis Patients at a Referral Center in Pará, Brazil (2005-2020)

Análise de Sobrevivência de Pacientes com Miastenia Gravis em um Centro de Referência no Pará, Brasil (2005-2020)

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ABSTRACT

Objective: To evaluate the profile and survival of patients diagnosed with Myasthenia Gravis, by reviewing medical records of neurological consultations at a referral service in the interior of Pará (Brazil), between 2005 and 2020.
Methods: a historical, observational and retrospective cohort study. 36 participants were included. Survival analysis methods were used to identify prognostic factors for disease remission at the observation time of 36 months. The correlation between the variables and the death outcome was performed using the chi-square test.
Results: Most patients were women (66.6%) and had the generalized form of the disease (86.1%). The most prevalent symptoms were: ophthalmoparesis (97.2%), fatigability (75%) and dysphagia (72.2%). Among the complications, 19.4% had myasthenic crisis. The dosage of anti-acetylcholine receptor (AChR) antibody was positive in 58.3% and 69.4% underwent electroneuromyography, and 72% of them had electrodecrement. Most of the patients responded to the staggered standard treatment and achieved remission (83.3%), while 16.6% died. Survival analysis showed through Kaplan-Meier curves and Log-rank test that the variables related to poor control were male gender (p=0.01), thymus disease (p=0.02) and use of cyclosporine (p=0.02). The factors that influenced the death outcome were male gender, cyclosporine and thymectomy.
Conclusion: The study showed that the evolution of people with Myasthenia Gravis over 15 years and the poor prognostic factors were equivalent to the international literature.

Keywords: Myasthenia gravis, survival analysis, neuromuscular junction.

RESUMO

Objetivo: Avaliar o perfil e a sobrevida de pacientes com diagnóstico de Miastenia Gravis, por meio da revisão de prontuários de consultas neurológicas em um serviço de referência no interior do Pará (Brasil), entre 2005 e 2020.
Métodos: estudo de coorte histórico, observacional e retrospectivo. 36 participantes foram incluídos. Métodos de análise de sobrevivência foram utilizados para identificar fatores prognósticos para remissão da doença no período de observação de 36 meses. A correlação entre as variáveis e o desfecho de óbito foi realizada por meio do teste qui-quadrado.
Resultados: A maioria dos pacientes eram mulheres (66,6%) e apresentavam a forma generalizada da doença (86,1%). Os sintomas mais prevalentes foram: oftalmoparesia (97,2%), fadiga (75%) e disfagia (72,2%). Dentre as complicações, 19,4% tiveram crise miastênica. A dosagem do anticorpo anti-receptor de acetilcolina (AChR) foi positiva em 58,3% e 69,4% realizaram eletroneuromiografia, sendo que 72% deles apresentaram eletrodecremento. A maioria dos pacientes respondeu ao tratamento padrão escalonado e obteve remissão (83,3%), enquanto 16,6% morreram. A análise de sobrevivência mostrou através de curvas de Kaplan-Meier e teste Log-rank que as variáveis relacionadas ao mau controle foram sexo masculino (p=0,01), doença do timo (p=0,02) e uso de ciclosporina (p=0,02). Os fatores que influenciaram no desfecho óbito foram sexo masculino, ciclosporina e timectomia.
Conclusão: O estudo mostrou que a evolução das pessoas com Miastenia Gravis ao longo de 15 anos e os fatores de mau prognóstico foram equivalentes à literatura internacional.

Palavras-chave: Miastenia gravis, análise de sobrevida, junção neuromuscular.

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Conflict of interest: The authors declare that the study was carried out in the absence of potential conflicts of interest.
Financing statement: There was no financing.

INTRODUCTION

Myasthenia Gravis (MG) is an autoimmune pathology, resulting from the production of autoantibodies against acetylcholine receptors (anti-AChR), present in the postsynaptic portion of the neuromuscular junction, resulting in weakness and fatigability of voluntary muscles.[1]

Based on the pattern of muscle weakness, myasthenics can be grouped into five categories within four groups with different evolutions: ocular, generalized mild, generalized moderate, acute fulminating, severe with late onset.[2]

The disease has a variable course, and myasthenic crisis (MC) may occur, an acute complication that can lead to death.[3] It is incurable, however, with individualized treatment, morbidity and mortality can be reduced.[4]

It is a pathology that can evolve progressively, generating disabilities for the affected patient. However, insidious or abrupt presentations stand out. In Brazil, 3,268 hospital admissions were recorded in the period from 2015 to 2020, highlighting the North region with the highest mortality rate in the country in the same period.[5]

This study aimed to evaluate the survival of people diagnosed with Myasthenia Gravis, through The revision in medical records doctors of queries neurological in a service of reference in Santarém, Pará, Brazil, in the period between 2005 and 2020.

METHODS

This is a historical, observational and retrospective cohort study, in which we sought to characterize the sociodemographic, clinical and complementary exam profile and subsequent analysis of the survival of all research participants diagnosed with Myasthenia Gravis, assisted at the Unineuro clinic Tapajós, located in the municipality of Santarém, a city of approximately 308,000 inhabitants in the interior of Pará, in the period between 2005 and 2020. All medical records of participants diagnosed with Myasthenia Gravis available in this service were reviewed.

Composed of 36 participants, diagnosed with Myasthenia Gravis. Sociodemographic information, signs and symptoms, complications, complementary exams, use of therapeutic procedures, progression to remission or death.

The collected data were stored in Excel spreadsheets and analyzed using the statistical software Stata version 14. The numerical variables had their summary measurements calculated (mean and median, standard deviation), while the categorical variables were analyzed in terms of proportion in the sample.

Finally, survival analysis methods were carried out with remission as the outcome, trying to identify the variables that correlate with this event over the observation period of 36 months from the first consultation. Kaplan-Meier curves, log-rank test, Hazard ratio calculation were used for significant variables, with significance level $p < 0.05$.[6,7,8]

This work was developed in accordance with the ethical principles presented in Resolution 466/12 of the National Health Council, which describes the norms for research involving human beings, following the bioethical principles: respect for autonomy, beneficence, non-maleficence, justice and equity.

The identity of the participants was preserved using only initials instead of the name. The present study was approved by the Ethics and Research Committee of the University of the State of Pará under opinion nº 5,496,273.

RESULTS

In relation to Table 1 it was seen that the average age of onset of symptoms found was 28.71 years and the average time of illness at diagnosis was 15.5 months. There was a higher proportion of females (66.6 %). Patients aged over 18 years predominated (72.2%). Within the clinical forms, 5 patients (13.8%) had the ocular form of Myasthenia Gravis and the rest the generalized form. Most patients had more than one sign or symptom, the most frequent being: ophthalmoparesis (97.2%), fatigability (75%), dysphagia (72.2%), weakness of four limbs (61.1%), speech alteration (50%). Respiratory failure occurred in 19.4% of cases. Thymoma or thymic hyperplasia existed in 22.2%. Less than half of the patients were independent for activities of daily living (44.4%) and after treatment approximately 88.8% were independent.

Table 1. Descriptive statistics (mean and standard deviation and percentage in the group) of the general characteristics of patients with Myasthenia gravis in a reference service, period from 2005 to 2020.

	Myasthenia gravis (n=36)	Description
Age at disease onset, years (mean ± standard deviation)		28.71 ± 5.2
Time from illness to diagnosis, months (mean ± standard deviation)		15.57 ± 4.0
Gender		
female	24	66.6%
male	12	33.3%
Age years		45.2 ± 3.3
< 18 years old	10	27.7%
> 18 years old	26	72.2%
Clinical form		
eyepiece	5	13.8%
widespread	31	86.1%
Abnormalities		

ophthalmoparesis	35	97.2%
weakness of the 4 limbs	22	61.1%
fatigability	27	75%
dysphagia	26	72.2%
speech alteration	18	50%
loss of gait	3	8.3%
myasthenic crisis	7	19.4%
thymoma or thymic hyperplasia	8	22.2%
Independent for daily life before treatment	16	44.4%
Independent for daily life after treatment	32	88.8%

1,2

Source: results of the research

Most patients underwent some type of diagnostic test, the result of which can be seen in Table 2, in which 58.3% had anti-acetylcholine receptor antibodies present, 33.3% had no antibodies, 69.4% underwent electroneuromyography with 50% of participants showing electrode-decrement in electroneuromyography (which corresponded to 72% of tests performed).

Table 2. Descriptive statistics (percentage in the group) of the main diagnostic tests used during the investigation of Myasthenia gravis in a reference service, period from 2005 to 2020.

	Myasthenia gravis (n=36)	Description
anti-acetylcholine receptor (achr) antibody positive	21	58.3%
missing antibody	12	33.3%
electroneuromyography performed	25	69.4%
electrodecrement	18	50%
normal	07	19.4%
electroneuromyography not performed	11	30.5%

Source: results of the research

The Table 3 shows the mean age at the start of treatment (29.5 years), mean time until disease control (9.8 months), and mean time until death (9.2 years), in addition to the mean time from onset of symptoms to thymectomy (28 months), when it occurred. We can also see the distribution of patients regarding drug treatment. All received oral drug therapy, and 100% used pyridostigmine since the beginning of treatment. As some patients did not have complete control, it was necessary to introduce adjuvant therapy with corticosteroids (69.4 %) in addition to azathioprine (33.3%) or cyclosporine (25%) in patients resistant to corticosteroid therapy. A portion required thymectomy (19.5%) and 33.5% required hospitalization due to disease exacerbation. Remission of symptoms occurred in 83, 3 % of the participants, while 19.5% did not obtain control, with 16.6% evolving to death.

Table 3. Descriptive statistics (mean + standard deviation and percentage in the group) of data related to the treatment and evolution of patients with Myasthenia gravis, in a reference service, period from 2005 to 2020.

	Myasthenia gravis (n=36)	Description (mean+-SD)
age of initiation of treatment, year		29.5 ± 5.2
time to disease control, months		9.8 ± 4.9
time from symptom onset to thymectomy, months		28 ± 8.2
follow-up time, years		4.9 ± 0.8
Treatment		
Pyridostigmine	36	100%
corticoid	25	69.4%
Azathioprine	12	33.3%
Ciclosporin	9	25%
hospital internment	12	33.3%
thymectomy	7	19.4%
Response to treatment		
remission	30	83.3 %
death	6	16.6%
time to death, years		9.2 ± 1

Source: results of the research

The Figure 1 shows the Kaplan-Meier estimation curve of remission over time, where 25% of the patients had control in the first months of treatment, more than 50% controlled it in less than 12 months and approximately 20% of the patients did not control it at any time until the end of the observation time determined by the study.

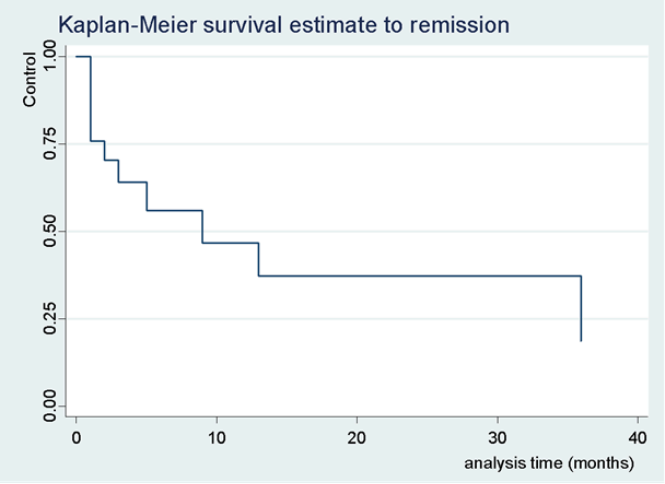

Figure 1. Myasthenia gravis symptom control curve using the Kaplan Meier estimator over 36 months

Source: results of the research

The Figure 2 shows Kaplan-Meier estimation curves regarding the control of Myasthenia gravis in the variables: A- Gender, B- Thymus disease and C- Cyclosporine. With regard to gender, the curves are quite

divergent over time. Male patients tended not to control over time, while females tended to control faster. Statistical tests showed a significant difference between the two groups (p=0.016 in Logrank with Hazard ratio =7). With reference to thymus disease, divergent curves are observed, showing that most patients with thymoma or thymic hyperplasia have a tendency to lack control. The value of p=0.02 in the Log-rank, with Hazard ratio = 6.9 confirmed the statistical difference. With regard to cyclosporine, the curves are quite divergent, where it can be noted that the highest percentage of patients who used cyclosporine tend not to control symptoms over time. Statistical tests proved a significant difference between the two groups (p=0.02 in Logrank with Hazard ratio =6.5).

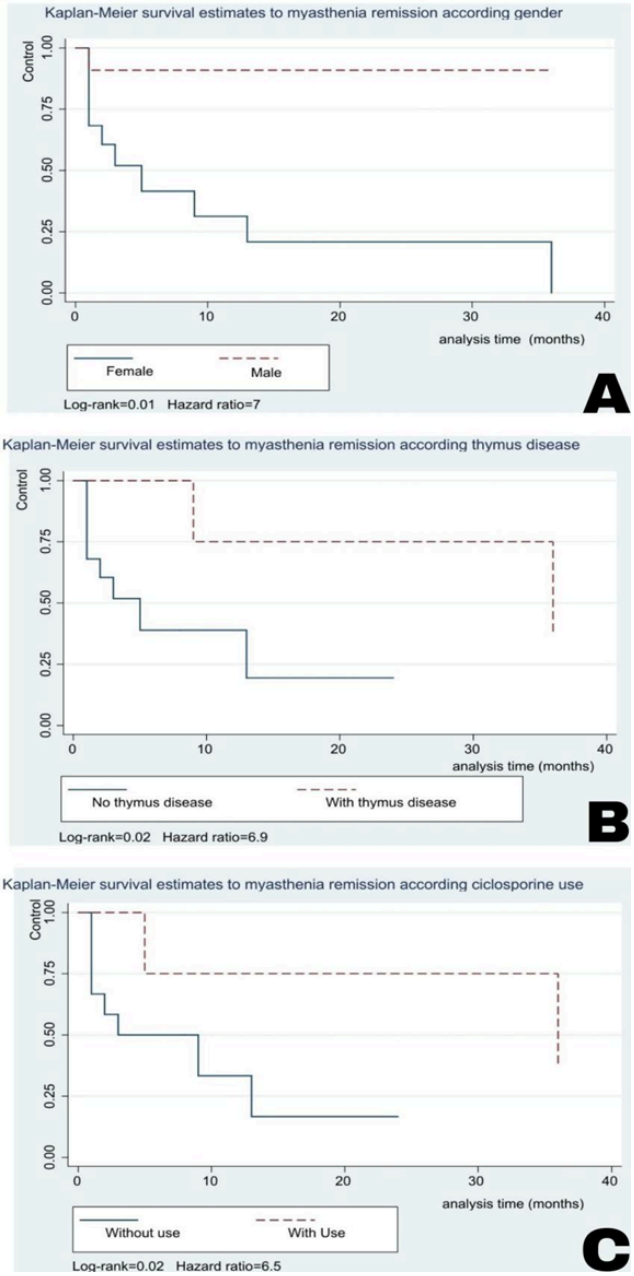

Figure 2. Curve estimated by Kaplan-Meier for control of Myasthenia gravis in relation to the variables: A- Gender, B- Thymus disease and C- Ciclosporin

Source: results of the research

The Table 4 statistically correlates the independent variables to symptom control (dependent variable), according to the Log-rank tests and their respective p and HR values. According to the analysis, the variables gender, thymoma or thymic hyperplasia and cyclosporine were statistically significant in influencing the need for a longer time until disease remission. The other variables were not significant.

Table 4. Inferential statistics: correlation between the independent variables and the dependent variable (non -remission of the disease), using the Log-rank test.

Independent variable X non-remission	p-value	Hazard Ratio (HR)
Gender	**0.01**	**7**
age > 18 years at onset of symptoms	0.16	-
loss of gait	0.14	-
dysphagia	0.3	-
speech alteration	0.2	-
ophthalmoparesis	0.07	-
weakness in 4 limbs	0.89	-
myasthenic crisis	0.06	-
thymoma or thymic hyperplasia	**0.02**	**6.9**
anti-acetylcholine receptor antibody	0.5	-
electrodecrement in electroneuromyography	0.8	-
independent of daily life before treatment	0.8	-
corticoid	0.9	-
Azathioprine	0.7	-
Ciclosporin	**0.02**	**6.5**
hospital internment	0.09	-
thymectomy	0.17	-

In bold values in **p** with significance statistic.

Source: results of the research

The Table 5 statistically correlates the independent variables and the outcome of death (dependent variable), using the chi - square test, showing their p and relative risk (RR) values. The variables gender, thymectomy and cyclosporine were statistically significant with the evolution to death. The remaining variables were not significant. According to the study, the variables gender, thymectomy and cyclosporine increased by 1.5; 6.9 and 6.2 times, respectively, the chance of death.

Table 5. Inferential statistics: Correlation between the independent variables and the dependent variable (death), using the chi - square test.

Independent variable X death	p-value	Relative risk (RR)
Gender	**0.04**	1.5
age > 18 years at onset of symptoms	0.08	-
dysphagia	0.08	-
thymoma or thymic hyperplasia	0.08	-
myasthenic crisis	0.37	-
anti-acetylcholine receptor	0.06	-
electrodecrement in electroneuromyography	0.11	-
independent of daily life before treatment	0.81	-
corticoid	0.08	-
Azathioprine	0.31	-
Ciclosporin	**0.012**	6.4
hospital internment	0.06	-
thymectomy	**0.04**	6.2

In bold values in **p** with significance statistic.

Source: results of the research

DISCUSSION

The study carried out the analysis of 36 cases diagnosed with MG between the years 2005 to 2020 in the interior of Pará state. There was a predominance of females, which is broadly in line with the national and world literature. In a 2010 meta-analysis study, the occurrence of MG is predominantly female in most studies over time.[9]

The mean age of patients with MG in our study was 28.7 years, a result close to that found in a 2013 survey, which showed a mean age of 41.6 years and similar to that obtained by a 2008 study, in which a clinical profile of patients with MG was drawn up at the University Hospital of the Federal University of Santa Catarina and had a mean age of 30.3 years[10,14].

Regarding the age group, in this study, the analyzed users were aged 18 years or over in higher prevalence (72.2%). This occurrence is analogous to the 2013 publication, where this occurred in more than 75%10 and also with the study on thymectomy carried out in the year 2000, in which the age group between 21 and 30 years was predominant.[12]

Within the clinical forms presented by the participants, the generalized form was predominant. These findings are consistent with the specialized literature.[13,10] On the other hand, in a study carried out in the province of Ouren se in Spain, the pure ocular form was more prevalent.[14] This fact corroborates the complexity and heterogeneity of the disease, in different peoples and regions, with a diversified clinical presentation, sometimes making diagnostic characterization difficult.

Geographic influences can have an impact on the evolution and survival of people with myasthenia in the Amazon, as it is known that 54.5% of the municipalities in the North region are made up of traditional peoples who generally inhabit areas that are difficult to access: riverside, quilombola communities and indigenous villages[15]. In most of these places there is no type of assistance, except that provided on an itinerant basis in specific government actions.

A dramatic example was the fact that one of the patients in the study lived in one of these remote communities without roads, went into crisis due to lack of medication and did not survive while being transported to the hospital by river in an “ambulancha”. In the story with the family, it was learned that she had been without pyridostigmine for a few days, which was only available in the urban center. Furthermore, it is possible that ethnic factors are relevant in the Amazonian context due to miscegenation, where 8.4% of the population is indigenous[15], which in turn may be related to different aspects in the regulation of immunity.

The most prevalent symptoms found in the 36 patients analyzed in our research were: ophthalmoparesis, weakness of the 4 limbs, fatigability, dysphagia and speech disorders. This occurrence is similar to what was reported in the 2010 study, carried out at the Walter Cantídio University Hospital of the Federal University of Ceará, through the review of 157 medical records. He found ptosis in 72.3% of patients, proximal weakness in 68.8% and dysphagia in 61.4%.[13]

With regard to complementary diagnostic methods, the present study revealed that most patients (58.3%) had a positive anti-acetylcholine receptor antibody. Regarding the patients who underwent electroneuromyography, 50% of them presented electrodedecrement in the exam (which corresponded to 72% of the tests performed). Such findings are consistent with those presented in a 2017 study, in which, when profiling patients with Myasthenia Gravis at the general hospital of Fortaleza in Ceará.[16]

The most used treatment in the patients analyzed in our study was pyridostigmine, followed by corticosteroids, azathioprine, cyclosporine and thymectomy. Interventions performed on patients in our study were very similar to most worldwide studies and guidelines.[17]

Disease remission is the goal of all patients and is characterized by the reduction or absence of signs and symptoms of MG over the years. It does not mean that the individual will be cured, and there may be relapses. Patients undergoing thymectomy adjuvant to clinical treatment are the most likely to enter remission.[18]

According to the response to treatment in the cases analyzed in this study, approximately 83, 3 % of the participants achieved remission, 19.5% did not have

remission. Such findings are similar to those obtained in the study by Braga (2008), where 60% of his 20 patients underwent thymectomy and 83% of them achieved remission. There is therefore evidence that thymectomy is related to a better long-term outcome.[19]

Regarding the level of independence before treatment in our study, 44.4% were classified as independent, while 55.6% of users were classified as dependent on help to perform activities of daily living. After treatment, the rate of independent patients increased significantly, highlighting the importance of adequate therapy. This is consistent with the 2014 literature, where 81.3% of participants were dependent before undergoing treatment.

Survival analysis

In our study, 25% of patients had control in the first months of treatment, more than 50% had control in less than 12 months and approximately 20% of patients had no control at any time. It was evident that the categorical variables gender, thymus disease and cyclosporine statistically influenced poor seizure control in the established observation period of 36 months. Such findings are in accordance with the literature.[20]

In male MG evolves more severely, with a high mortality rate and tendency to non-remission.[21] This fact may be correlated with situations that could decompensate MG and more affect the male public, such as: situations of emotional or financial stress and strenuous physical exercise.[22]

In this study, having disease in the thymus generated an elevated risk of non-remission. This is in line with the literature. Currently, it is believed that the thymus plays a key role in the pathophysiology of MG. The lack of regulation of the immune response interferes with the tolerance of both B cells and T cells in the thymus, culminating in an intense response against acetylcholine receptors, possibly evolving to thymoma or thymic hyperplasia. There is usually a reduction in symptoms after thymectomy.[23]

Despite the divergence of the Kaplan-Meier curves shown in Figure 2, suggesting that the majority of myasthenic patients who underwent thymectomy tend not to be in control, statistical significance was not proven over time. The reduced sample size may have influenced the result. It is believed that most patients with an indication for thymectomy already have a more severe disease burden and a worse prognosis.[24] Thymectomy would reduce symptoms and improve quality of life by approximately 70%.[17]

Participants in our research who used cyclosporine showed a statistically high risk of not controlling the disease. This fact is consistent with what is reported in the literature, as the use of cyclosporine in the treatment of MG is indicated only in more severe cases that are difficult to control, in situations where there is refractoriness to therapy with corticoids.[25]

Factors that influenced death

This study corroborates the thesis that MG is a disease that has a variable course and some of the patients progress to death even after adequate treatment. Death affected 16.6% of the participants. Such data confirms a drop in the mortality rate of MG from around 80% in the 60's to around 5 to 10% nowadays.[26]

In this context, myasthenic crisis occurred in 19.4% of our study. There was no statistical correlation with poor prognosis, which is probably due to the small sample size. It is the most severe phenotype of the disease, with a high risk of death, characterized by respiratory failure requiring invasive or non-invasive mechanical ventilation, and approximately 15 to 25% of patients have crises in their lifetime, typically in the first two years of diagnosis.[13]

We analyzed the factors that influenced death and observed that they were similar to the variables related to poor control: male gender; cyclosporine; and thymectomy. The chi-square test was chosen for correlation with death, as this outcome could have occurred outside the observation window of the survival analysis (36 months).

It should be noted, however, that the present study contains some limitations such as a small sample size, the use of data collected from only one reference service, geographical restrictions, in addition to a short observation period for survival analysis, factors that may limit the findings, and may not represent the majority of patients with Myasthenia Gravis in different Brazilian regions, given their demographic and health heterogeneity. There is also the risk of bias related to the data collected, as this is a retrospective study, subject to incomplete records, as well as the absence of a control group, making it impossible to compare the results. Therefore, larger and more comprehensive samples in terms of territory, as well as for a longer period of time, are necessary for better geographic and statistical representation.

CONCLUSIONS

The research patients had similar characteristics to other international studies. Survival analysis identified that male gender, thymic disease, and cyclosporine use were the most significant factors influencing disease remission over the 36-month observation period. Male gender, thymectomy and use of cyclosporine were correlated with a higher risk of death in the sample.

It is possible that specific characteristics of the geographic context inherent in the interior of the Amazon - differentiated ethnic origin (population with indigenous miscegenation) and difficulty in obtaining access to specialist doctors, diagnostic tests and adequate treatments - could also have influenced the outcomes. We believe that

longer studies with larger samples may be important to confirm our findings.

We hope that the study will contribute to the implementation of measures by public health agencies in the region aimed at the target audience, improving care at the regional level for people with Myasthenia Gravis.

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