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Research article

Real world study on prevalence, treatment and economic burden of myasthenia gravis in Italy

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ABSTRACT

The purpose of this study was to investigate the epidemiology, management, and economic burden of myasthenia gravis in settings of real clinical practice. The analysis used administrative databases covering around 12 million subjects across Italy and included all adult patients with hospitalization discharge diagnosis or active exemption code for myasthenia gravis or with ≥1 pyridostigmine prescription from 2011 to 2018. The estimated prevalence of myasthenia gravis during 2018 was in the range 13.5–29.3/100,000 people (depending on the criteria applied), corresponding to 8190–17,728 alive patients, when reproportioning data to the entire Italian population. Overall 4397 patients with myasthenia gravis (mean age 61.7 years, 46.6% males) were included. A large pyridostigmine use was observed (84.0%–46.8% from 1st to 3rd year of follow-up), followed by corticosteroids (54.5%–44.6% from 1st to 3rd year of follow-up) and non-steroidal immunosuppressants (16% over follow-up). Total direct healthcare costs for myasthenia gravis were 4-times higher than those of the general population (€3771 and €869, respectively), and up to 9-fold increased when considering patients with exacerbation (€7827). These findings showed the epidemiologic burden of myasthenia gravis and the complexity of the therapeutic management for the affected patients, with large use of treatments and elevated healthcare expenditures.

Abbreviations: Pyrido, pyridostigmine; CS, corticosteroids; NSISTs, non-steroidal immunosuppressant therapies; PP/PE, Plasmapheresis/plasma exchange; IVIg, intravenous immunoglobulins.

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1. Introduction

Myasthenia gravis (MG) is a neurological autoimmune disorder of the neuromuscular transmission that affects the neuromuscular junction of skeletal muscle [1]. The reduced transmission is caused by the presence of autoantibodies against the acetylcholine receptor of the postsynaptic membrane [2]. MG is classified as a rare disease, although over the past decades the improvement of diagnosis, disease management and ultimately overall longer life expectancy [3,4] led to steadily rising numbers, with the European prevalence estimated between 1.1 and 3.6 cases per 10,000 people [5–9]. MG treatments aim at controlling the disease, inducing remission or minimal manifestations state, while minimizing the risk for adverse events [10,11]. According to the Italian guidelines for the diagnosis and treatment of MG [10], the acetylcholinesterase inhibitor pyridostigmine is the entry MG therapy [12]. Commonly immunosuppressive agents are also used if the acetylcholinesterase inhibiting approach is unable to adequately control disabling symptoms. Steroids are generally prescribed as frontline therapy in view of their rapid and strong immunomodulatory activity [11]. Women under 40 years of age are more commonly affected (female/male ratio of 3/1 for early-onset MG), while after the fifth decade of life, a male predominance is observed (female/male ratio 2/3) [3]. MG causes fluctuating muscle weakness, a phenomenon referred to as fatigability [13]. Most patients initially start with ocular symptoms, like ptosis and/or diplopia without pupillary abnormalities, and then the disease involves bulbar, neck, and proximal limb muscle [14,15]. The clinical presentation might have a wide symptoms spectrum, from mild ocular symptoms up to severe generalized weakness or to the involvement of respiratory muscles leading to respiratory failure, namely myasthenic crisis [4]. Although most patients present ocular symptoms at onset, above 80% commonly progress to generalized MG (gMG) within 2 years, and up to 20% remain affected by ocular MG (oMG) [10,14]. Around 15–20% of MG patients can experience a crisis, typically within the first 2 years after diagnosis [15].

However, given that immunosuppression is a life-long treatment, steroid-sparing regimens are preferred in the long-term. Among nonsteroidal immunosuppressive therapies (NSIST), azathioprine is the first-choice among steroid-sparing agents for MG patients [10], followed by other NSISTs, like mycophenolate mofetil, cyclosporine, tacrolimus, and cyclophosphamide.

Efgartigimod is available for compassionate use and not currently reimbursed for MG by the Italian National Health Service (INHS). Similarly rituximab, although mentioned by the Italian guidelines, has an off-label use, while eculizumab was only recently approved for reimbursement for the indication of refractory MG [16].

Is indicated but however not reimbursed for refractory MG and Short-term therapies, such as intravenous immunoglobulin (IVIg] or plasma exchange (PE), are generally administered to manage disease crisis due to the rapid onset of action, or to stabilize patients before surgery. IVIg may be used as a periodic treatment in patients intolerant to NSISTs [10,11]. Regarding surgical approaches, thymectomy is indicated for MG with evidence of thymoma or in non-thymomatous (ntMG) patients with acetylcholine receptor antibody-positive MG, but thymectomy remains controversial in elderly patients elderly population without thymoma (late onset MG) and patients with a longer disease duration [1], Moreover, a small proportion of patients develop a treatment-refractory disease, as they do not respond to conventional regimens based on acetylcholinesterase inhibitors, corticosteroids, and/or NSIST and require other pharmacological interventions [17].

It should be noted that most of these treatment options, especially in the long-term, may present side effects, thus impairing patients' quality of life (QoL) and increasing the risk of complications such as infections, diabetes, liver damage [18].

Hence, in spite of the efforts of currently available pharmacological options to keep the disease under control, MG patients show anyhow a poorer QoL, due to physical disability with its negative rebounds on daily activities [4,19]. MG imposes a considerable economic burden, especially for patients that present myasthenic crises and severe complications [20].

In the context of rare diseases, the limited numbers of patients can complicate the feasibility of clinical studies. On the other hand, data from real-world evidence can shed light on the epidemiology and the management of such diseases.

The present study was undertaken to estimate the prevalence of MG patients in Italy, to describe their characteristics and treatment patterns, and to evaluate the direct healthcare costs for INHS in a real-world setting of Italian clinical practice.

2. Methods

2.1. Data source

This was a retrospective observational study integrating data from administrative databases of a sample of healthcare departments geographically distributed across Italy, covering a population of around 12 million health-assisted subjects. The following databases were browsed: demographic database, which contains all demographic data (age, gender, date of death); pharmaceutical database, that includes the direct and the indirect pharmaceutical distribution flow providing reimbursement requests submitted by pharmacies and INHS hospitals for outpatients use (i.e. drug package ID, Anatomical Therapeutic Chemical -ATC- code, prescription date, number of packages and costs per package); hospitalization database, which contains all hospitalizations data. This information originates from Discharge Hospital Records and consist of admission and discharge dates, diagnosis codes classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), diagnosis Related Group (DRG) and DRG-related charge; outpatient specialist service database, which contains all information about diagnostic tests and specialist visits; payment exemption database, collecting exemption codes and exemption data.

To guarantee patients' privacy, an anonymous univocal numerical code was assigned to each subject included in the study, in full compliance with the European General Data Protection Regulation (GDPR) (2016/679). All the results of the analyses were produced as aggregated summaries, which could not be connected, either directly or indirectly, to individual patients. Informed consent was not

required as it was impossible to obtain (pronouncement of the Data Privacy Guarantor Authority, General Authorisation for personal data treatment for scientific research purposes – n.9/2014). This study has been notified and approved by the local Ethics Committee of the LHUs involved in the study: Comitato Etico Interprovinciale Area 1 (A.O.U. Foggia, ASL Foggia, ASL BAT) (Prot. N 28/CE/2019, 02/04/2019 and Prot. N70/CE/2019,18/09/2019); Comitato Etico Sezione Area Centro Regione Calabria (Prot. N 28/CE/2019, 02/04/2019); Comitato Etico per le Sperimentazioni Cliniche (CESC) della Provincia di Vicenza (Prot. N 285, 26/11/2018); Comitato Etico Lazio 2 (Prot N 0006877, 15/01/2020 and 0087354, 15/05/2019); Comitato Etico ASL Lecce (Prot. N 34, 04/07/2019); Comitato Etico Campania Centro (Prot. N 381/CE/19, 04/11/2019); Servizio Coordinamento Comitato Etico Comitato Campania Sud (Prot. N 43 and N 46, 12/06/2019); Comitato Etico Palermo 1 (Prot. N 09/2019, 14/10/2019); Comitato Etico Lazio 1 (Prot N 1997/CE Lazio 1, 30/10/2019 and 1166/CE Lazio 1, 12/10/2020 and 1080/CE Lazio 1, 23/09/2020); Comitato Etico per la Sperimentazione Clinica della provincia di Venezia e IRCCS S. Camillo (28/07/2020).

2.2. Study population

All adult patients with a diagnosis of MG between January 2011 and December 2018 were included. The diagnosis of MG was identified by the presence of at least one hospitalization discharge diagnosis at primary or secondary level for MG (ICD-9-CM: code: 358.00 MG without acute exacerbation; ICD-9-CM code: 358.01 MG with acute exacerbation) (searched between January 2011 and December 2018) or at least one active exemption code for MG (RFG101; 034) (searched for the whole period within the exemption database) or at least one prescription for pyridostigmine (ATC code: N07AA02) (proxy of MG diagnosis) (searched between January 2011 and December 2018). The date of the first match with one of the inclusion criteria for MG within inclusion period was defined as the index date. For patients with exemption code before 2011, the index date corresponded to the first date of data availability within the inclusion period. All included patients were characterized during all available period prior the index date (at least 1 year) (characterization period) and were observed for at least 1 year after the index date (follow-up period). Follow-up period ended with death or end of data availability within the databases, whichever occurred first.

Patients aged <18 years or with less than 1 year of data availability after index date were excluded. Moreover, since pyridostigmine is also prescribed to treat some non-motor symptoms in other neurological disorders (i.e. atonic colon in Parkinson's disease), patients included by pyridostigmine only (without exemption code or hospitalization for MG) were excluded if they had a diagnosis for Parkinson's disease (at least one prescription of anti-parkinson drugs [ATC code: N04] or one hospitalization with diagnosis at any levels for Parkinson's disease [ICD-9-CM code: 332]) or spinal cord injury (one hospitalization with diagnosis at any levels for spinal cord injury [ICD-9-CM codes: 806, 952]).

Since for some Healthcare Departments the data availability period ended before December 2018, prevalence was calculated on patients alive at 01/01/2018 and stratified by gender. Data were reproportioned to the Italian population.

2.3. Study variables

During the characterization period, the general comorbidity profile of included patients was assessed using the Charlson Comorbidity Index, a scoring systems given based on the sum of 19 weighted comorbidities to predict ten-year mortality [21]. The following treatments for MG were evaluated prior to index date and during follow-up: pyridostigmine, immunosuppressants [azathioprine (ATC code: L04AX01), cyclosporin (ATC code: L04AD01), cyclophosphamide (ATC code: L01AA01), methotrexate (ATC codes: L01BA01, L04AX03), mycophenolate (ATC L04AA06), sirolimus (ATC L04AA10), tacrolimus (ATC code: L04AD02)], IVIg (ICD-9-CM: 99.14), PE or plasmapheresis (ICD-9-CM: 99.71, 99.76), corticosteroids for systemic use (ATC code: H02). Rituximab is not currently indicated neither reimbursed by INHS for MG as off-label use, while eculizumab was only approved for reimbursement for the indication of refractory MG in September 2022, thus after the closure of patients' inclusion period of the present analysis [16]. Thymectomy was identified by presence of procedure code ICD-9-CM 07.8. Treatment line sequences were described in terms of number of lines, mean duration for each line and mean time to switch to subsequent line. Switch was defined as change of therapy from the previous one, while add-on was considered when another therapy was added to the current one. A change of line was detected in case of patients switching to another therapy or combining a new one. Refractory patients were identified by the presence of at least one of the following criteria during follow-up: multiple hospitalization, repeated PE or IVIg utilization, combination of at least 3 drugs (other than pyridostigmine) and high dose pyridostigmine. During characterization and follow-up, the most frequent classes of prescribed treatments were evaluated, with a focus on cardiovascular drugs and treatments for psychiatric disorders (anxiolytic agents, antidepressants, antipsychotics, mood stabilizers) and the most frequent hospitalizations grouped by Major Diagnostic Categories (MDC). The included MG population was compared with a control group of health-assisted subjects without MG in 2019 ("Non-MG population").

Healthcare direct costs sustained by the INHS were computed in terms of expenses for overall drug prescriptions, all-cause hospitalizations and outpatient services and reported in Euros (€), using INHS purchase price. The hospitalization costs referred to DRG tariffs, which represent the reimbursement levels by the INHS to healthcare providers. The costs of instrumental and laboratory tests were defined according to tariffs applied at a regional level. In the economic analysis, costs per patient were reported for each year of follow-up and stratified by number of lines, and also compared to those of the non-MG population.

2.4. Statistical analysis

Continuous variables are given as mean ± standard deviation (SD), and categorical data as frequency counts and percentages. The latter were calculated using the number of observations with non-missing values as the denominator. Chi-square test with contingency tables was used to for comparisons for MG patients one year before index date, at first, second and third year of follow-up and non-MG population. A p value < 0.05 was considered as significant and all statistical analyses were carried out using STATA SE, version 12.0.

3. Results

From a sample of 12,047,847 health-assisted subjects, overall 4397 MG patients were included in the analysis, with an average age of 61.7 years, a proportion of male gender of 46.6%, and mean Charlson index of 1.1 (Table 1).

3.1. Disease prevalence

In the sample population, the prevalence as to 01/01/2018 resulted to be 29.3 patients per 100,000 health-assisted subjects (Fig. 1A). Gender stratification revealed a prevalence of 31.0 and 27.6 MG cases per 100,000 females and males, respectively. Data projected to the national population estimated a total of 17,728 alive MG patients (9618 men, 8110 women) in Italy (Fig. 1B).

To better refine the prevalence, a sensitivity analysis was performed without using pyridostigmine prescription as the unique inclusion criterion. This resulted in an overall prevalence of 13.5 MG cases per 100,000 subjects (14.4 per 100,000 females, 12.7 per 100,000 males), with a corresponding projection of 8190 patients (4456 women and 3734 men) with MG in Italy.

3.2. Disease treatment

MG-related treatments prescribed during follow-up, are reported in Table 2. A considerable use of pyridostigmine was observed during the whole follow-up (84.0%, 52.5% and 46.8%, at the first, second and third year of follow-up, respectively). Around 16% of patients received NSISTs, mainly azathioprine, while approximately 1–3% of patients underwent IVIg or PE. Corticosteroid use decreased from 54.5% during the first year of follow-up to 44.6% at the third year. No treatment was reported for 378 (8.6%) patients for all the available follow-up.

Among 4019 treated patients, first line therapy was mainly represented by pyridostigmine (78.6%). A total of 3114 (77.5% of patients in first line) moved to a second line after a mean (±SD) time of 8.8 (±15.7) months. The most frequent treatment sequence was pyridostigmine followed by corticosteroids (67.2%). Among patients in second line, 32.5% moved to a third line after a mean (±SD) of 12.5 (±18.0) months. The most common combination was pyridostigmine followed by corticosteroids and NSISTs (33.6%). Lastly, 20% of patients in third line switched to a fourth one (Fig. 2). Overall, 35.9% (1580 out of the 4397 patients included in the study) were deemed as refractory, as they fulfilled at least one criterion selected for refractory MG.

3.3. Concomitant diseases and treatments

As shown in Table 3, antibacterials were the most frequently prescribed drugs during the characterization and follow-up periods (58.8–65.4%), followed by *anti*-acid drugs and proton pump inhibitors (61.3–72.3%). The same drug classes accounted for 46.0% and 27.8% respectively, among the non-MG population. Similarly, around 60% of patients had at least one prescription of cardiovascular therapies, and over half of patients were prescribed with 2 different classes among agents acting on the renin-angiotensin system, antithrombotic agents and lipid modifying agents. In comparison, the same prescriptions were observed in 36.2% of the non-MG population. Antidepressants were prescribed to 16.0–19.8% of patients, mostly as continuous use. Mood stabilizers were twice as

Table 1
Demographics of included patients at baseline. Continuous variables are presented as mean ± standard deviation, and categorical data as frequency counts and percentages in brackets.

Variable	Patients with myasthenia gravis
N. patients	4397
Age, years	61.7 ± 16.8
Age ranges, years	
18–24	91 (2.1%)
25–34	247 (5.6%)
35–44	443 (10.1%)
45–54	602 (13.7%)
55–64	840 (19.1%)
65–74	1036 (23.6%)
75–84	885 (20.1%)
≥85	253 (5.8%)
Male gender	2047 (46.6%)
Charlson Comorbidity Index	1.1 ± 1.4

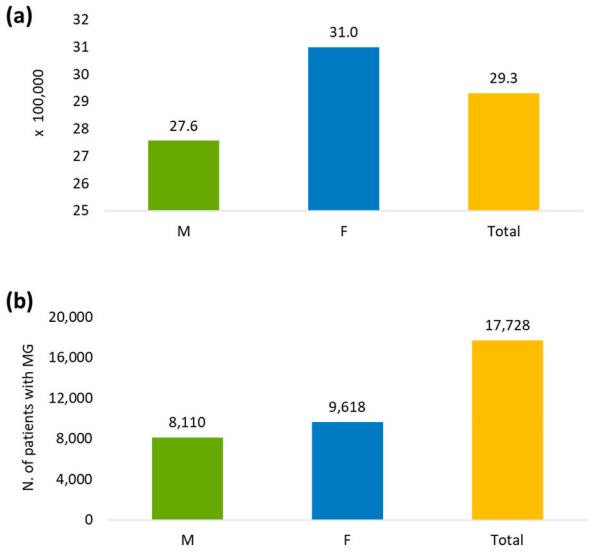


Fig. 1. (A) Prevalence rate per 100,000 health-assisted subjects with MG in Italy at 01/01/2018, and **(B)** projection on the national population.

Table 2
Treatments prescribed to the study population during follow-up. Data are given as frequency counts and percentages in brackets.

Type of treatments	First year of follow-up* (n = 4397)	Second year of follow-up (n = 3994)	Third year of follow-up (n = 3114)
Pyridostigmine	3692 (84.0%)	2098 (52.5%)	1456 (46.8%)
Plasma exchange (PE)	93 (2.1%)	51 (1.3%)	33 (1.1%)
Intravenous immune globulins (IVIg)	142 (3.2%)	85 (2.1%)	53 (1.7%)
Non-steroidal immunosuppressive treatment (NSISTs)	714 (16.2%)	655 (16.4%)	489 (15.7%)
•Azathioprine	601 (13.7%)	539 (13.5%)	386 (12.4%)
•Cyclosporin	53 (1.2%)	50 (1.3%)	49 (1.6%)
•Mycophenolate	17 (0.4%)	24 (0.6%)	16 (0.5%)
•Methotrexate	58 (1.3%)	54 (1.4%)	46 (1.5%)
Corticosteroids	2397 (54.5%)	1897 (47.5%)	1390 (44.6%)
With no pyridostigmine prescription	705 (16.0%)	1896 (47.5%)	1658 (53.2%)

*Index date included.
Note: Treatments prescribed to <4 patients were not reported for data privacy. Sirolimus: N = 0 in all years, Cyclophosphamide: N = 6 (0.1%) during first year of follow-up, N = 7 (0.2%) during second year of follow-up, N = 4 (0.1%) during third year of follow-up. Eculizumab and rituximab were not reported as they were currently not reimbursed for MG at the time of the data collection.

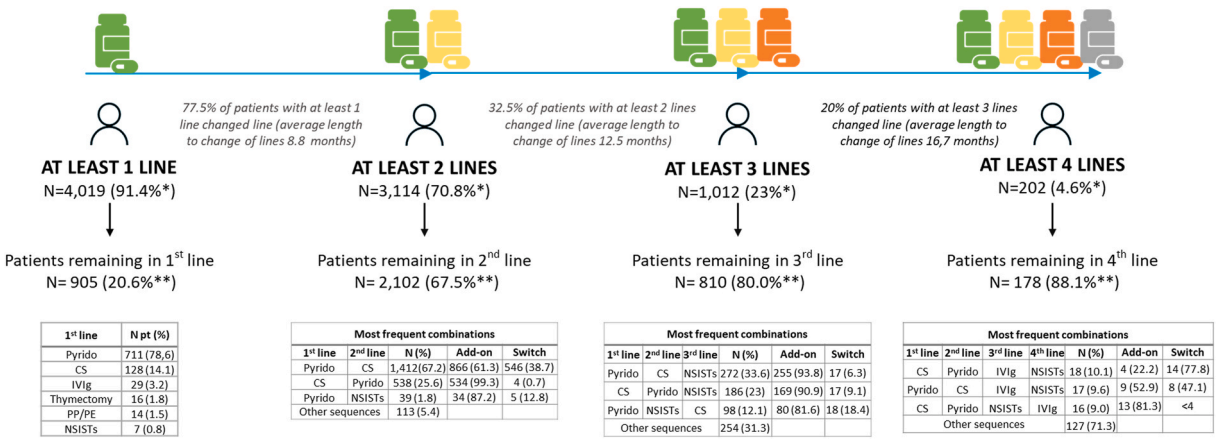
frequent among MG patients (2.4–3.2%) compared to the non-MG population. The most frequent hospitalization was due to nervous system diseases, followed by circulatory and musculoskeletal. Except for nervous system, all hospitalizations were 3 times higher in MG than in the general population (Table 4). As expected, chi-square test showed that at all times of observation, the patients treated with the considered medications or hospitalized for the above-mentioned concomitant diseases were markedly more represented in MG and in non-MG population (highly significant, $p < 0.01$).

3.4. Patient costs

The mean total annual costs per patient were €3771 for the first year, €2827 for the second and 2555 for the third year of follow-up, mainly driven by hospitalizations (€2198 for the first, €1316 for the second and €1054 for the third year) and drugs (€1,148, €1122 and €1122). Mean total annual direct healthcare costs for non-MG population accounted for €869 (€319 for hospitalizations, €367 for drugs, €184 for outpatient services) (Fig. 3).

As shown in Fig. 4, total mean costs increased with later lines of treatment from €2007 to €7019 from first to fourth line. These rising expenditures were not only related to drugs (€681 to €2347), but also to outpatients services (€318 to €1053). Hospitalization costs were around €1000 for patients in first and second line and increased among patients in third or fourth line of therapy (€1204 and €3619).

Patients with exacerbation had a mean cost during the first year of follow-up of €7827 (€5810 for hospitalization), €5415 during the second year (€3360 for hospitalization) and €4045 during the third year (€2137 for hospitalization) (Fig. 5).



1st line	N pt (%)
Pyrido	711 (78,6)
CS	128 (14.1)
IVIg	29 (3.2)
Thymectomy	16 (1.8)
PP/PE	14 (1.5)
NSISTs	7 (0.8)

Most frequent combinations				
1st line	2nd line	N (%)	Add-on	Switch
Pyrido	CS	1,412(67.2)	866 (61.3)	546 (38.7)
CS	Pyrido	538 (25.6)	534 (99.3)	4 (0.7)
Pyrido	NSISTs	39 (1.8)	34 (87.2)	5 (12.8)
Other sequences		113 (5.4)		

Most frequent combinations					
1st line	2nd line	3rd line	N (%)	Add-on	Switch
Pyrido	CS	NSISTs	272 (33.6)	255 (93.8)	17 (6.3)
CS	Pyrido	NSISTs	186 (23)	169 (90.9)	17 (9.1)
Pyrido	NSISTs	CS	98 (12.1)	80 (81.6)	18 (18.4)
Other sequences			254 (31.3)		

Most frequent combinations						
1st line	2nd line	3rd line	4th line	N (%)	Add-on	Switch
CS	Pyrido	IVIg	NSISTs	18 (10.1)	4 (22.2)	14 (77.8)
Pyrido	CS	IVIg	NSISTs	17 (9.6)	9 (52.9)	8 (47.1)
CS	Pyrido	NSISTs	IVIg	16 (9.0)	13 (81.3)	<4
Other sequences				127 (71.3)		

Fig. 2. Therapy sequences during follow-up period by number of lines.
*Percentages calculated on overall patients (N = 4397). **Percentages calculated on patients with at least the corresponding line.

4. Discussion

Differently from randomized clinical trials, real world studies allow the observation of patients in uncontrolled clinical practice settings, paving the way to actual evaluations of disease impact at public health level (through epidemiological analyses), and to a direct sight on the therapeutic management of patients. This is especially true for rare diseases where the population is fragile and numerically reduced and requires a highly individualized care organization by the health services. For this reason, we used administrative data to provide an up-to-date epidemiology of MG in Italy, together with an overview of MG management and economic burden for the INHS.

The epidemiologic scenario of MG is rapidly evolving [3]. To the best of our knowledge, estimations of MG prevalence for Italy referred to previous decades and have been limited to specific geographic areas ranging from 8 to 24 cases per 100,000 individuals [22–24]. Recent data estimating the number of MG patients at the national level are missing. Our findings report an overall prevalence of 29.3 MG patients per 100,000, slightly higher compared to prevalence estimates previous reported for Italy, in line with recent evidence suggesting an increase in MG prevalence [3]. Our data are consistent with the reported European prevalence range of 77–317 per million inhabitants [4].

The use of pyridostigmine as a proxy for MG could have overestimated the prevalence of the disease. For this reason, we conducted a sensitivity analysis considering only hospitalization or exemption code diagnosis of MG. Prevalence drastically decreased to 13 cases. Although the numbers of MG in Italy are currently unknown, data retrieved from patient associations estimated around 15,000 patients (from 10,000 up to 20,000) [25,26]. Based on the present study, we calculated around 17,728 patients currently living in Italy with MG in 2018, of which above 14 thousand might be with gMG, considering that only 20% of the patients remain with oMG [10,14].

Treatment lines were coherent with the Italian guidelines [10]. Pyridostigmine was the most prescribed first line treatment, and azathioprine the most commonly prescribed among NSISTs. An extensive use of corticosteroids during follow-up was also noticed. Although therapies proved to improve symptoms [27], their long-term use can result in several side effects, complications, and ultimately poorer QoL [18,28]. The chronic use of corticosteroids is also associated with increased mortality [29]. We found that one out of four patients required three concomitant therapies to manage MG, with the most frequent combination being pyridostigmine, followed by corticosteroids and then NSISTs. Our study did not provide data on the benefit of this approach, but 20% of these patients necessitated a fourth add-on treatment. It is possible that failures might be underestimated due to the lack of approved drugs for refractory MG, leading to a high treatment inertia. Refractory patients were 35.9% of our total population, and such proportion appears to be markedly higher compared to the previously reported values of 10–15%, feasibly explicated by the wide selection criteria used in this study (i.e. multiple hospitalization, plasma exchange/PE or IVIg utilization, combination of at least 3 drugs and high dose of pyridostigmine). Taken together, these findings further emphasize the demanding clinical and therapeutic management of MG patients, often burdened by a complex clinical status and need of comedications, with all the related cost repercussions for the healthcare systems. Hence, there is an important unmet need for innovative, effective, and well-tolerated therapies.

As expected, our data confirmed a greatly increased requirement of various types of medications in MG patients with respect to unaffected control subjects, in particular for *anti*-acid drugs, anti-bacterial agents, cardiovascular drugs, and antidepressants/mood stabilizers. The same tendency was reported in a national cohort study by Andersen et al. who described a widespread use in of comedications MG patients, noticeably broader compared to the general population [30]. Antidepressant use was also self-reported by around 10% of patients in a survey submitted to MG patients by the German Myasthenia Association [31]. Our results corroborate the relevant disease burden carried by MG patients, that might be further worsened by the treatments administered for MG itself. Therefore, pre-existing pathological conditions should deserve much attention by the clinicians in the choice of therapeutic regimens for MF.

Table 3
MG and non-MG population drug prescriptions during characterization and follow-up period. Data are given as frequency counts and percentages in brackets.

Drugs (ATC)	1 year before index date (N = 4397)	First year of follow-up[a] (n = 4397)	Second year of follow-up (n = 3994)	Third year of follow-up (n = 3114)	Non-MG population (~5 M)	p
Antibacterials for systemic use (J01)						
≥1 patient	2747 (62.5%)	2876 (65.4%)	2420 (60.6%)	1832 (58.8%)	(46.0%)	<0.001
1-2 patients	1564 (35.6%)	1569 (35.7%)	1295 (32.4%)	965 (31.0%)	(33.7%)	<0.001
≥3 patients	1183 (26.9%)	1307 (29.7%)	1125 (28.2%)	867 (27.8%)	(12.3%)	<0.001
Drugs for acid related disorders (A02)						
≥1 patient	2752 (62.6%)	3181 (72.3%)	2643 (66.2%)	1908 (61.3%)	(27.8%)	<0.001
1-2 patients	640 (14.6%)	555 (12.6%)	452 (11.3%)	336 (10.8%)	(10.9%)	<0.001
≥3 patients	2112 (48.0%)	2626 (59.7%)	2191 (54.9%)	1572 (50.5%)	(16.8%)	<0.001
Corticosteroids for systemic use (H02)						
≥1 patient	1993 (45.3%)	2590 (58.9%)	2058 (51.5%)	1455 (46.7%)	(14.6%)	<0.001
1-2 patients	829 (18.9%)	720 (16.4%)	558 (14.0%)	437 (14.0%)	(12.2%)	<0.001
≥3 patients	1164 (26.5%)	1870 (42.5%)	1500 (37.6%)	1018 (32.7%)	(2.4%)	<0.001
Anti-inflammatory/antirheumatic products (M01)						
≥1 patient	1869 (42.5%)	1806 (41.1%)	1514 (37.9%)	1204 (38.7%)	(23.9%)	<0.001
1-2 patients	1176 (26.7%)	1134 (25.8%)	918 (23.0%)	717 (23.0%)	(17.5%)	<0.001
≥3 patients	693 (15.8%)	672 (,15.3%)	596 (14.9%)	487 (15.6%)	(6.4%)	<0.001
Drugs for obstructive airway diseases (R03)						
≥1 patient	1123 (25.5%)	1202 (27.3%)	1062 (26.6%)	798 (25.6%)	(12.8%)	<0.001
1-2 patients	743 (16.9%)	787 (17.9%)	724 (18.1%)	537 (17.2%)	(9.0%)	<0.001
≥3 patients	380 (8.6%)	415 (9.4%)	338 (8.5%)	261 (8.4%)	(3.8%)	<0.001
Vitamins (A11)						
≥1 patient	889 (20.2%)	1307 (29.7%)	1227 (30.7%)	889 (20.2%)	(13.8%)	<0.001
1-2 patients	467 (10.6%)	627 (14.3%)	602 (15.1%)	352 (11.3%)	(7.6%)	<0.001
≥3 patients	422 (9.6%)	680 (15.5%)	625 (15.6%)	525 (16.9%)	(6.2%)	<0.001
Overall cardiovascular drugs**						
≥1 class	2520 (57.3%%)	2697 (61.3%%)	2260 (56.6%%)	1679 (53.9%%)	(36.2%)	<0.001
≥2 class	2254 (51.3%%)	2421 (55.1%%)	2059 (51.6%%)	1532 (49.2%%)	(32.7%)	<0.001
Antidepressants (N06A)						
≥1 patient	748 (17.0%)	870 (19.8%)	683 (17.1%)	497 (16.0%)	(6.2%)	<0.001
1-2 patients	293 (6.7%)	340 (7.7%)	235 (5.9%)	182 (5.8%)	(2.0%)	<0.001
≥3 patients	455 (10.3%)	530 (12.1%)	448 (11.2%)	315 (10.1%)	(4.1%)	<0.001
Antipsychotics (N05A)						
≥1 patient	105 (2.4%)	142 (3.2%)	121 (3.0%)	100 (3.2%)	(1.9%)	<0.001
1-2 patients	66 (1.5%)	76 (1.7%)	58 (1.5%)	56 (1.8%)	(0.6%)	<0.001
≥3 patients	39 (0.9%)	66 (1.5%)	63 (1.6%)	44 (1.4%)	(1.3%)	0.0415
Mood stabilizers (N05AN01, N03AF01, N03AF02, N03AG01, N03AX09)						
≥1 patient	120 (2.7%)	128 (2.9%)	106 (2.7%)	72 (2.3%)	(1.4%)	<0.001
1-2 patients	43 (1.0%)	49 (1.1%)	38 (1.0%)	22 (0.7%)	(0.3%)	<0.001
≥3 patients	77 (1.8%)	79 (1.8%)	68 (1.7%)	50 (1.6%)	(1.1%)	<0.001

[a] Index date included; **Cardiovascular drugs analyzed were agents acting on the renin-angiotensin system, antithrombotic agents, lipid modifying agents.

Table 4
MG patients included and the non-MG population all-cause hospitalizations during characterization and follow-up periods. Data are given as frequency counts and percentages in brackets.

Hospitalizations (MDC)	1 year before index date (N = 4397)	First year of follow-up* (n = 4397)	Second year of follow-up (n = 3994)	Third year of follow-up (n = 3114)	Non-MG population (~5 M)	p
Nervous system (MDC 1)	374 (8.5%)	846 (19.2%)	265 (6.6%)	151 (4.8%)	(0.5%)	<0.001
Circulatory system (MDC 5) 146 (3.3	146 (3.3%)	164 (3.7%)	122 (3.1%)	80 (2.6%)	(1.1%)	<0.001
Musculoskeletal system and connective tissue (MDC 8)	136 (3.1%)	99 (2.3%)	89 (2.2%)	80 (2.6%)	(1.1%)	<0.001
Digestive system (MDC 6)	135 (3.1%)	146 (3.3%)	96 (2.4%)	74 (2.4%)	(0.8%)	<0.001
Respiratory system (MDC 4)	119 (2.7%)	211 (4.8	124 (3.1%)	68 (2.2%)	(0.6%)	<0.001
Eye (MDC 2)	87 (2.0%)	45 (1.0%)	35 (0.9%)	21 (0.7%)	(0.2%)	<0.001
Myeloproliferative DDs (poorly differentiated neoplasms) (MDC 17)	68 (1.5%)	91 (2.1%)	40 (1.0%)	31 (1.0%)	(0.2%)	<0.001
Kidney and urinary tract (MDC 11)	54 (1.2%)	56 (1.3%)	55 (1.4%)	29 (0.9%)	(0.4%)	<0.001
Endocrine, nutritional and metabolic system (MDC 10)	47 (1.1%)	39 (0.9%)	33 (0.8%)	10 (0.3%)	(0.2%)	<0.001

*Index date included.

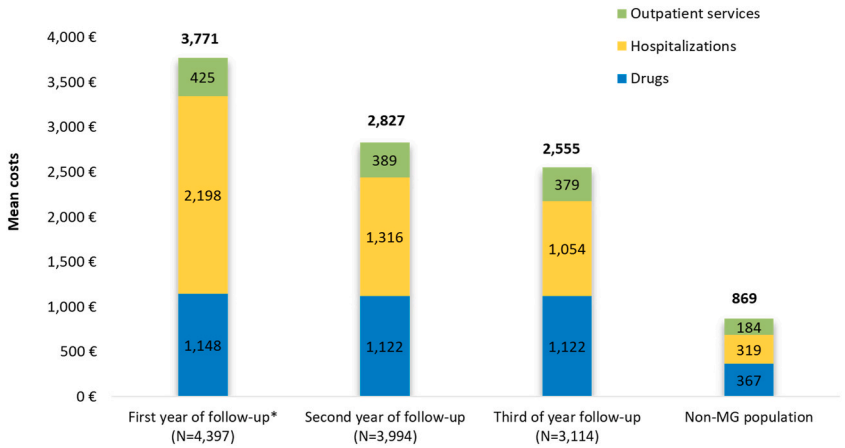


Fig. 3. Mean annual healthcare direct costs during follow-up (total costs are indicated in bold).
*Index date included.

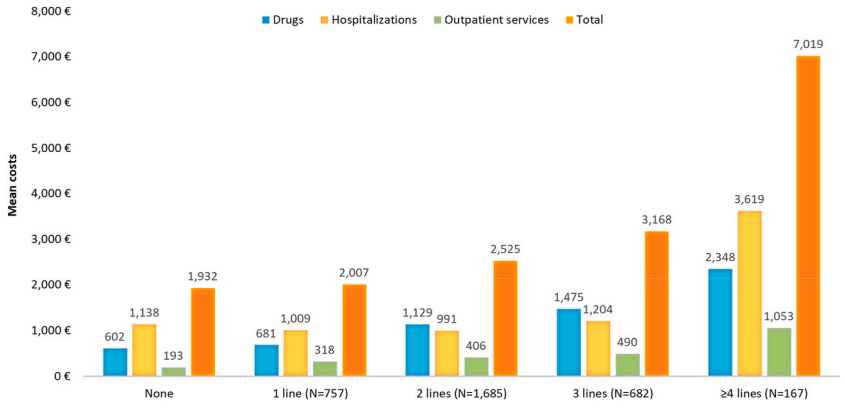


Fig. 4. Mean annual healthcare direct costs stratified by treatment line. Note: Patients deceased during follow-up were excluded.

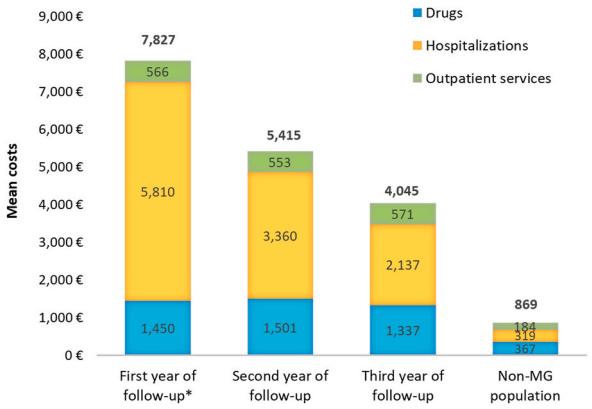


Fig. 5. Mean annual healthcare direct costs during follow-up in patients with exacerbation at inclusion (total costs are indicated in bold). *Index date included

Consistently with the clinical status described in these patients, cost analyses showed that expenses for MG management were around 4 times higher than those calculated for the general population. Moreover, costs grew as patients move forward in treatment lines, especially for patients with 3 or 4 lines of therapy. For these patients, we observed elevated hospitalization costs, underlining the considerable efforts in treating refractory MG with available therapies. Of note, higher costs were also detected in patients with exacerbation as compared to other MG patients during the whole follow-up. A 9-fold increase was observed when comparing mean total costs per patient with exacerbation during first year of follow-up to that of the general population. The main strength points of the present analysis are its novelty and the application of a real-life approach to a rare disease, a research area that in suffers from the absence of reliable epidemiological data and scarce feasibility of large clinical trials in view of the small population. Up to now, information on prevalence and incidence of MG in Italy have been only estimated by patients' association. Moreover, to the best of our knowledge, mean annual costs related to MG patients have not yet been reported for Italian MG patients.

Nevertheless, the study has some limitations due to its retrospective nature and data source, based on administrative data, that did not allow us to describe clinical phenotypes related to the MG form or antibody status, and to discriminate among ocular or generalized MG. We could not recall any data on disease severity, nor ascertain the underlying reason beyond switching therapy. The presence of pyridostigmine as a proxy of MG diagnosis could have overestimated the number of patients during prevalence calculation. This overestimation might be also partly related to dual role of pyridostigmine in both diagnostic and therapeutic pathway of patients with MG, as in the last decades, the pyridostigmine test has been used as a valuable alternative to the edrophonium test in case of a suspected MG diagnosis [32,33]. Moreover, we might have possibly also overrated the cases of refractory patients, as they were identified through a set of criteria to be considered as diagnosis proxies. Lastly, it was not possible to retrieve information on the actual rituximab use in MG, as in Italy it is not indicated nor reimbursed for MG.

5. Conclusions

The present real-world study provides the epidemiological and economic scenario of MG in Italy, with a thorough characterization of the patient's journey in terms of therapeutic pathways and clinical burden. Up to now, epidemiological data on MG in Italy had been reported for specific areas only. We provide estimates based on a population of around 12 million across Italy. Our results revealed a prevalence spanning from 13 to 29.3 MG patients per 100,000, corresponding to 17,728 patients currently living with MG in Italy. The analysis of treatment patterns showed a relevant use of MG therapies, especially corticosteroids, which could lead to harmful side effects after a long-term exposure. Finally, we found a heavy economic burden of these patients, which is up to 9-times higher if compared to the general non-MG population, highlighting the complexity of the therapeutic management of MG.

Author contribution statement

Giovanni Antonini, Francesco Habetswallner, Maurizio Inghilleri, Renato Mantegazza, Carmelo Rodolico, Francesco Saccà, Manlio Sgarzi, Luca Degli Esposti: conceived and designed the study; Femke deRuyck, Sandra Paci, Glenn Phillips, Laura Crippa: analyzed and interpreted the data; Chiara Veronesi: analyzed and interpreted the data, contributed to analysis tools or data; Valentina Perrone: conceived and designed the study; wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper (any other financial relationship of the coauthors, anyhow unrelated to the manuscript, has been disclosed in the text).

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